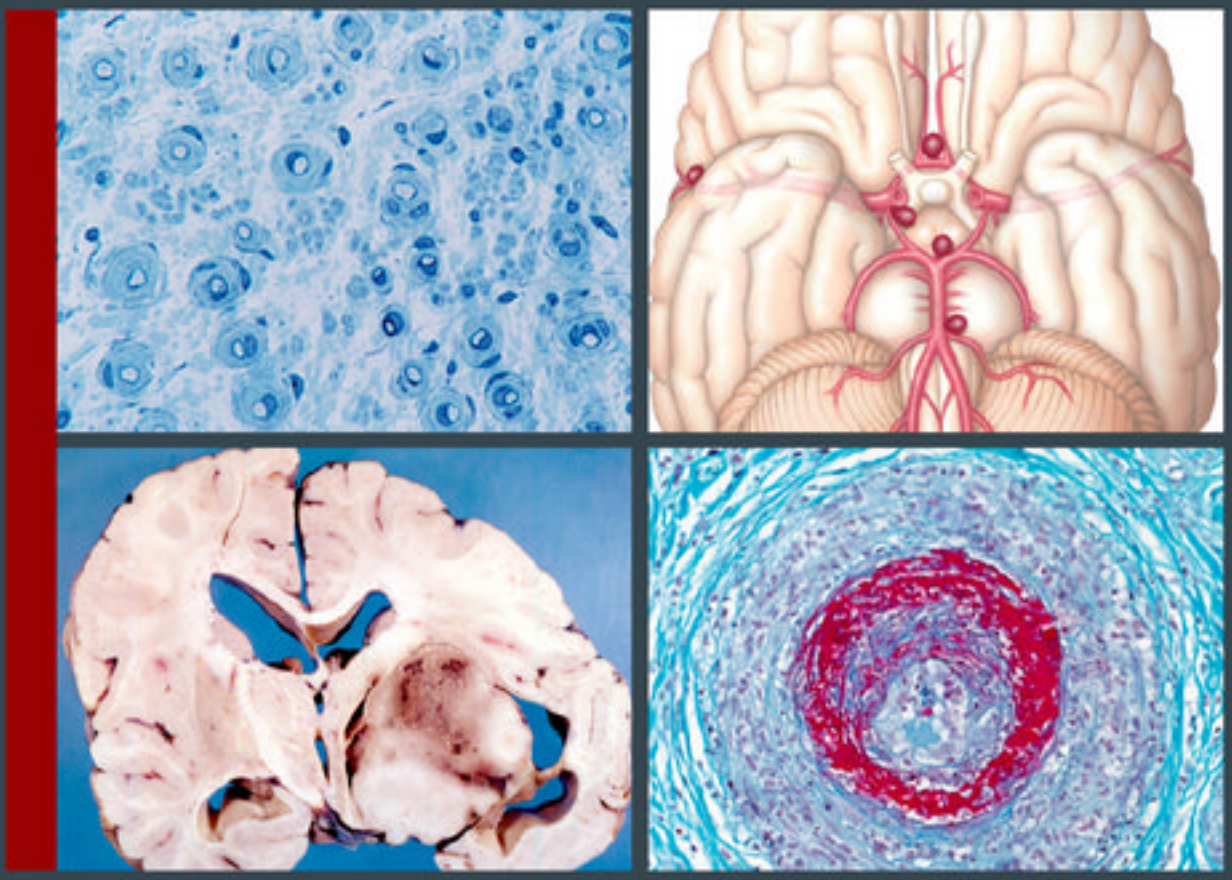
Mayo Clinic Neurology Board Review

Clinical Neurology for Initial Certification and MOC



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MAYO CLINIC NEUROLOGY BOARD REVIEW: CLINICAL NEUROLOGY FOR INITIAL CERTIFICATION AND MOC

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To my family for their patience and understanding. To the students and residents that inspire me.

Kelly D. Flemming, MD

To Amie, Katherine, Nathaniel, and Charlotte for their limitless patience and support. To the brilliant, talented residents of the Neurology Residency Program at Mayo Clinic in Rochester, Minnesota, without whom I would not have the best job in the world.

Lyell K. Jones Jr, MD

Foreword

The Department of Neurology at Mayo Clinic has a long-standing dedication to excellence in clinical neurology and values-driven care to our patients and to the education of colleagues across the career continuum, in all fields of medicine. Our ongoing dedication to education comes at a time of evolution and remarkable advances in the field and in an era of increasing subspecialization. Diagnostic imaging allows us to see more detail in a noninvasive manner, and there are few areas of the field unaffected by the tools of molecular genetics. Treatment options are increasing in number and improving in efficacy, and evidence-based management strategies have been advocated for many neurologic disorders. All these factors contribute to the excitement of being in such a dynamic specialty. There is an ongoing need for a core fund of knowledge for all providers to patients with neurologic disease. The current textbook takes the broad range of subspecialty neurology and distills a tremendous amount of information into a 2-volume text, the *Mayo Clinic Neurology Board Review*.

The current textbook is edited by 2 outstanding Mayo Clinic clinician-educators. They have sought the input of their colleagues from all neurology subspecialties and from neurosurgery, psychiatry, and neuro-ophthalmology, developing a concise review textbook of neurology. The book provides the most important information needed as one is studying for neurology board examinations or for a maintenance of certification (MOC) examination. The extensive use of superb diagrams and tables within the context of concise text provides a framework for efficient learning and attainment of information. The textbook is available as 2 separate volumes, so readers can select the material that is most relevant to them. For those in training or preparing for initial board certification examinations, the first volume nicely summarizes the basic neuroscience, neuroanatomy, and psychiatric information that will be of use for that examination. Volume 2 will provide an outstanding review of clinical neurology for those studying for their initial neurology board examination, for applicants for recertification, for advanced practice clinician colleagues in neurology, and for colleagues in fields of psychiatry, neurosurgery, physical medicine and rehabilitation, family medicine, and internal medicine.

Several other features make the book of tremendous interest. There are over 300 self-assessment questions providing the reader with feedback regarding potential areas requiring further study. For those using the book for recertification, there is an overview of the MOC process, and *American Medical Association Physician's Recognition Award Category 1 Credits* for continuing medical education and self-assessment are provided for those who are interested.

For a neurologist in training or in practice, the text will provide an excellent review for an in-service examination, for neurology boards or MOC, or as a well-written, high-level, beautifully illustrated summary of the field. For the non-neurologist, there is a wealth of information presented in a learner-friendly manner that will demystify many aspects of the evaluation and management of neurology patients, who are seen so commonly in most any field of medicine.

I congratulate Drs Flemming and Jones and all their contributing colleagues on the completion of this superb textbook. The legacy of the collective Mayo Clinic Department of Neurology, across all sites, continues as

the Department enters its second century of existence—a group of colleagues with the highest level of dedication to excellence in the care of patients in clinical practice, to the education of their colleagues, and to the advancement of the field through innovative clinical and basic science research. This book is a testament to that legacy. Most importantly, this textbook will provide readers with an additional tool to solidify their knowledge base, leading to improved clinical care of patients with neurologic disorders.

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Preface

Neurology is an exciting and rapidly expanding area of medicine. We have designed *Mayo Clinic Neurology Board Review* to assist both physicians-in-training who are preparing for the initial American Board of Psychiatry and Neurology (ABPN) certification examination and neurologists who are preparing for recertification. Trainees and other physicians in related specialties such as psychiatry, neurosurgery, or physiatry may also find this book useful in preparation for their own certification examinations. While we have erred on the side of thoroughness, *Mayo Clinic Neurology Board Review* is not intended to replace an in-depth textbook or serve as a guide to the most current therapies. Instead, this book provides a core of essential knowledge of both basic and clinical aspects of neurology. The emphasis is on clinical knowledge related to diagnostic and therapeutic approaches to patient management. In addition, this text has an expansive array of illustrations, pathology, and radiologic images.

With this book, we have acknowledged that there are different needs for those who are taking the initial board examination and for those who are recertifying. Thus, this book is published in 2 volumes: Volume 1 covers basic sciences and psychiatry, and Volume 2 covers clinical neurology. It is intended that people taking the board examination for the first time will purchase both Volume 1 and Volume 2, whereas those recertifying may wish to buy only Volume 2. In both volumes, we have included high-yield facts and questions for your review.

This volume, which is Volume 2 of *Mayo Clinic Neurology Board Review*, contains an extensive review of clinical neurology required for the recertification examination. If you are preparing for the initial certification examination, you should also purchase and review Volume 1 (in other words, Volume 2 alone does not provide complete preparation for the initial certification). Volume 1 contains an extensive review of the basic neuroscience, neuroanatomical, and psychiatric material required for the initial certification examination.

Those who are preparing for the recertification examination will be aware of the multifaceted process of Maintenance of Certification (MOC). *Mayo Clinic Neurology Board Review* uniquely offers not only a navigation guide to the MOC process but actual *American Medical Association Physician's Recognition Award Category 1 Credit* for continuing medical education and self-assessment that can be applied to MOC. Readers who are interested in claiming these credits may go to www.cmestore.mayo.edu to find the corresponding self-study course and further details on purchasing and documenting earned credits toward MOC, which have been approved for this purpose by the ABPN.

The faculty responsible for this text includes Mayo Clinic staff physicians in the Department of Neurology, the Department of Neurologic Surgery, the Department of Ophthalmology (Neuro-ophthalmology Team), the Department of Physical Medicine and Rehabilitation, the Division of Sleep Medicine, the Division of Infectious Diseases, and the Department of Psychiatry and Psychology at all 3 sites: Minnesota, Arizona, and Florida. We are deeply grateful to these incredibly talented experts who have provided such high-quality content. We also thank Nima Mowzoon, MD, for creating many of the wonderful illustrations and for spending countless hours gathering many of the figures that appear in this work.

We want to thank the staffs of the Mayo Clinic Section of Scientific Publications, the Mayo Clinic Division of Media Support Services, and the Mayo School of Continuous Professional Development for their contributions. The support of Mayo Clinic Scientific Press and Oxford University Press is also greatly appreciated.

Cover images, clockwise from upper left: Figure 40.1B, Semithin sections of peripheral nerve in Charcot-Marie-Tooth disease; Figure 15.1, Common locations of intracranial aneurysms; Figure 40.8B, Fibrinoid necrosis appears red with trichrome stain in vasculitis; Figure 56.10A, Glioblastoma multiforme.

Kelly D. Flemming, MD
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Continuing Medical Education Information

Activity Description and Target Audience

This educational activity is part of a larger curriculum regarding the clinical practice of neurology; the curriculum includes several continuing medical education (CME) offerings at Mayo Clinic. This year is the first year that this educational resource will be available for CME and Maintenance of Certification (MOC) Part II credit. The resource will provide a broad-based review of the knowledge required for all neurologists in practice. There is no other review activity in the United States like this one; this Mayo Clinic offering is an innovative solution providing preparatory material and simultaneous CME and MOC credit. This activity is a comprehensive review of all aspects of neurologic disease evaluation, diagnosis, and treatment. This review is appropriate for neurologists, neurology trainees, providers in related specialties, and generalists.

Accreditation and Credit Designation Statement

Mayo Clinic College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide CME for physicians.

Mayo Clinic College of Medicine designates this enduring material for a maximum of 77.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This text also features ABFN-approved self-assessment activities. Once you review the content, a post-test and evaluation are accessible online at ce.mayo.edu (search *Mayo Clinic Neurology Board Review*). Fees will apply depending on the CME or MOC desired. The Mayo School of Continuous Professional Development (CPD) requires learners score at least 80% to pass; they are allowed 1 retake. Upon passing, a certificate of attendance and completion will be available online for your immediate receipt.

Learning Objectives

1. Demonstrate mastery of the broad medical knowledge requirements for clinical practice.

2. Demonstrate an understanding of the multifaceted MOC process.

3. Demonstrate an understanding of the concepts of medical professionalism and interpersonal and communication skills and how they apply in complex practices reflected in today's health care environments.

How to Request or Obtain Credit

Once you review the content, a post-test and evaluation are accessible online at www.cmestore.mayo.edu. The Mayo School of Continuous Professional Development (CPD) requires that learners score at least 80% to pass; they are allowed 1 retake. Upon passing, a certificate of attendance and completion is awarded from the Mayo School of CPD and will be available online for your immediate receipt.

Owing to the extensive length of the book, the ability to claim credit has been divided into segments. This allows the learner to claim credit on smaller portions of the book as desired.

An individual report providing the questions, the learner's answers, the correct answers, and references to seek additional information will be provided for each participant. Comparable responses of the participants will also be provided.

Disclosures

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), Mayo Clinic College of Medicine (Mayo School of CPD) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. The course director(s), Planning Committee members, faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label or investigational use of pharmaceuticals or instruments that are described within this book. Disclosure of these relevant financial relationships is published so that participants may formulate their own judgments regarding the material. Disclosures are shown starting on the following page.

Commercial Support

No commercial support was received in the production of this activity.

Questions

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Faculty, Planning Committee, and Provider Disclosure Summary

Neurology Board Review Book

As a provider accredited by ACCME, Mayo Clinic College of Medicine (Mayo School of CPD) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee Members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of these relevant financial relationships will be published in activity materials so those participants in the activity may formulate their own judgments regarding the presentation.

Listed below are individuals with control of the content of this program who have disclosed.

Relevant Financial Relationship(s) with Industry:

Name	Nature of Relationship	Company
Bradley Boeve, MD	*Clinical Trials* Royalties	*Cephalon, Allon Pharmaceuticals, GE Healthcare* Publication of book entitled *Behavioral Neurology of Dementia*
	Honoraria Scientific Advisory Board Research Support	American Academy of Neurology Tau Consortium National Institute of Aging and Mangurian Foundation
Bart Demaerschalk, MD	*Consultant* Grant Research Support	*Genentech, Inc.* Genentech, Inc.
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References to Off-Label and/or Investigational Usage(s) of Pharmaceuticals or Instruments

Name	Manufacturer	Product/Device
David F. Black, MD	Bracco Diagnostics	Gadobenate Dimeglumine—Gadolinium use with power-injectors (such as MRA)
Bradley F. Boeve, MD		Dr. Boeve may have mentioned the use of several medications that are not FDA-approved for the indications that are reviewed, which may include the use of melatonin, clonazepam, cholinesterase inhibitors, carbidopa/levodopa, dopamine agonists, selective serotonin reuptake inhibitors, a typical neuroleptics, lithium, glycogen synthase kinase-3 beta inhibitors, anti amyloid immunotherapies, putative tau-active agents, mematine, sedative/hypnotics, and psychostimulants for the management of cognitive impairment, neuropsychiatric disorders, parkinsonism, sleep disorders, and autonomic dysfunction.
Melinda S. Burnett, MD		Treatment of essential tremor: Generic primidone, Inderal LA, clonaxepam, alprazolam, topiramate, gabapentin, thalamotomy for essential tremor; clonazepam and gabapentin and sodium valproate for orthostatic tremor; clonazepam, sodium valproate, tetrabenazine, haloperidol, trihexyphenidyl, and carbamazepine for palatal tremor; sodium valproate, clonazepam up to 15 mg a day, piracetam, levetiracetam, Zonisamide, primidone, acetazolamide, and phenobarbital for myoclonus; clonazepam and 5-hydroxytryptophan for essential myoclonus; Clonazepam, sodium valproate, tetrabenazine, and gamma-hydroxybutyric acid for myoclonus-dystonia; drugs above and SSRI's for Lance-Adams
Eoin P. Flanagan, MB, BCh	Pfizer Multiple manufacturers Forest Pharmaceuticals Multiple manufacturers	• Donepezil in multiple sclerosis • Acetylcholinesterase inhibitors in vascular dementia • Memantine • Corticosteroids and long term immunosuppressive treatments in autoimmune and paraneoplastic encephalitis
Anhar Hassan, MB, BCh		Idebenone
Keith A. Josephs, MD		• Levodopa for some patients with MSA, PSP, or CBS • Fludrocortisone or midodrine for OH in MSA • Dexromethorphan & quinidine for pseudobulbar affect in PSP • Clonazepam for myoclonus and dystonia in CBS • Botulinum toxin injections for dystonia in CBS
Simon Kung, MD		• The use of lithium and liothronine are off-label for the treatment of depression. • The use of oxcarbazepine is off-label for the treatment of bipolar disorder.
Andrea N. Leep Hunderfund, MD		• Carbidopa/levodopa, opioids, carbamazepine and benzodiazepines is off-label for restless legs syndrome. • Oral magnesium and riboflavin are off-label for migraine prophylaxis.
Andrew McKeon, MB, BCh, MD		All treatments for autoimmune neurological disorders are off-label
Wolfgang Singer, MD	Several generic medications	Several medications used for disorders that are rare enough that FDA approved medications are sparse.
Eric J. Sorenson, MD		Anticholinergic medications and Botox are off-label for sialorrhea
James C. Watson, MD	Multiple	Pharmacologic agents are used off-label for the treatment of neuropathic pain.

Section
I

Neurology Intensive Care

Eelco F. M. Wijdicks, MD, *editor*

1 Impaired Consciousness and Coma

S. ARTHUR MOORE, MD; EELCO F. M. WIJDICKS, MD, PHD

Introduction

Impaired consciousness and coma can result from multiple causes. Clues to the cause may be ascertained from the initial history and physical examination. In patients with coma, the examination focuses on the level of consciousness and arousal, respirations, pupillary and extraocular eye movement findings, and motor response. Some of these physical examination findings may have important prognostic significance. Select tests, including head imaging and laboratory studies, may further aid in the diagnosis of impaired consciousness. When all brain and brainstem functions cease and there is a known, irreversible brain injury responsible, the condition is referred to as brain death.

This chapter reviews the anatomy of consciousness and provides historical and physical examination clues to determining the cause of impaired consciousness. Aspects of the neurologic examination important for coma and brain death are discussed.

Consciousness

Definition of Consciousness

Consciousness is defined as the presence of awareness and arousal. Awareness describes one's ability to assimilate content, and arousal refers to a state of wakefulness in which one is able to interact with the environment. A workable clinical definition of "being conscious" is that a person is attentive, thinking, and deciding. When we are conscious, we are awake, alert, vigilant, aware, and having thoughts and intentions.

If awareness and being awake are separated components, a person can be aware and awake (the reader of this book), not aware and not awake (coma), or awake but not aware (vegetative state).

Anatomy of Consciousness

Awareness is the more diffuse cerebral process involving the bilateral cerebral hemispheres and their interactions with the thalamus (particularly the reticular nucleus), hypothalamus, and brainstem.

Arousal is primarily governed by the ascending reticular activating system (ARAS). The ARAS (Figure 1.1) is a collection of nuclei extending throughout the pons and midbrain tegmentum whose input is derived mainly from somatic and special sensory afferents of the spinal and cranial nerves. Output of the ARAS is primarily to the reticular nucleus of the thalamus via the central tegmental tract. If the ARAS acts as a switchboard for incoming sensory information, the reticular nucleus of the thalamus, through its interactions with the cerebral cortex, acts as a switch, limiting and focusing the information that reaches conscious perception and allowing concentration on only those sensory inputs that are most important while filtering out background noise.

In addition to the thalamic output, the ARAS also has connections with the hypothalamus as part of the limbic system, as well as descending output to nuclei involved in promoting the awake state, such as the raphe nuclei and locus ceruleus. These nuclei themselves have diffuse projections throughout cortex via noradrenergic and serotonergic synapses that serve to reinforce the awake state.

Any pathologic process that affects the anatomical structures mentioned above can result in a disruption of consciousness, as would be expected. For instance, bilateral cerebral hemispheric dysfunction resulting from an acute toxicity or acute metabolic derangement will likely result in altered awareness. Unilateral cortical lesions (eg, a stroke)

Abbreviations: ARAS, ascending reticular activating system; CN, cranial nerve

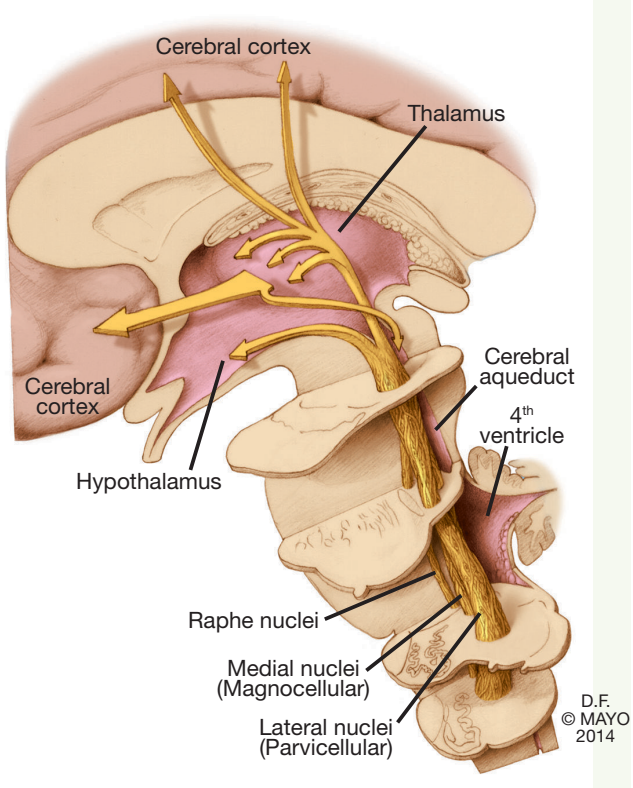


Figure 1.1 *Neuroanatomy of Consciousness.*
The ascending reticular activating system is responsible for arousal and projects to the thalamus, hypothalamus, raphe nuclei, and locus ceruleus. The cerebral hemispheres interpret content of awareness.
(Adapted from Wijdicks EFM. Catastrophic neurologic disorders in the emergency department. 2nd ed. Oxford [UK]: Oxford University Press; c2004. Chapter 8, Altered arousal and coma; p. 53–93. Used with permission of Mayo Foundation for Medical Education and Research.)

are unlikely to reduce consciousness without considerable mass effect resulting in opposite hemispheric dysfunction because of diffuse bilateral projections from the arousal centers. Similarly, bilateral diencephalic lesions are typically required to affect consciousness. In contrast, a single lesion frequently results in disruption of the midbrain reticular formation given its location in the tightly packed brainstem. These are typically pontine hemorrhages or cerebral infarcts with swelling pushing against the brainstem.

Disorders of Consciousness

Table 1.1 reviews the spectrum of disorders of consciousness. Delirium is a state of rapidly (over the course of hours) fluctuating alterations of consciousness and cognition due to a general medical condition that results in a global disruption in cognition. Although many of the same conditions that lead to coma can also result in delirium, the most common causes of delirium include metabolic derangements, infection, and toxicity. Factors predisposing patients to the development of delirium include older age, an underlying mild cognitive impairment or dementia, and a prolonged hospitalization or recent surgical procedure. Delirium is discussed in more detail in Chapter 28, "Syndromes of Cognitive Dysfunction." Coma refers to impairment in both wakefulness and awareness. This chapter describes the clinical approach to coma and impaired level of consciousness.

Clinical Approach to Coma and Impaired Consciousness

Historical Evaluation

As with any medical condition, the approach to the patient in a coma begins with the history. Timely availability of family members or other witnesses can be invaluable for refining the differential diagnosis (Box 1.1). Questions should focus on the circumstances surrounding the event. For instance, how was the patient found? What were the immediate events before the onset of an alteration in consciousness? Was it abrupt or was there a gradual decline? Family members are especially helpful in detailing the patient's recent and past medical history and medications, all of which could be contributors to the current state. Did the patient have access to pills or over-the-counter drugs or herbs? Has the patient had a psychiatric consultation or admission and made a prior suicide attempt? Is there a history of drug or drinking habits? The next question should focus on the possibility of a central nervous system infection. Did the patient use antibiotics for some "infection," and was there rapid onset of fever and headache? Was the patient confused while there was fever, and were there difficulties getting the words out?

Physical Examination

After a history is obtained, further refining of the differential diagnosis is accomplished through the physical examination. The primary goals of the physical examination are to gauge the level of consciousness and to identify focal or general findings that may help localize the lesion or, perhaps, indicate an underlying cause.

The most common scale used to define the level of consciousness is the Glasgow Coma Scale. The scale is divided into 3 parts, including eye, verbal, and motor responses; the maximal total score is 15 (Table 1.2). A second score, which is becoming more popular, is the FOUR score. With a maximum score of 16, the FOUR score has 4 elements: motor and eye responses, brainstem reflexes, and respiratory pattern (Figure 1.2). These coma scales are generally performed in the process of a more comprehensive neurologic examination.

The neurologic examination of a patient in a coma typically begins with general observations. For instance,

Table 1.1 • Disorders of Consciousness

State	Description
Drowsiness	Mild-to-moderate decreased level of alertness and interest in the environment Needs prodding to do a task May have avoidance reactions to noxious stimuli
Stupor	Decreased level of alertness Can only be aroused by vigorous stimuli
Coma	Absent alertness Eyes closed No response to noxious stimuli other than reflexive, such as extensor or flexor posturing No perception of external stimuli
Persistent vegetative state	Transitioning from coma to prolonged coma Arousal present, including sleep-wake cycles, but no awareness Eyes may be open, especially during the day Roving eye movements
Minimally conscious state	Makes eye contact or orients and tracks stimuli Abulic, emotionless May mouth words or some intelligible speech May withdraw from and fend off noxious stimuli without appreciable emotional reaction
Delirium	Rapidly fluctuating change in cognition Agitated and wild or subdued Commonly attributable to a general medical condition Frequent findings include disorientation, misperception of sensory stimuli including hallucinations
Akinetic mutism	Alert appearing but unable to recognize content Lack of spontaneous motor activity
Locked-in syndrome	Paralysis of extremities and cranial nerves with the common exception of vertical eye movements No impairment of sensation or consciousness (may fluctuate) Often due to large pontine lesions that spare the reticular activating system
Psychogenic unresponsiveness	Considered only after excluding other potential causes of unresponsiveness Forced gaze that changes in direction Non-epileptic abnormal movements Characteristic responses to the hand-drop test or eye opening with tickling of nose hairs

obvious signs of trauma, such as Battle sign (bruising of the mastoid bone) or raccoon eyes (periorbital ecchymosis), may each suggest skull base fractures. Fever is an important symptom. Hypothermia is typically associated with alcohol intoxication or an overdose of barbiturates. Hyperthermia can occur with cocaine, tricyclic antidepressant, phencyclidine, and salicylate intoxication. Dryness of skin indicates barbiturate poisoning or use of anticholinergic agents. The classic foul breaths should be known and are occasionally helpful. They are dirty toilet odor with uremia, fruity sweat odor with ketoacidosis, fishy or musty odor with acute hepatic failure, onion odor with paraldehyde, and garlic odor with organophosphates.

Once general observations have been completed, a cranial nerve examination and evaluation of the motor response to pain follow.

The Eyes: Pupil Size and Light Response

The eyes are first evaluated by lifting the lids and assessing the pupils, both their initial size and the response to light.

Box 1.1 • Classification and Major Causes of Coma

Structural brain injury
- Hemisphere
  - Unilateral (with displacement)
    - Intraparenchymal hematoma
    - Middle cerebral artery occlusion
    - Hemorrhagic contusion
    - Cerebral abscess
    - Brain tumor
  - Bilateral
    - Penetrating traumatic brain injury
    - Multiple traumatic brain contusions
    - Anoxic-ischemic encephalopathy
    - Aneurysmal subarachnoid hemorrhage
    - Multiple cerebral infarcts
    - Bilateral thalamic infarcts
    - Cerebral venous thrombosis
    - Lymphoma
    - Encephalitis
    - Gliomatosis

- Acute disseminated encephalomyelitis
- Cerebral edema
- Multiple brain metastases
- Acute hydrocephalus
- Acute leukoencephalopathy

Brainstem

- Pontine hemorrhage
- Basilar artery occlusion
- Central pontine myelinolysis
- Brainstem hemorrhagic contusion

Cerebellum (with displacement of brainstem)

- Cerebellar infarct
- Cerebellar hematoma
- Cerebellar abscess
- Cerebellar glioma

Acute metabolic-endocrine derangement

- Hypoglycemia
- Hyperglycemia (nonketotic hyperosmolar)
- Hyponatremia
- Hypernatremia
- Addison disease
- Hypercalcemia
- Acute hypothyroidism
- Acute panhypopituitarism
- Acute uremia
- Hyperbilirubinemia
- Hypercapnia

Diffuse physiologic brain dysfunction

- Generalized tonic-clonic seizures
- Poisoning, illicit drug use
- Hypothermia
- Gas inhalation
- Acute (lethal) catatonia, malignant neuroleptic syndrome

Psychogenic unresponsiveness

- Hysterical
- Malingering

Adapted from Wijdicks EFM. The practice of emergency and critical care neurology. Oxford (UK): Oxford University Press; c2010. Chapter 12, "Comatose"; p. 104–36. Used with permission of Mayo Foundation for Medical Education and Research.

Table 1.2 • Glasgow Coma Scale

Points	Eye Opening	Verbal Response	Motor Response
6	. . .	. . .	Obeys commands
5	. . .	Oriented	Localizes pain
4	Spontaneous	Confused	Withdraws in response to pain
3	To speech	Inappropriate	Flexion (decorticate)
2	To pain	Incomprehensible	Extension (decerebrate)
1	None	None	None

Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.

Midposition, fixed pupils indicate disruption of both parasympathetic and sympathetic tone as well as disruption of the efferent pathway of the pupillary light reflex (cranial nerve [CN] III) and can be indicative of severe midbrain dysfunction such as from an infarct or transtentorial herniation. However, other causes such as medications (atropine), eyedrops, or toxins must also be excluded.

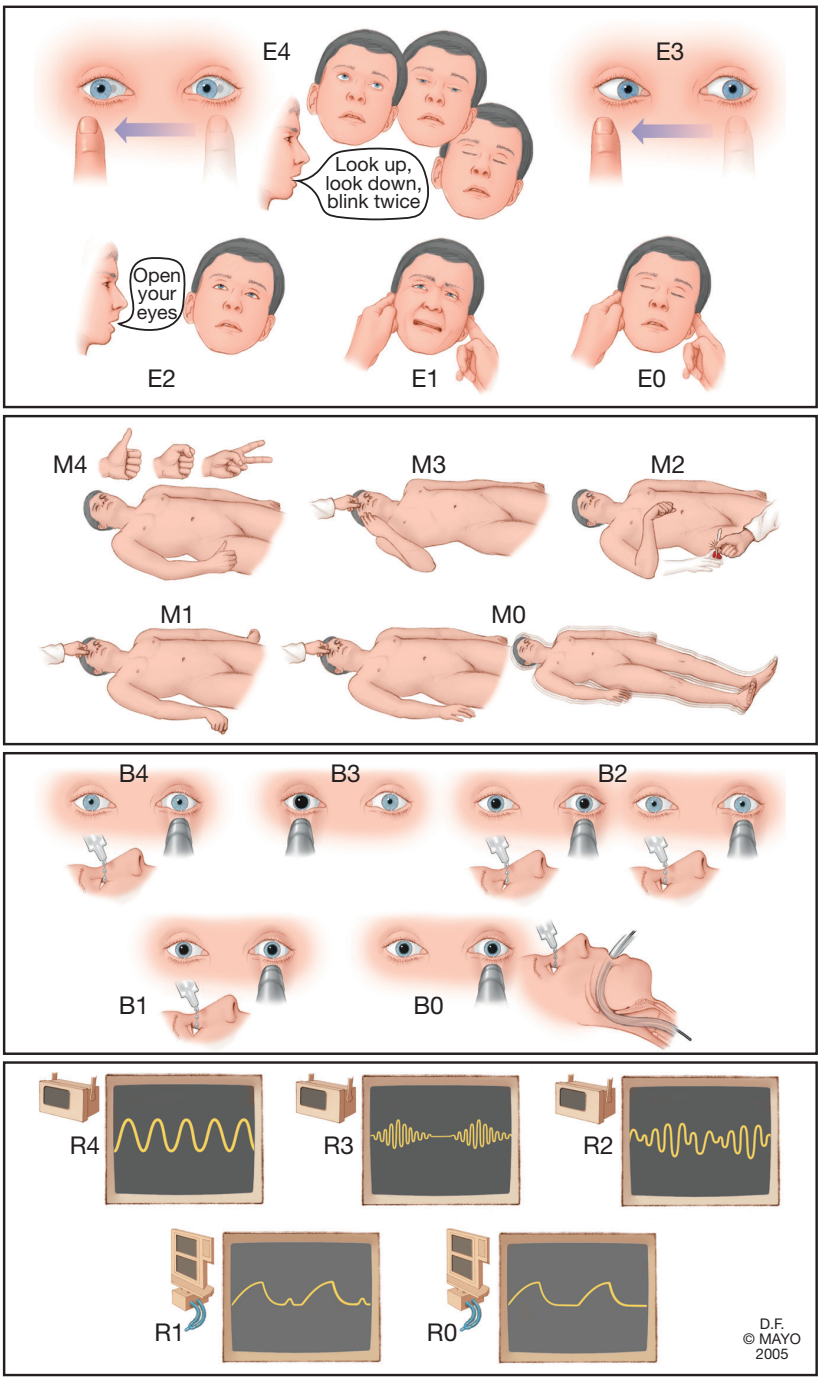
Small or pinpoint pupils that are unresponsive (or minimally responsive) to light are associated with interruption of the sympathetic supply to the eye, leading to unopposed parasympathetic activation via CN III. The most common central nervous system lesion causing this phenomenon is a large pontine hemorrhage. However, heroin or other opioids can cause a similar clinical picture and should be considered. Also, lesions in the upper brainstem (above the red nucleus) can result in pinpoint pupils by disrupting the descending sympathetic outflow from the hypothalamus.

When sympathetic activation of the pupils is unopposed, the result is fixed and dilated pupils. Midsize light-fixed pupils are due to a midbrain lesion and always indicate more severe injury and loss of brainstem function. Maximally dilated pupils (>8 mm) are due to a lesion of CN III nuclei in the mesencephalon or compression of the peripheral fibers. Poorly reactive pupils can indicate a lesion in either the afferent (CN II) or the efferent (CN III) pathways and can be differentiated by observing both the direct and the consensual responses in each eye.

A unilateral fixed pupil is due to a CN III lesion from compression of the midbrain, retraction of CN III, or pressure of the nerve against the clivus due to mass effect.

The Eyes: Position and Movement

The physical findings discussed above are typically associated with a midline position, but certain situations lead to deviation of the eyes in one direction, known as a gaze preference. A horizontal gaze preference can result from a lesion involving the pons or the frontal cortex, or it can be a sign of ongoing seizure activity. With a pontine lesion, patients look toward the side of a hemiparesis if the lesion also includes the descending corticospinal tract. Perhaps even more important for a comatose patient, the oculocephalic maneuver (discussed below) will not overcome this gaze preference. With a lesion involving the frontal cortex (specifically, the frontal eye fields), patients look away from the hemiparesis if the corticospinal tract is involved. The oculocephalic maneuver will be able to overcome a gaze preference due to a lesion in the frontal cortex because the pons and midbrain structures responsible for the reflex remain intact.



Eye response
- 4 = eyelids open or opened, tracking, or blinking to command
- 3 = eyelids open but not tracking
- 2 = eyelids closed but open to loud voice
- 1 = eyelids closed but open to pain
- 0 = eyelids remain closed with pain

Motor response
- 4 = thumbs-up, fist, or peace sign
- 3 = localizing to pain
- 2 = flexion response to pain
- 1 = extension response to pain
- 0 = no response to pain or generalized myoclonus status

Brainstem reflexes
- 4 = pupil and corneal reflexes present
- 3 = one pupil wide and fixed
- 2 = pupil or corneal reflexes absent
- 1 = pupil and corneal reflexes absent
- 0 = pupil, corneal, and cough reflexes absent

Respiration
- 4 = not intubated, regular breathing
- 3 = not intubated, Cheyne-Stokes breathing
- 2 = not intubated, irregular breathing
- 1 = breathes above ventilatory rate
- 0 = breathes at ventilator rate or apnea

Figure 1.2 *The FOUR Score.*

(Adapted from Wijdicks EFM. The practice of emergency and critical care neurology. Oxford [UK]: Oxford University Press; c2010. Chapter 12, "Comatose"; p. 104–36. Used with permission of Mayo Foundation for Medical Education and Research.)

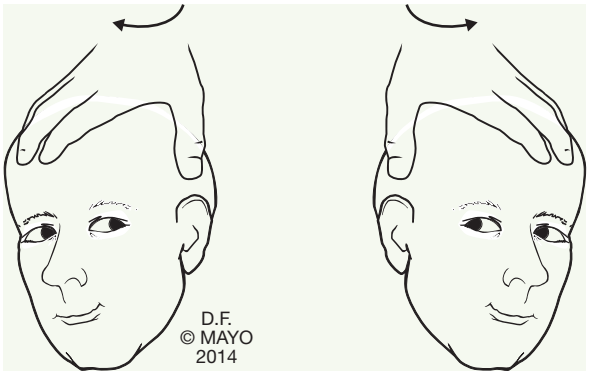


Figure 1.3 *Intact, or Normal, Oculocephalic Response.* (Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 1.3 • Cranial Nerve Reflexes

Reflex	Afferent Limb	Efferent Limb	Central Lesion Location[a]
Pupillary light	CN II	CN III	Upper midbrain
Corneal	CN V	CN VII	Lower midbrain to upper pons
Oculocephalic	CN VIII	CN III, IV, VI	Upper midbrain to lower pons
Gag	CN IX	CN X	Medulla
Cough	CN X	CN X Cervical spinal nerves (C3, 4, 5)	Medulla to cervical spinal cord

Abbreviation: CN, cranial nerve.

[a] Lesions are those within the central nervous system that can produce an absent reflex. Peripheral lesions involving the individual cranial nerves can also lead to an absent reflex, but these are not discussed here.

The oculocephalic, or vestibulo-ocular, reflex (doll's eyes) can be elicited to assess the integrity of multiple brainstem structures (Figure 1.3). The maneuver itself involves rotating the head horizontally or vertically while observing the eyes for movement. Because of the movement involved, a cervical spine injury should be conclusively ruled out before this maneuver is attempted. In a patient with a normally functioning brainstem, eyes will move in an *opposite* direction to the head movement and appear to remain fixated on a point in space (much like a doll's eyes, for which the reflex is named). If a lesion exists, the eyes will move along with the head, remaining in midposition with respect to the bony orbits. A normal oculocephalic reflex implies intact function within the pontine and midbrain pathways involving CNs III and IV (horizontal movements), CNs III and VI (vertical movements), and the medial longitudinal fasciculus connecting CN III with CN VI.

Caloric testing similarly tests the integrity of multiple brainstem nuclei, including the vestibular nuclei. The test is performed by first raising the head of the bed to 30° and then instilling cold water in one ear (ensure the eardrum is intact first). If the brainstem is intact, the current within the semicircular canals via CN VIII results in tonic deviation of the eyes toward the ear with the cold water through pathways involving CN III, CN VI, and the medial longitudinal fasciculus. The mnemonic COWS (cold-opposite, warm-same) applies to the fast-phase nystagmus component of the reflex in a patient with intact frontal lobes and a normal brainstem and does not apply to the tonic phase elicited in a comatose patient.

Spontaneous eye movements, rather than those elicited by testing, also occasionally occur in comatose patients. Roving eye movements, in which the eyes slowly move back and forth in the horizontal plane, imply both an intact brainstem and bilateral cerebral hemispheric dysfunction. Ocular bobbing, which involves a rapid downward eye movement followed by slow upward deviation, indicates a pontine lesion. Skew deviation, in which the eyes are no longer conjugate, suggests an acute brainstem injury, typically to CNs III and IV in the midbrain.

Other CN reflexes that can be tested as part of the coma examination and their clinical implications are listed in Table 1.3.

The Motor Examination

In a comatose patient, motor responses are typically evaluated by applying a painful stimulus to the supraorbital nerve, temporomandibular joint, or the nail bed. Motor responses are generally described as localizing or reflexive, and reflexive responses include extensor posturing or a lack of response.

A localizing response is one in which the patient reaches toward the noxious stimulus (ie, the patient localizes to the stimulus). For instance, when pressure is applied to the supraorbital nerve, the patient's hand may reach toward the stimulated eye.

Decorticate posturing is defined as slow flexion at the elbow, wrist, and fingers (Figure 1.4A). Conventional wisdom is that decorticate posturing results from a lesion above the red nucleus because cortical influence has been interrupted but the rubrospinal tracts, pontine reticulospinal tracts, and medullary vestibulospinal tracts remain intact. However, many comatose patients have both decorticate and decerebrate posturing simultaneously, and these motor responses are nonlocalizing.

Decerebrate posturing is defined as extension of the upper extremities at the elbow, wrist, and fingers, typically accompanied by pronation (Figure 1.4B). As might be

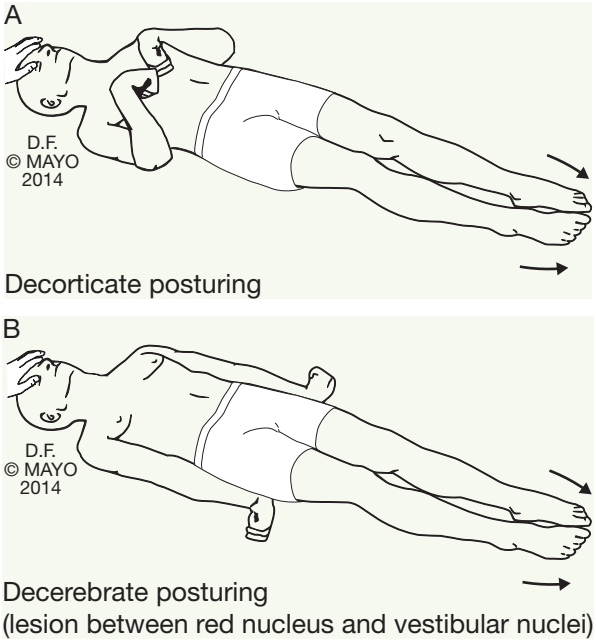


Figure 1.4 *Decorticate (A) and Decerebrate (B) Posturing.* (Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

expected by the above-mentioned rule of thumb, a lesion below the red nucleus is normally responsible. There is impairment of the corticospinal tracts and the rubrospinal tracts but the influence of the pontine reticulospinal tracts and medullary vestibulospinal tracts remains intact. In both decorticate and decerebrate posturing, the lower extremity extends. As such, noting the lower extremity response is not typically clinically useful.

An absent response to pain in all extremities is generally considered to indicate a lesion below or at least involving structures below the vestibular nuclei. At this point, all of the pathways responsible for reflexive movement that originate in the brain, with the possible exception of the medullary reticulospinal tract, are extinguished. In this circumstance, movement can still be elicited, but it is generally a function of spinal cord reflexes. One such reflex that is commonly confused with withdrawal from a painful stimulus is the triple flexion response observed in the lower extremities in response to pain. This reflex involves flexion of the hip and knee and dorsiflexion of the ankle. It differs from withdrawal in many respects, the most identifiable of which is that it is reproducible with each painful stimulus and shows no variation.

Respiratory Patterns

The respiratory pattern in comatose patients is often difficult to observe because many of these patients require mechanical ventilation. Even though a spontaneous ventilator mode can be used to observe a patient's intrinsic breathing pattern, the localization value of the patterns themselves is not firmly established, and thus this approach should never take the place of a comprehensive examination.

Cheyne-Stokes breathing (Figure 1.5A) is a respiratory pattern characterized by a progressive increase in respiratory volume and rate followed by a gradual decrease in rate and volume that may lead to a brief period of apnea. This pattern can be associated with any cause of reduced responsiveness and, as such, is generally considered to be poorly localizing.

Apneustic breathing (Figure 1.5B) may occur when a lesion is at the pontine level. This is characterized by gasping inspiration, a pause at full inspiration, and then release. Cluster breathing (Figure 1.5C), characterized by periods of apnea followed by a cluster of progressively more shallow breaths until another period of apnea, and central neurogenic hyperventilation (Figure 1.5D), distinguished by a considerable elevation in respiratory rate with relatively low tidal volumes, can each indicate bihemispheric or pontine lesions.

Ataxic breathing (Figure 1.5E) indicates a lesion of the lateral tegmentum within the lower pons. The distinguishing feature of this respiratory pattern is that no true pattern exists. Respirations tend to be erratic in both timing and volume. Periods of ataxic breaths are often preceded or followed by brief periods of apnea and commonly deteriorate into agonal respirations.

- Midposition, fixed pupils indicate disruption of both parasympathetic and sympathetic tone as well as disruption of the efferent pathway of the pupillary light reflex (cranial nerve [CN] III) and can be indicative of severe midbrain dysfunction such as from an infarct or transtentorial herniation.
- Small or pinpoint pupils that are unresponsive (or minimally responsive) to light are associated with interruption of the sympathetic supply to the eye, leading to unopposed parasympathetic activation via CN III.
- Because of the movement involved in the oculocephalic maneuver, a cervical spine injury should be conclusively ruled out before it is attempted.
- For caloric testing, if the brainstem is intact, the current within the semicircular canals via CN VIII results in tonic deviation of the eyes toward the ear with the cold water through pathways involving CN III, CN VI, and the medial longitudinal fasciculus.
- Decorticate posturing is defined as slow flexion at the elbow, wrist, and fingers (Figure 1.4A).
- Decerebrate posturing is defined as extension of the upper extremities at the elbow, wrist, and fingers, typically accompanied by pronation (Figure 1.4B).

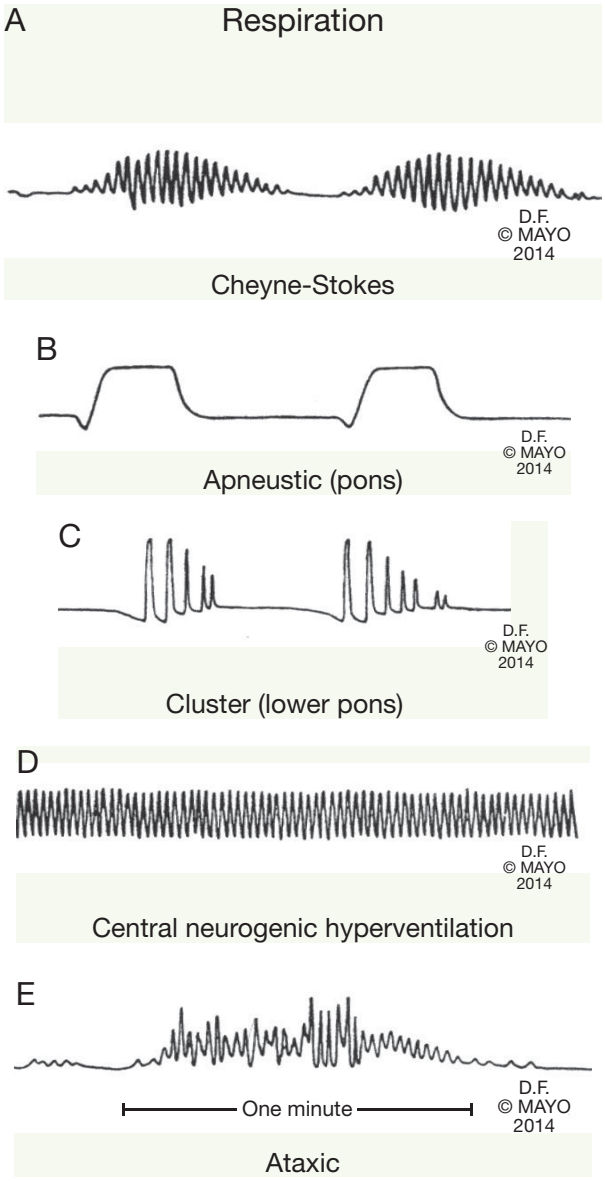


Figure 1.5 *Respiratory Patterns in Patients With Altered Consciousness. A, Cheyne-Stokes. B, Apneustic. C, Cluster. D, Central neurogenic hyperventilation. E, Ataxic respiration.* (Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 1.4 • Clinical Management of Comatose Patients

Airway, breathing, circulation	Assess airway Intubate when deoxygenation, airway obstruction, tachypnea, or apneic episodes are present Check oxygen saturation, administer oxygen as needed Assess blood pressure and pulse Place cardiac monitor
Stat laboratory tests	Check glucose finger stick Arterial blood gas Electrolytes, complete blood count, calcium, magnesium, ammonia, drug levels, PT, PTT Consider toxin screen
Supportive measures	Thiamine 50–100 mg IV Naloxone 1 ampule IV Glucose D-50 IV (at least 25 mL)
Examination	If signs or symptoms are suggestive of meningitis (altered mental status, fever, meningismus), consider empiric antibiotics and perform lumbar puncture if safe If signs or symptoms suggest herniation (progressive obtundation, decorticate or decerebrate posturing, unilateral CN III palsy), initiate measures to lower ICP If clinical evidence of seizures, load with antiepileptic medication
CT	CT of head without contrast Check and clear cervical spine
Lumbar puncture	Consider lumbar puncture to rule out subarachnoid hemorrhage or infection if no evidence on CT of mass effect and no other cause for coma is found
Other	Treat specific metabolic, CT, or lumbar puncture results Obtain further clinical history

Abbreviations: CN, cranial nerve; CT, computed tomography; D-50, 50% dextrose in distilled water; ICP, intracranial pressure; IV, intravenous; PT, prothrombin time; PTT, partial thromboplastin time.

Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.

Management of Patients With Impaired Consciousness

As with any patient, the first steps in management of patients with impaired consciousness are the ABCs: airway, breathing, and circulation. However, in a comatose patient, attention to the airway is paramount. Once the patient is stabilized with intubation, if necessary, and an electrocardiographic monitor is in place, laboratory values should be obtained immediately to rule out potentially reversible yet emergent causes of coma. Testing should include a point-of-care glucose, arterial blood gas, full electrolyte panel including magnesium, calcium, and phosphorus, a complete blood count, ammonia, drug screen, and coagulation panel.

Similarly, emergency medications can be given that may potentially reverse a coma and, even if not needed, will not harm the patient. These include thiamine, naloxone, and glucose in the form of D-50 (50% dextrose in distilled water). An emergency computed tomography scan of the head without contrast should also be obtained, and the cervical spine should be cleared.

The clinical history, physical examination, and initial laboratory studies will help to guide further decision making. If the history is suggestive of meningitis, empiric antibiotic therapy should be initiated before a lumbar puncture but after specimens for peripheral blood cultures have been obtained. A lumbar puncture can also be performed if subarachnoid hemorrhage is suspected and computed tomography shows no evidence of herniation. Any clinical suspicion of ongoing seizure activity should be emergently treated with an intravenous benzodiazepine such as lorazepam. If there is evidence of a herniation syndrome, mannitol should be considered and a neurosurgeon consulted while awaiting results of computed tomography. Table 1.4 summarizes clinical management recommendations, and Table 1.5 lists hints to the cause based on the initial history, examination, and basic studies. Table 1.6 lists causes of impaired consciousness due to poisoning.

Table 1.5 • Hints to the Cause of Impaired Consciousness Based on Initial Clinical Evaluation

Clinical Feature	Possible Causes
Battle sign, periorbital ecchymosis	Consider trauma
Hyperthermia	Cocaine, tricyclic antidepressants, phencyclidine (PCP, angel dust), salicylate intoxication
Hypothermia	Cold exposure, alcohol intoxication, barbiturate overdose
Metabolic acidosis	Lactic acidosis, ketoacidosis, organic acid intoxication (salicylates, ethanol, methanol, formaldehyde, ethylene glycol, paraldehyde), massive rhabdomyolysis
Dry skin	Barbiturate poisoning, anticholinergic agents, botulism
Pinpoint pupils	Pontine lesion, opioid toxicity, organophosphate poisoning
Ophthalmoplegia	Botulism poisoning, Wernicke encephalopathy
Dilated pupils	Theophylline poisoning, lesion with rostrocaudal deterioration to level of the medulla, bilateral third nerve palsy, serotonergic psychedelics (lysergic acid diethylamide [LSD], mescaline), anticholinergics (atropine, scopolamine), stimulants (cocaine, amphetamines)

Table 1.6 • Selected Causes of Impaired Consciousness Due to Poisoning

Type of Poisoning	Features
Organophosphate	Mnemonic MUDDLES: miosis, urination, diarrhea, diaphoresis, lacrimation, excitation, and salivation
Methanol	Can cause blindness, metabolic acidosis, headache, confusion, and coma. Delayed parkinsonism due to effects on the putamen
Carbon monoxide	Headache, dizziness, seizures, impaired consciousness, heart arrhythmia
Salicylate (aspirin)	Tinnitus, deafness, tachycardia, nausea, vomiting, sweating, respiratory alkalosis (early) followed by metabolic acidosis
Acetaminophen (Tylenol)	Nausea, vomiting, hepatic necrosis, confusion, encephalopathy
Iron	Nausea, vomiting, diarrhea, abdominal pain, jaundice, coma
Tricyclic antidepressant overdose	Hallucinations, hyperreflexia, myoclonus, seizures, impaired consciousness, dilated pupils, hyperpyrexia, dry mouth, flushing, bowel or bladder paralysis, tachyarrhythmias, conduction abnormalities

- In patients with impaired consciousness, emergency medications given to potentially reverse a coma include thiamine, naloxone, and glucose in the form of D-50 (50% dextrose in distilled water).

Brain Death

Definition

Brain death is the irreversible cessation of all brain and brainstem function due to a known, irreversible, and mostly supratentorial injury. In the United States, brain death remains a clinical diagnosis and no ancillary testing is required in adults, although institutional requirements may vary widely. The determination of brain death in the pediatric population typically requires 2 examinations with a fixed interval between them.

Clinical Examination

In all cases of brain death, an irreversible cause of brain dysfunction should be proved and confounding factors conclusively eliminated or corrected before testing. Severe hypothermia and hypotension should be reversed with a core temperature of more than 32°C and systolic blood pressure more than 90 mm Hg; severe metabolic derangements

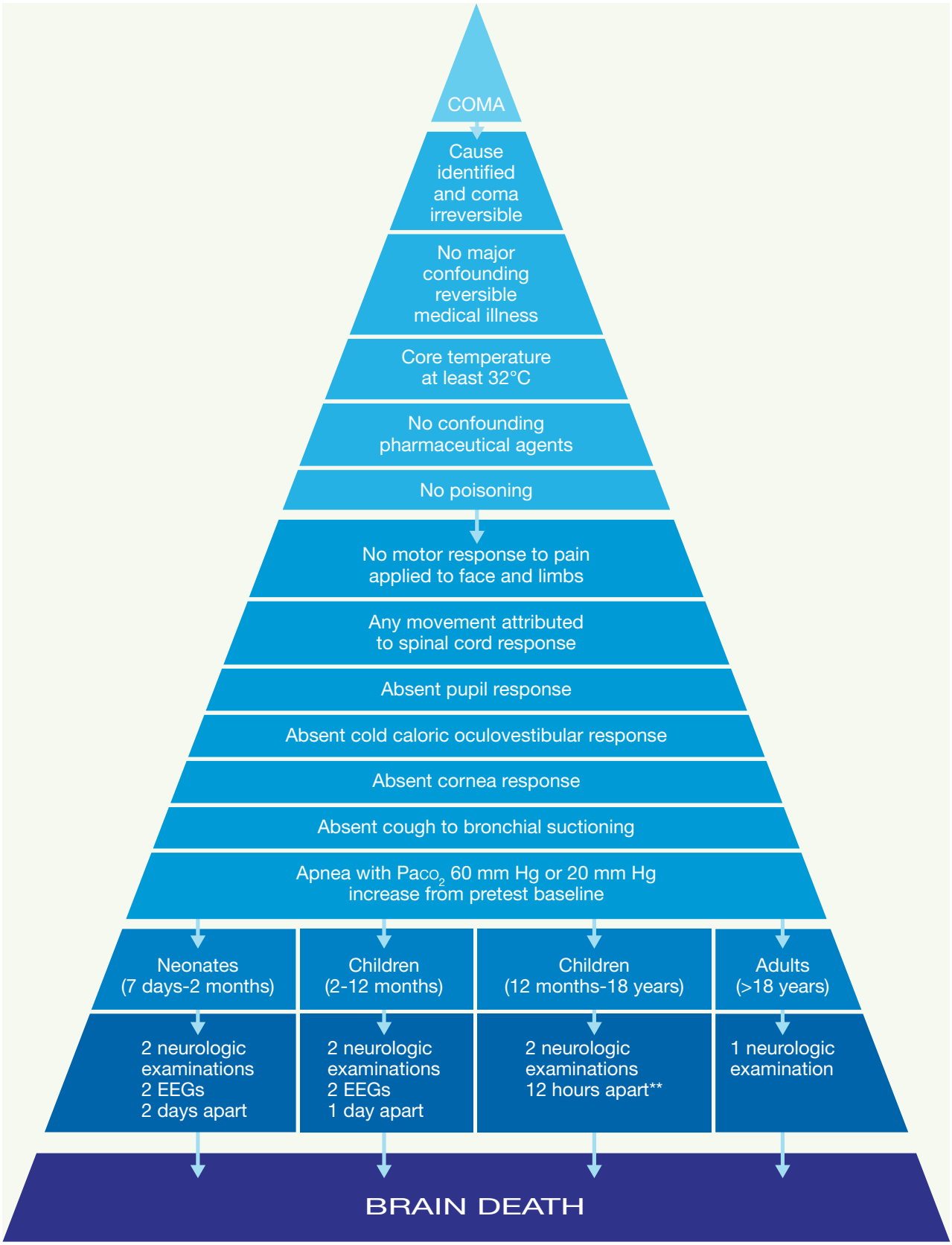


Figure 1.6 *Approach to Brain Death.*
(Adapted from Wijdicks EFM. The bare essentials: coma. Pract Neurol. 2010 Feb;10[1]:51–60. Used with permission.)

should be corrected with replacement or removal as necessary; sedating or paralytic medications should be out of the patient's system (typically about 5 half-lives, although this can be longer in patients with renal or hepatic failure); and extraneous toxins should be ruled out. Testing can proceed once these criteria are met.

The brain death examination begins in a comatose patient with an attempt to elicit a motor response. The absence of motor responses, except those that can be attributable to spinal cord reflexes, is consistent with brain death. Any decorticate or decerebrate posturing implies an intact brainstem and excludes brain death. Spinal cord reflexes can include several movements that may appear inconsistent with death, including rapid flexion of the arms, multifocal myoclonic movements, and even raising one or all limbs off the bed and sitting up (the Lazarus sign), and these should not be confused with purposeful movements.

A cranial nerve examination normally follows evaluation of the motor responses. Presence of any cranial nerve reflexes excludes a diagnosis of brain death. Those tested include the pupillary light response, corneal reflexes, the cold-water caloric oculocephalic reflex, the gag reflex, the cough reflex with tracheal suctioning, and frontal release reflexes such as sucking or rooting.

Diagnostic Testing

The final test to be performed as part of the brain death examination is the apnea test. This test is perhaps the most commonly overlooked component of the brain death examination, but it is critical because it assesses the patient's respiratory drive and should be performed in all patients in whom cranial nerve reflexes and motor responses are absent. Requirements for the apnea test, in addition to those listed above for the general brain death examination, include a core temperature of less than 36.5°C, a positive fluid balance, a $Paco_2$ more than 40 mm Hg, and a Pao_2 more than 200 mm Hg. The arterial gas levels are achieved through preoxygenation and alteration of the set respiratory rate, if needed. Typically, the patient is preoxygenated with 100% O_2 for 15 to 30 minutes before testing.

A baseline arterial blood gas value is obtained and the ventilator is turned off. A catheter inserted close to the level of the carina continues to supply oxygen at a rate of 6 L/minute. The patient is closely watched for any evidence of attempted respiration. Given that the $Paco_2$ level increases 3 to 6 mm Hg per minute, an arterial blood gas test is repeated at 10 minutes. The test is considered positive if there is no breathing effort when the arterial Pco_2 is more than 60 mm Hg or if there is an increase of 20 mm Hg in Pco_2 above a normal baseline value. It is important, when performing the apnea test, to 1) allow enough time for the $Paco_2$ to increase to the appropriate level and 2) remember that patients with chronic hypercapnea (such as occurs with chronic obstructive pulmonary disease) have higher $Paco_2$ levels at baseline, leading to reduced test reliability and the need for further confirmatory testing.

Confirmatory testing can include electroencephalography, cerebral angiography, transcranial Doppler, or cerebral nuclear scanning. Figure 1.6 provides a brief outline of brain death criteria and testing.

- Brain death is the irreversible cessation of all brain and brainstem function due to a known, irreversible, and mostly supratentorial injury.
- Severe hypothermia and hypotension should be reversed with a core temperature of more than 32°C and systolic blood pressure more than 90 mm Hg; severe metabolic derangements should be corrected with replacement or removal as necessary; sedating or paralytic medications should be out of the patient's system (typically about 5 half-lives, although this can be longer in patients with renal or hepatic failure); and extraneous toxins should be ruled out.
- When an apnea test is performed to confirm brain death, the arterial blood gas test is considered positive if there is no breathing effort when the arterial Pco_2 is more than 60 mm Hg or if there is an increase of 20 mm Hg in Pco_2 above a normal baseline value.

2 Principles and Management of Alterations in Intracranial Pressure

HEIDI T. WOESSNER, MD; WILLIAM D. FREEMAN, MD

Introduction

Definitions

Intracranial pressure (ICP) is a reflection of the total volume inside the skull. Normal ICP is 0 to 10 mm Hg. Intracranial hypertension is defined as sustained ICP of more than 20 mm Hg. Increased ICP may lead to a reduction of cerebral perfusion pressure (CPP), a shift of brain tissue, and, as a result, secondary brainstem injury. Monitoring of increased ICP provides the opportunity to effectively treat damaging pressure waves and is needed to prevent irreversible damage.

Physiology

The 3 constituents of intracranial volume are the brain, cerebral spinal fluid (CSF), and blood. These elements sit within the fixed volume of the skull. If one of these 3 components increases in volume, the other 2 must compensate by reducing volume. If they cannot compensate, ICP increases. This compensatory mechanism is known as The Monro-Kellie doctrine (Figure 2.1).

When ICP is suspected to be increased, it must be measured by direct or indirect means. Once ICP is measured, it can be used to calculate CPP, according to the equation CPP = MAP – ICP, where MAP is mean arterial pressure. CPP is the driving pressure, or forward flow, that allows brain cerebral blood flow (CBF). Normal CPP depends on whether the patient has normal blood pressure or is hypertensive. In a patient with a normal blood pressure of 120/80 mm Hg (MAP = 93 mm Hg and ICP = 5 mm Hg), CPP is 83 mm Hg. In most cases of traumatic brain injury or stroke, CPP is typically kept at a minimum of 65 mm Hg or more. In a patient with chronic hypertension, "normal" CPP is shifted rightward depending on the chronic MAP (Figure 2.2). When ICP is more than 20 mm Hg, CPP becomes compromised and decreases to less than 50 mm Hg and ischemia can occur. When CPP reaches zero, global brain ischemia, infarction, and brain death can

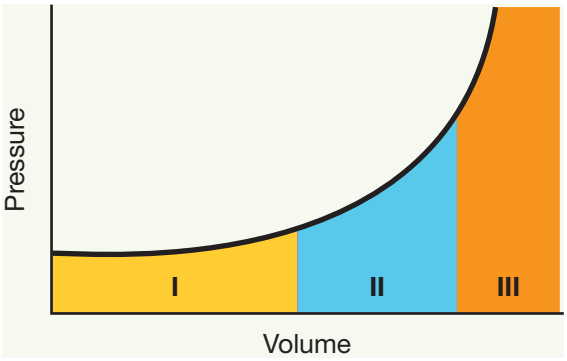


Figure 2.1 *Pressure-Volume Curve.*
In zone I, compensatory mechanisms are optimal. In zone II, compensatory mechanisms fail. There is a slow increase (period of spatial compensation). In zone III, virtually irreversible increased intracranial pressure and herniations occur. There is a rapid increase (period of spatial decompensation).
(Adapted from Wijdicks EFM. The clinical practice of critical care neurology. 2nd ed. Oxford [UK]: Oxford University Press; c2003. Chapter 9, Intracranial pressure; p. 107–25. Used with permission of Mayo Foundation for Medical Education and Research.)

Abbreviations: CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CVR, cerebrovascular resistance; ICP, intracranial pressure; MAP, mean arterial pressure

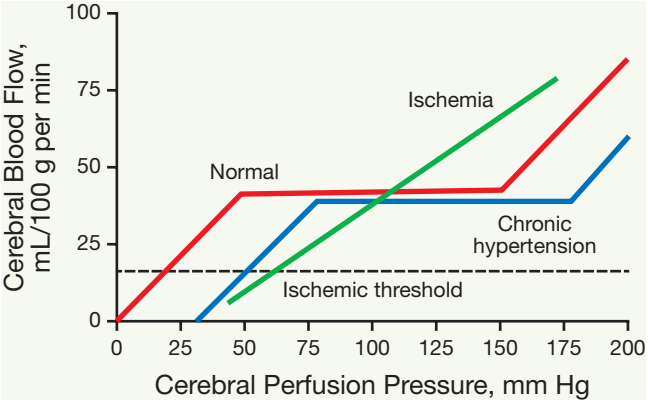


Figure 2.2 *Cerebral Autoregulation.*
In normal states, cerebral blood flow (CBF) is held constant over a range of cerebral perfusion pressure (CPP) values due to varying cerebrovascular resistance (CVR). In stroke and brain injury, CVR becomes constant (k), and thus CBF varies linearly with CPP values (linear relationship).
(Adapted from Rose JC, Mayer SA. Optimizing blood pressure in neurological emergencies. Neurocrit Care 2004;1[3]:287–99. Used with permission.)

occur unless immediately reversed. In normal states, CBF is held constant across a range of CPP values termed *cerebral autoregulation*, which is due to varying cerebrovascular resistance (CVR) (CBF = CPP/CVR). In stroke and brain injury, CVR becomes constant (k) and CBF varies linearly with CPP (Figure 2.2). The ischemic threshold is less than 20 mL/100 g per minute CBF, and gray matter typically has higher requirements (about 80–100 mL/100 g per minute) than white matter (about 50 mL/100 g per minute). Normal CBF is typically between 50 and 100 mL/100 g per minute.

Blood-Brain Barrier

Capillary endothelial cells form the most significant barrier between the brain and blood. This blood-brain barrier is composed of high-resistance junctions that limit the movement of large and nonsoluble molecules and charged substances. Water is able to move somewhat freely, but it is largely regulated by electrolyte pumps. There is high demand from the brain for glucose and essential amino acids that is met by specialized pumps for transport.

The 2 major fluids of the brain are CSF and interstitial fluid. CSF is similar to plasma, but with less protein and fewer cells. The choroid plexus produces CSF, protrudes into the ventricles, and is lined with ependymal cells. Adenosine triphosphatase protein and carbonic anhydrase work together to create this plasma ultrafiltrate. Capillaries contribute to the production of CSF, which is a lymph-like fluid for the brain and circulates between cells. Water moves back and forth via osmotic gradients among the cells, blood, and interstitial space.

CSF drains out via the ventricles into the subarachnoid spaces. CSF volume is approximately 140 mL, and approximately 500 mL is produced in a 24-hour period. Hydrocephalus can occur with increased production, decreased absorption, or physical obstruction. Even with increased ICP, CSF production still occurs. Arachnoid granulations allow drainage of CSF into the blood. Increases in ICP result in increases in CSF drainage through arachnoid granulation. Blood, such as from a subarachnoid hemorrhage, can cause obstruction and subsequent hydrocephalus. Acetazolamide, which inhibits carbonic anhydrase, has been shown to decrease production of CSF.

Pathologic ICP

If the volume of the blood, brain, or CSF increases, the body has compensatory means to prevent an increase in ICP. When this mechanism fails, ICP becomes so high that CPP, and therefore CBF, is decreased to the point of brain ischemia. When ICP equals MAP, CPP is zero, and intracranial circulation arrest occurs (recall CPP = MAP – ICP).

ICP follows the laws of elastance (change in volume over the change in pressure) and compliance (change in pressure over the change in volume). Small changes in volume are easily compensated by displacing CSF and venous blood, leading to only a minimal increase in ICP; in this case, compliance is high. When larger volumes cause further increases in ICP, compliance decreases; in other words, the brain is unable to take on any further volume.

First, CSF is shifted to spinal subarachnoid spaces and arterial and venous structures collapse; thereby, blood volume is reduced. Further increase of ICP can lead to herniation from compression and shift of brain tissue (herniation). Last, arterial blood can be shifted to extracranial carotid arteries, but, unfortunately, cerebral ischemia results.

Cardiac waves allow visualization of the dynamics of ICP. There are normally 3 waves, P1, P2, and P3, which are seen in compliant ICP waveforms and are blunted in the setting of abnormal intracranial compliance (Figure 2.3). Lundberg (Acta Psychiatr Scand Suppl. 1960;36[149]:1–193) described abnormally prolonged ICP increases, called Lundberg waves, which all indicate poor intracranial compliance.

- Intracranial hypertension is defined as sustained ICP of more than 20 mm Hg.
- CPP = MAP – ICP.
- The ischemic threshold is less than 20 mL/100 g per minute CBF.
- Hydrocephalus may occur as a result of overproduction of CSF (rare), ventricular obstruction, or reduced reabsorption of CSF.

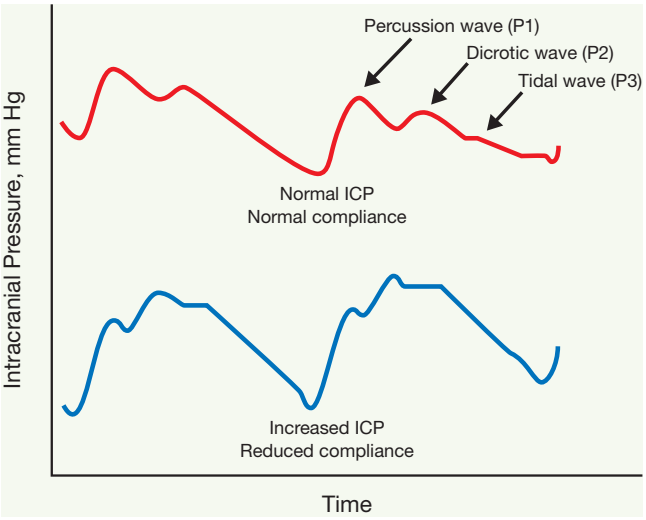


Figure 2.3 *Intracranial Pressure (ICP) Waveform. Upper image is a normal ICP waveform. Bottom image is a noncompliant waveform.*
(Adapted from Chesnut RM, Marshall LF. Management of head injury: treatment of abnormal intracranial pressure. Neurosurg Clin N Am 1991 April;2[2]:267–84. Used with permission.)

Increased ICP

Causes of Increased ICP

There are several causes of increased ICP, including space-occupying lesions, brain edema (cytotoxic, vasogenic, interstitial), hydrocephalus by way of increase in intracranial volume (intracranial hemorrhage) that overwhelms the compensatory mechanism, impaired regulation of intracranial blood flow in the arterial, capillary, or venous phase (obstructive hydrocephalus and marked increased ICP), and impaired CSF absorption (communicating hydrocephalus). Venous thrombosis can prevent reabsorption of CSF.

Cerebral swelling, or edema, has many causes that can be categorized into vasogenic, cytotoxic, or interstitial, although all 3 can overlap.

Vasogenic edema is typically caused by disruption of the blood-brain barrier, wherein fluid leaks out of the capillaries into the extracellular space. This fluid contains blood and protein, which increases the oncotic pressure and pulls water from surrounding areas. Proteases and free radicals from leukocytes within the fluid degrade the basement membrane of the capillaries, further worsening the edema. This fluid tends to flow to areas of least resistance and move toward the fiber tracts instead of more cortically. Because there is no direct damage to the cell, edema can resolve with correction of the capillary damage. Vasogenic edema is most common in patients with masses such as tumors or abscesses.

In cytotoxic edema, damage to the cell membrane prevents control of the movement of fluid between cells. The death of tissue from stroke, toxins (acute hepatic failure), or trauma causes loss of adenosine triphosphatase function and energy failure. Loss of adenosine triphosphatase function prevents cell control of the movement of fluid between the cell and the surrounding interstitium. Cytotoxic edema occurs in the early stages of cerebral ischemia.

In interstitial edema, fluid accumulates in the interstitial spaces from hydrocephalus. Edema is caused by CSF being pushed into extracellular fluid in the periventricular white matter. Interstitial edema may occur in patients with hydrocephalus.

Clinical Presentation of Increased ICP

Examination

A basic neurologic examination is the best way to determine clinical deterioration of the patient and early signs of impending herniation. Essential components for the conscious patient include language, oculomotor function, visual fields in all quadrants, pupillary examination, facial symmetry, and motor examination of proximal and distal strength. In the sedated and intubated patient or the patient with impaired consciousness, the essentials include a Glascow Coma Scale, pupillary examination, visual pursuit or oculocephalic reflex, blink to threat or corneal reflex, gag reflex, and response to noxious stimuli in all 4 extremities.

The earliest signs are headache and hypertension. The Cushing triad includes hypertension, bradycardia, and abnormal breathing. Often, though, this triad of symptoms can be the sign of impending herniation. Other signs and symptoms include change in mental status, vomiting, hiccups, diplopia, and pupillary changes.

Herniation Syndromes

Herniation is defined as the passage of an organ past a boundary into an area where that organ should not be. Cerebral herniation syndromes were originally described based on postmortem findings and do not always correlate with physical examination findings, as described below. However, sometimes patients do present with clinical herniation findings suggestive of increased ICP (Figure 2.4).

Uncal herniation, or lateral transtentorial herniation, occurs when the medial temporal lobe herniates downward past the tentorium. In this herniation, the medial temporal lobe herniates under tentorium cerebelli into tentorial incisura, displacing the midbrain. Patients present with *ipsilateral* pupillary dilatation due to compression of the third cranial nerve and decreased mental status. Uncal herniation may also compress the posterior cerebral artery with subsequent infarction (Figure 2.5).

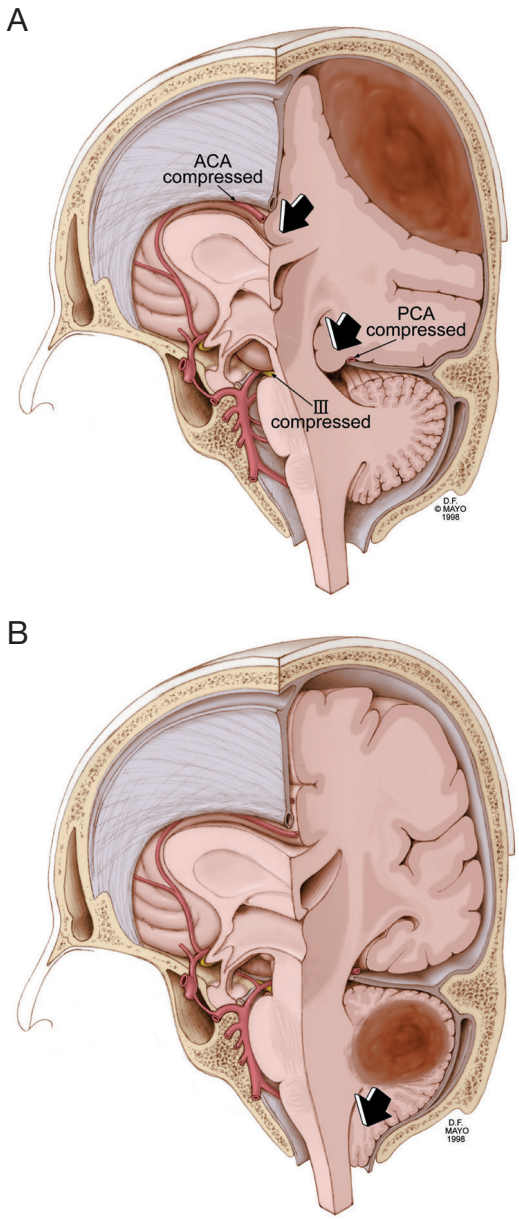


Figure 2.4 *Herniation Syndromes.*
A, Uncal herniaton from a subdural hematoma. Bottom right aspect of figure shows the uncus of temporal lobe herniating over the tentorium cerebelli, with vascular compression of the posterior cerebral artery (PCA) and mechanical compression of the third cranial nerve (CN III). Upper half of figure shows subfalcine herniation with brain herniating under the falx cerebri with vascular compression of the anterior cerebral artery (ACA). B, Posterior fossa hemorrhage causing downward cerebellar tonsillar herniation through the foramen magnum.
(Adapted from Wijdicks EFM. Catastrophic neurologic disorders in the emergency department. 2nd ed. Oxford [UK]: Oxford University Press; c2004. Chapter 8, Altered arousal and coma; p. 53–93. Used with permission of Mayo Foundation for Medical Education and Research.)

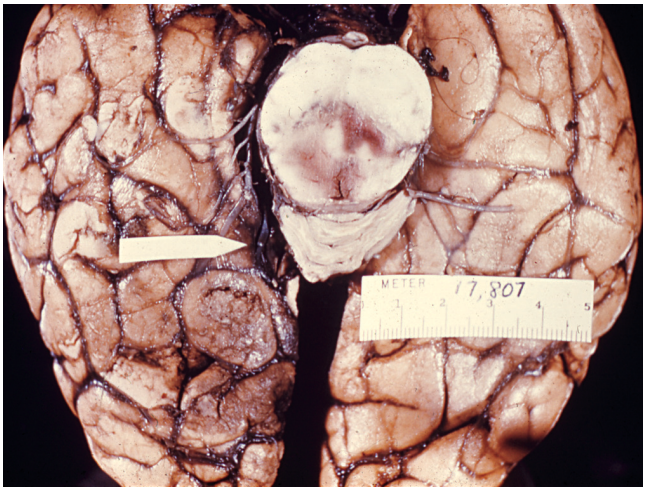


Figure 2.5 *Uncal Herniation.*
Compression of posterior cerebral artery (arrow) by uncal herniation produces ipsilateral occipital infarction. Note midline Duret hemorrhage in brainstem.
(Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

In tonsillar (cerebellar cone or foraminal impaction) herniation, downward herniation of cerebellar tonsils through the foramen magnum leads to compression of the medulla. Patients present with respiratory arrest, episodic extensor posturing, decrease in mental status, and cardiac dysrhythmias. In addition, the herniation prevents CSF flow from the cranium to the spinal cisterns, further worsening ICP.

Subfalcine (cingulate or supracallosal) herniation results in contralateral leg weakness and decreased mental status. Also, there can be changes in personality, and larger herniation will have anterior cerebral artery infarction. This herniation is a result of the cingulate gyrus herniating under the falx cerebri. A frontoparietal mass exerts force on the cingulate gyrus, forcing the brain under the falx.

Central transtentorial herniation results from diffuse edema. The brain develops bilateral downward herniation of both medial temporal lobes through the tentorial notch, compressing the midbrain. Patients often first have a decline in mental status and consciousness. This is followed by respiratory decompensation, extensor posturing, bilateral pupil dilatation, and palsy of the fourth cranial nerve. If herniation continues, Duret hemorrhage of the brainstem may develop (due to shearing of basilar perforators) (Figure 2.6), pituitary stalk shearing (resulting in diabetes insipidus), and bilateral occipital infarctions (due to compression of the posterior cerebral arteries).

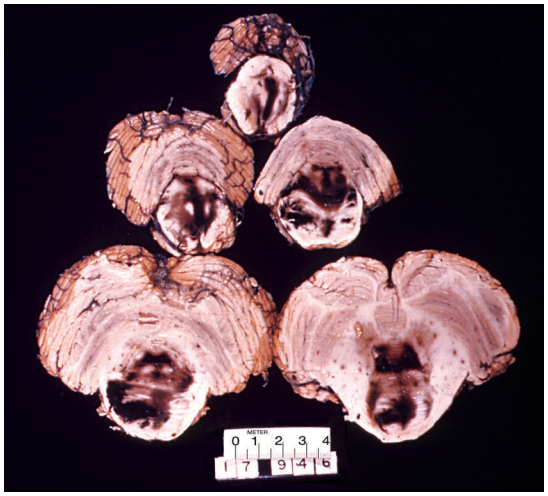


Figure 2.6 *Duret Hemorrhages Produced by Severe Downward Herniation.*
(Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

Upward transtentorial herniation occurs when a posterior fossa mass creates upward herniation of posterior fossa contents through the tentorial notch, usually due to excessive ventricular CSF drainage. Often the cerebral aqueduct or fourth ventricle becomes occluded, and obstructive hydrocephalus results. Patients often present with bilateral pupillary dilatation, extensor posturing, and decrease in mental status. A homonymous hemianopsia can occur if the posterior cerebral artery is occluded, or venous infarction can occur if the great vein of Galen is obstructed.

One entity, referred to as normal-pressure herniation, occurs with herniation or displacement of the brain tissue in the setting of normal ICPs. Patients clinically deteriorate, and management is unchanged from that for other types of herniation.

Monitoring Increased ICP

A considerable change in examination results that cannot be reasonably explained should prompt imaging. Computed tomography without contrast is a practical form of imaging. It is relatively fast and can be obtained fairly easily. It can reasonably evaluate for common causes of changes in mental status, including hydrocephalus, bleeding, and infarction.

A more invasive means of measuring ICP is by way of an intraventricular catheter. It is considered the standard for monitoring ICP. In addition to its use for quantitative measurement, an intraventricular catheter can be therapeutic. It can be used to drain CSF and thus provide a means of decreasing ICP. With all invasive techniques, there are risks, including hemorrhage and infection.

Treatment of Increased ICP

Medical Treatment of Increased ICP

The goals of medical management of increased ICP (Box 2.1) are to maintain brain perfusion and prevent hypotension without considerable contribution to an increase in ICP. Antihypertensives such as labetalol are the first choice as a vasodilator, producing cerebral vasculature dilatation and subsequent hyperemia. Normal saline should be used over hypotonic saline, which will diffuse into the tissue and lead to edema and worsen the ICP.

Patient position can contribute to ICP. Ensuring that the head of the bed is 30 degrees allows a decrease in hydrostatic pressure and facilitates venous drainage and therefore decreases ICP. Also, the neck should be in the neutral position, facing forward, and not be hyperextended or flexed to one side or the other. Neck flexion can compress the internal jugular vein and thereby decrease venous drainage and subsequently increase ICP.

In patients who are intubated, temporary measures can be used to decrease increased ICP. Decreasing CO_2 leads to vasoconstriction, thereby decreasing ICP in viable brain and providing room for diseased (not vasoreactive) brain to be edematous without compromising other structures. Although this can be done relatively quickly, it should be used for only a short time because vasoconstriction can lead to ischemia or later rebound increase in ICP. In a stable ventilated patient without increased ICP, adequate sedation should be used to prevent coughing, which can increase ICP.

Mild to moderate hypothermia (32°–34°C) can be used to reduce ICP via reduction in cerebral metabolic rate of oxygen and CBF, especially when ICP is refractory to conventional osmotherapy and other interventions. Decrease in brain temperature decreases metabolic demand and can help decrease ICP. Adverse effects include infection, coagulation and hemorrhagic complications, electrolyte abnormalities, and shivering. Hypothermia can be used to reduce ICP in patients who are sedated, intubated, and under neuromuscular blockade until ICP is controlled by another means (surgical decompression). Further

Box 2.1 • Medical Treatment of Increased Intracranial Pressure

- Head of bed at 30 degrees
- Normal saline
- Hyperventilation (short term)
- Hypothermia

prospective trials are needed on longer-term use (>24–48 hours) of hypothermia for refractory ICP.

Pharmacologic Treatment of Increased ICP

Among the pharmacologic treatments (Box 2.2), mannitol can be used as a temporizing measure for increases in ICP by increasing serum osmolarity, thereby pulling fluid out of tissue and, in an edematous brain, decreasing ICP. Typically, it is administered as a bolus of 0.5 to 1.5 g/kg via a peripheral intravenous infusion with crystal filter. It is filtered by the kidney and not resorbed; because it can lead to considerable diuresis, a Foley catheter should be placed before administeration to prevent urinary retention. This diuresis can lead to hypotension requiring fluids and pressors and to depletion in many electrolytes, including potassium, magnesium, and phosphorus. Mannitol is contraindicated in patients with congestive heart failure and severe renal disease.

Glucocorticoids are most effective in edema from intracranial tumors and are less effective in traumatic brain injury, ischemic stroke, or hemorrhage. They work by down-regulating brain aquaporin, decreasing the transport of water into the brain and surrounding glial cells. Dosing in patients with brain tumors who have vasogenic edema is typically 4 mg every 6 hours (intravenously or orally), but sometimes a one-time dose of 10 mg intravenously can be given in patients with acute herniation from brain tumors. Corticosteroids can cause hyperglycemia, diabetes, acute agitation, tremors, peptic ulcers, or immunosuppression; impair wound healing; or worsen preexisting diabetes.

Anesthetics, such as propofol, can be given in refractory ICP. Propofol decreases cerebral brain metabolism (cerebral metabolic rate of oxygen) with subsequent reduction in CBF, which reduces global ICP (similar to barbiturates). It has the benefit of having a short half-life, which allows periods of discontinuing its use for intermittent clinical monitoring. Caution should be used, because it can cause hypotension requiring vasopressors, hypertriglyceridemia (pancreatitis and nutrition adjustments), metabolic acidosis, seizure, and, in young patients, propofol infusion syndrome, which can cause severe acidosis, acute shock syndrome, and death.

Some centers use hypothermia with short-acting sedation (midazolam or propofol) over barbiturate-induced coma for management of refractory ICP because barbiturates, used over days, can build up in adipose tissue (large volume of distribution). Thus, barbiturate coma can lead to subsequent difficulty with neurologic prognosis or brain death determination because of the buildup of residual barbiturates lingering in the patient's system, whereas hypothermia can be reversed and use of short-acting sedatives discontinued.

Invasive Treatment of Increased ICP

Invasive treatment of increased ICP varies by cause (Box 2.3). Intracranial masses causing increased ICP should be evaluated by a neurosurgeon for possible resection. Hematomas, especially epidural hematomas, should be evacuated, especially because they are under arterial pressure, as opposed to subdural hematomas, which are under venous pressure. Rarely, postoperative pneumocephalus can be treated with oxygen at an F_{IO_2} of 100% via ventilator or facemask. Some lesions causing increased ICP cannot be resected, such as stroke and intracerebral hemorrhages. For these instances, craniectomy can create an area of the brain to herniate outward, relieving ICP.

CSF drainage can be a temporizing measure in patients with an intraventricular catheter. Normally, the catheter is placed at the level of the foramen of Monro, which is located at the tragus of the ear. The manometer can be placed at various levels. When catheter pressure exceeds the set value, CSF drains out. Lumbar drains can also be used but can be in place for only a few days. The advantage of a lumbar drain is its ability to remove blood from the CSF that has settled into the lumbar region. Risks include herniation of the cerebellar tonsils, uncal herniation, or spinal coning. Complications include headache, epidural or tissue bleeding, infection, and radicular pain.

- Cytotoxic edema occurs in the early stages of cerebral ischemia.
- The Cushing triad includes hypertension, bradycardia, and abnormal breathing.
- Patients with uncal herniation present with *ipsilateral* pupillary dilatation due to compression of the third cranial nerve and decreased mental status.

Box 2.2 • Pharmacologic Treatment of Increased Intracranial Pressure

Mannitol (short term)
Glucocorticoids (vasogenic edema)
Propofol
Barbiturates

Box 2.3 • Invasive Treatment of Increased Intracranial Pressure

Resection of mass lesion (if applicable)
Drainage of cerebrospinal fluid
Hemicraniectomy (select patients)

- Patients with central transtentorial herniation often first have a decline in mental status and consciousness; this is followed by respiratory decompensation, extensor posturing, bilateral pupil dilatation, and palsy of the fourth cranial nerve.
- Among the pharmacologic treatments (Box 2.2), mannitol can be used as a temporizing measure for increases in ICP by increasing serum osmolarity, thereby pulling fluid out of tissue and, in an edematous brain, decreasing ICP.

Specific Situation: Malignant Ischemic Stroke

Large ischemic strokes may result in substantial brain edema. Typically, edema develops within several hours of an ischemic stroke and peaks at 72 to 120 hours. Risk factors for malignant cerebral edema after stroke include young age and large distribution of infarction from large artery disease, such as the middle cerebral artery or internal carotid artery territories.

Patients presenting with sign and symptoms of malignant stroke should receive medical therapy for cerebral edema. Early hemicraniectomy may be considered.

In a pooled meta-analysis of patients with malignant infarction of the middle cerebral artery, decompressive hemicraniectomy undertaken within 48 hours reduced mortality and increased favorable functional outcome in patients 60 years old or younger (Lancet Neurol. 2007 Mar;6[3]:215–22). Patients should be considered on a case-by-case basis. In some instances, hemicraniectomy may be indicated when the edema is severe. For patients with cerebellar infarction with subsequent edema and mass effect, or cerebral aqueductal compression, a posterior fossa decompression may be indicated.

Low ICP

Low ICP may be due to spontaneous or traumatic CSF leak. The low ICP syndrome due to spontaneous CSF leak is discussed in Chapter 53, "Secondary Headache Disorders."

3 Status Epilepticus

SARA E. HOCKER, MD; MATTHEW T. HOERTH, MD

Introduction

Status epilepticus has historically been defined as a condition in which epileptic activity persists for 30 minutes or more in the form of prolonged seizures or repeated isolated seizures without recovery in between. As a means of facilitating early treatment and preventing brain injury, the accepted operational definition is seizure duration longer than 5 minutes *or* 2 or more seizures with incomplete interictal recovery. Refractory status epilepticus is defined as seizure activity that continues despite adequate doses of 2 appropriately selected antiepileptic agents, typically a benzodiazepine followed by fosphenytoin, valproic acid, or phenobarbital. Status epilepticus is classified into generalized and partial types. Generalized types include 1) generalized tonic-clonic, 2) absence, 3) myoclonic, 4) tonic, and 5) clonic. Partial types include 1) simple partial (motor, sensory, visual, auditory, or language) and 2) complex partial.

- The accepted operational definition of status epilepticus is seizure duration longer than 5 minutes *or* 2 or more seizures with incomplete interictal recovery.

Epidemiology and Etiology

The incidence of status epilepticus is 6.8 to 41 cases per 100,000 persons annually. It is not believed to have a predilection for any particular sex or racial or ethnic group. The age frequency of status epilepticus follows a J-shaped curve; the frequency is high in children, and the incidence increases with advancing age.

Most episodes of status epilepticus develop without a prior history of seizures, and these are almost always caused by acute brain injury or acute toxic or metabolic disturbances. The most common types of acute brain injury causing status epilepticus are vascular events (predominantly acute ischemic stroke), brain tumors, meningitis or encephalitis, trauma, metabolic derangements, or acute febrile illnesses in children. Among persons with epilepsy who are followed in an epilepsy clinic, one study showed that 10% to 25% of children and 5% of adults will have at least 1 episode of status epilepticus during their lifetime. Precipitating factors among patients with a history of epilepsy include low levels of antiepileptic drugs, abrupt changes in antiepileptic drug regimen or discontinuation for localization of the epileptic focus, drug intoxication or withdrawal, systemic infection or metabolic derangement, or progression of the underlying disease responsible for the seizures. Remote symptomatic lesions cause approximately 30% of cases of status epilepticus, and 5% are idiopathic or unknown. The remainder are due to acute brain insults such as traumatic brain injury, central nervous system infection, or ischemic or hemorrhagic stroke. Status epilepticus becomes refractory in 12% to 43% of cases.

Pathophysiology

Seizures are sustained by excess excitation (glutamate and *N*-methyl-d-aspartate) and reduced inhibition (γ-aminobutyric acid, GABA). The failure of inhibitory processes is increasingly thought to be the major mechanism leading to status epilepticus. The majority of seizures terminate spontaneously; prolonged seizure activity results in pathologic changes after 30 minutes and neuronal death after 60 minutes. Morbidity and mortality are directly correlated with duration. Neuronal death occurs because of

Abbreviation: GABA, γ-aminobutyric acid

large increases in intracellular calcium caused by prolonged exposure to excitatory neurotransmitters and systemic and metabolic disturbances, including hypoxia, hypoglycemia, and increased intracranial pressure. Pharmacoresistance occurs with sustained seizure activity because of 1) reduced GABA inhibition, 2) decreased availability of existing GABA receptors, and 3) changes in gene expression altering ion channels, receptors, cell metabolism, and neuronal connectivity.

Clinical Features

Diagnosis is based on results of neurologic examination that are consistent with seizure activity and confirmed by electroencephalography (Figure 3.1). Generalized tonic-clonic status epilepticus is characterized by coma, increased tone, and rhythmic jerking of the extremities followed by a depressed level of consciousness, with or without a focal neurologic deficit, lasting hours to days. Nonconvulsive status epilepticus has 2 main forms. In the first type, the patient has progressive or intermittent confusion. Affected patients generally have a good prognosis. In the second type, sometimes referred to as "subtle" status epilepticus, the patient is acutely ill and stuporous and may or may not have rhythmic muscle twitches or eye deviation.

Evaluation and Management

An algorithmic approach to status epilepticus is outlined in Figure 3.2. Following a protocol for treatment has itself been shown to reduce morbidity and mortality in status epilepticus. Emergency investigations should first include an assessment of the airway, breathing, and circulation. Glucose value and oxygen status should be checked rapidly. Oxygen should be provided, and thiamine should be administered before correction of hypoglycemia. Initial laboratory evaluation includes blood gases, renal and hepatic function, calcium and magnesium values, complete

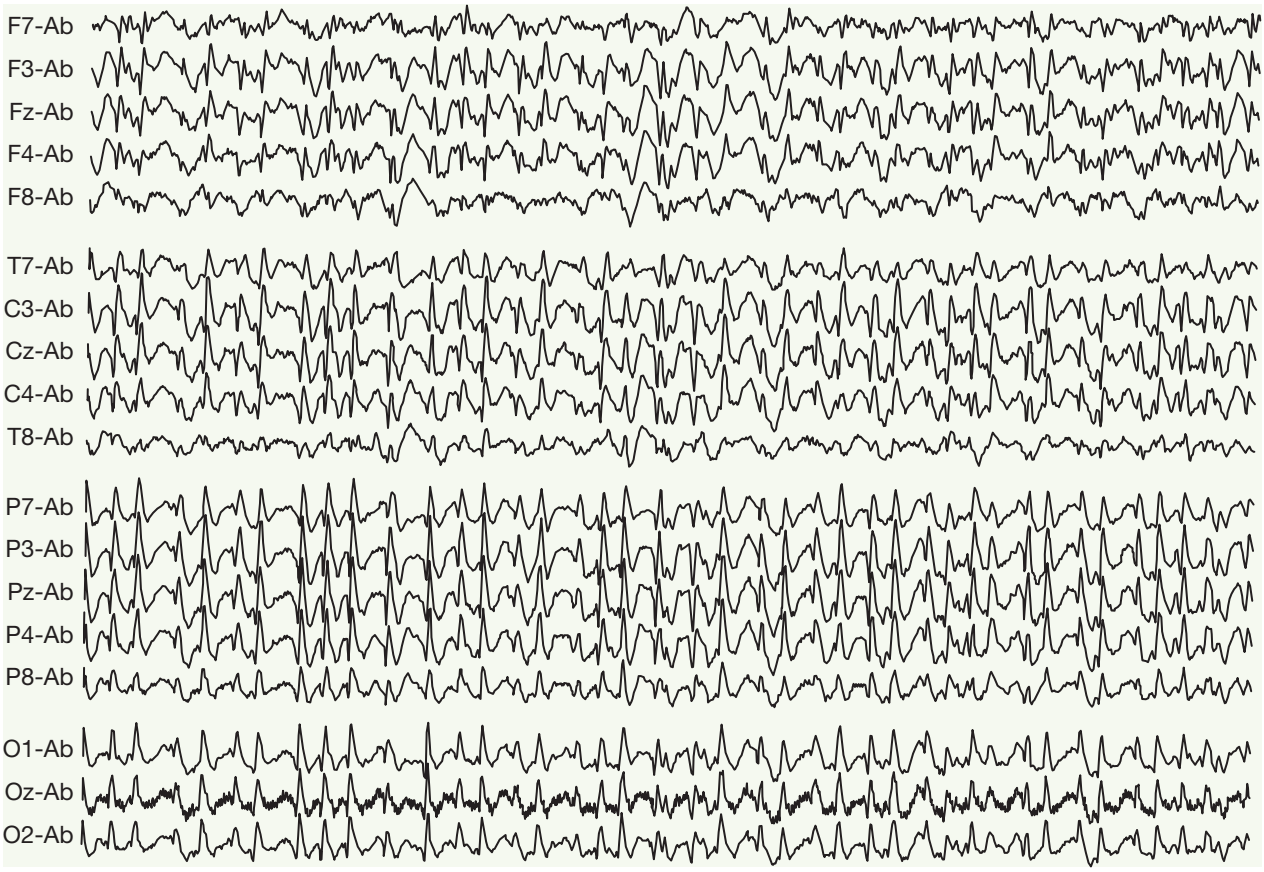


Figure 3.1 *Nonconvulsive Status Epilepticus.*
Electroencephalogram shows continuous, diffuse rhythmic activity.
(Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

blood count, toxicologic tests, and determination of anticonvulsant levels. Correction of metabolic abnormalities and control of hyperthermia are necessary for the treatment of status epilepticus and prevention of recurrent seizures. Electrocardiography and neuroimaging are recommended in all patients. Consider lumbar puncture and cerebrospinal fluid analysis if fever is present, recent behavioral or speech changes are reported, or no cause is readily apparent.

Details of medications are listed in Table 3.1. Pharmacologic treatment should occur simultaneously with the evaluation detailed above. Benzodiazepines should be administered while monitoring the airway. Advantages of benzodiazepines include rapid onset of action, efficacy, and versatility (can be given intravenously, intramuscularly, buccally, or rectally). If seizures persist, administer 20 mg/kg phenytoin equivalents of fosphenytoin. It is effective 10 to 30 minutes after intravenous administration. In the absence of intravenous access, it can be administered intramuscularly; however, this approach requires a longer absorption time. An additional 5 to 10 mg/kg can be considered if seizures persist. Intravenous valproic acid may be considered as an alternative to fosphenytoin if the patient already takes valproic acid, has an allergy to phenytoin, or is hemodynamically unstable. If the status epilepticus is caused by drug withdrawal, replace the withdrawn drug immediately by parenteral administration, if possible.

If seizures persist after adequate doses of benzodiazepine and of fosphenytoin or valproic acid, consider intubation, transfer to an intensive care unit, infusion of an anesthetic agent (midazolam, propofol, or pentobarbital), and continuous electroencephalography. Treat to burst suppression for 12 to 48 hours, and then gradually withdraw sedation guided by the electroencephalogram. Ensure that maintenance antiepileptic drug administration is continued at therapeutic doses.

Alternative antiepileptic agents, including lacosamide and levetiracetam, are currently not recommended as first- or second-line agents for control of status epilepticus.

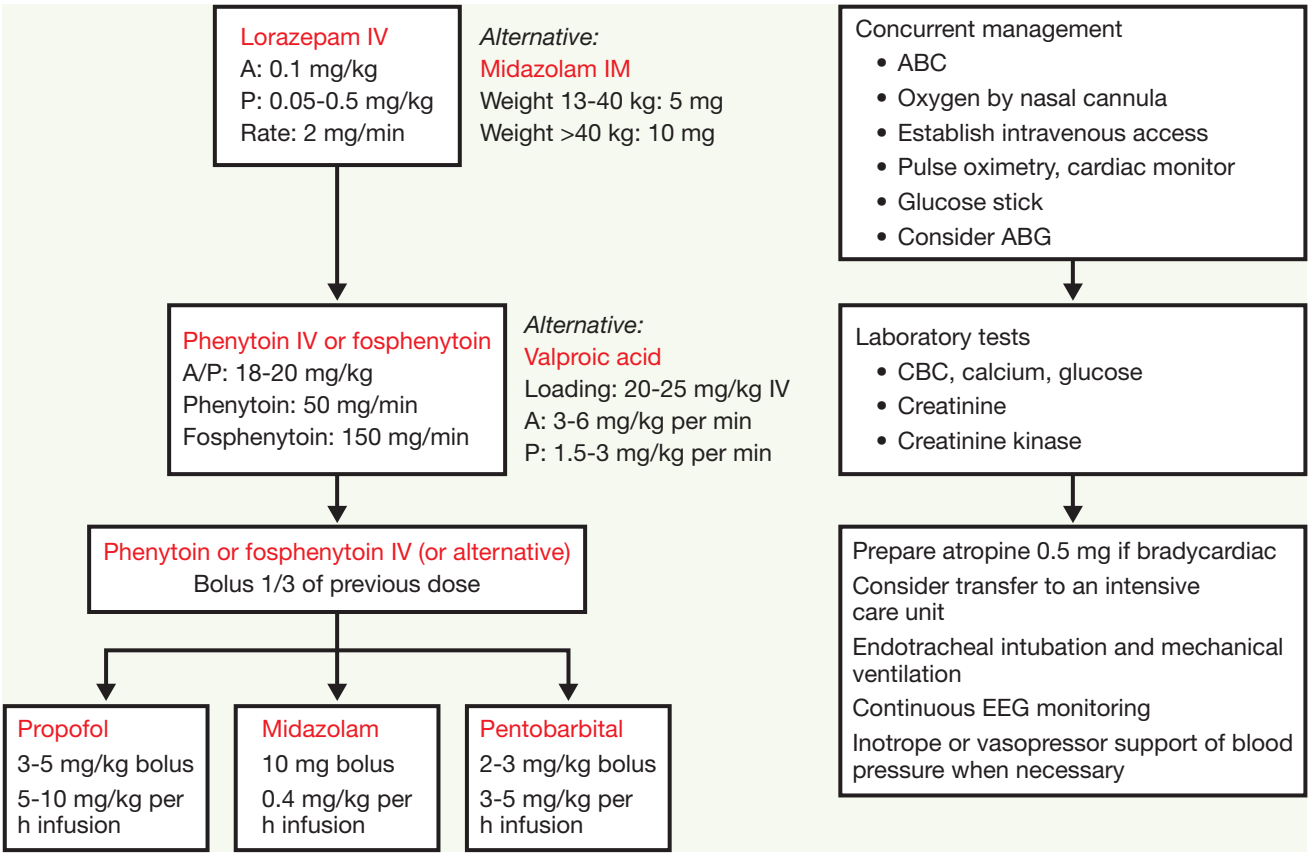


Figure 3.2 *Management of Status Epilepticus.*
A incidates adult; ABC, airway, breathing, circulation; ABG, arterial blood gas; CBC, complete blood count; EEG, electroencephalography; IM, intramuscularly; IV, intravenously; P, pediatric.
(Adapted from Wijdicks EFM. Catastrophic neurologic disorders in the emergency department. 2nd ed. Oxford [UK]: Oxford University Press; c2004. Chapter 10, Status epilepticus and recurrent seizures; p. 106–20. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 3.1 • Medications Used to Manage Status Epilepticus

Medication	Loading Dose, Intravenous	Maintenance Dose	Therapeutic Level, µg/mL
Lorazepam	0.1 mg/kg (typically, start with 1–2 mg, then increase if seizures continue)		NA
Diazepam	0.15 mg/kg		NA
Phenytoin/fosphenytoin	18–20 mg/kg	300 mg/d (adults) 4–6 mg/kg per d (children)	10–20
Valproic acid	20–25 mg/kg		50–100
Phenobarbital	20 mg/kg	200–320 mg/d (adult) 3–6 mg/kg per d (children)	10–40
Propofol	3–5 mg/kg	6–10 mg/kg per h	NA
Midazolam	0.2 mg/kg	0.1–0.4 mg/kg per h	NA
Pentobarbital	2–3 mg/kg	3–5 mg/kg per h	NA
Lacosamide	200–400 mg		NA
Levetiracetam	1,000–3,000 mg		NA

Abbreviation: NA, not applicable.

Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.

Although they are widely used, their effectiveness and safety are not clearly established in this setting. These agents may be selected on a case-by-case basis for refractory status epilepticus, such as for patients in whom endotracheal intubation is not an option and for patients in whom medications that do not depress the breathing drive or result in upper airway collapse are preferred.

Refractory status epilepticus is defined as failure of seizure activity to cease after appropriate doses of 2 medications. The evidence-based treatment of refractory cases is poorly established. The literature provides multiple case series and case reports. Attempted therapies reported include, but are not limited to, valproic acid, lidocaine, levetiracetam, chloral hydrate, lacosamide, diazepam, electroconvulsive therapy, topiramate, ketogenic diet, ketamine, and inhalational anesthetics.

- Glucose value and oxygen status should be checked rapidly in patients with status epilepticus.
- Correction of metabolic abnormalities and control of hyperthermia are necessary for the treatment of status epilepticus and prevention of recurrent seizures.
- Benzodiazepines should be administered while monitoring the airway in patients with status epilepticus.
- If seizures persist after adequate doses of benzodiazepine and of fosphenytoin or valproic acid, consider intubation, transfer to an intensive care unit, infusion of an anesthetic agent (midazolam, propofol, or pentobarbital), and continuous electroencephalography. Treat to burst suppression.

Systemic Complications

Many physiologic changes accompany status epilepticus and may result in systemic complications (Box 3.1). The tachycardia, cardiac dysrhythmias, hyperglycemia, and hypertension that occur in the early stages of status epilepticus are thought to result from a surge in catecholamines. As status epilepticus continues, blood pressure may decrease to below a patient's baseline. Hyperthermia can result from the vigorous muscle activity and sympathetic surge that occur with generalized convulsive status. There is often a transient marked acidosis with both respiratory and metabolic components. Unlike hyperthermia, which is proconvulsant, acidosis has an anticonvulsant effect and thus does not in itself require treatment in the early stages because it resolves with termination of the seizure. A mild leukocytosis resulting predominantly from demargination is common and may be present in the serum or cerebrospinal fluid. Convulsive status epilepticus can cause hypoxia

Box 3.1 • Systemic Complications of Status Epilepticus

Hyperthermia
Hypoxia
Acidosis
Mild leukocytosis
Rhabdomyolysis
Trauma

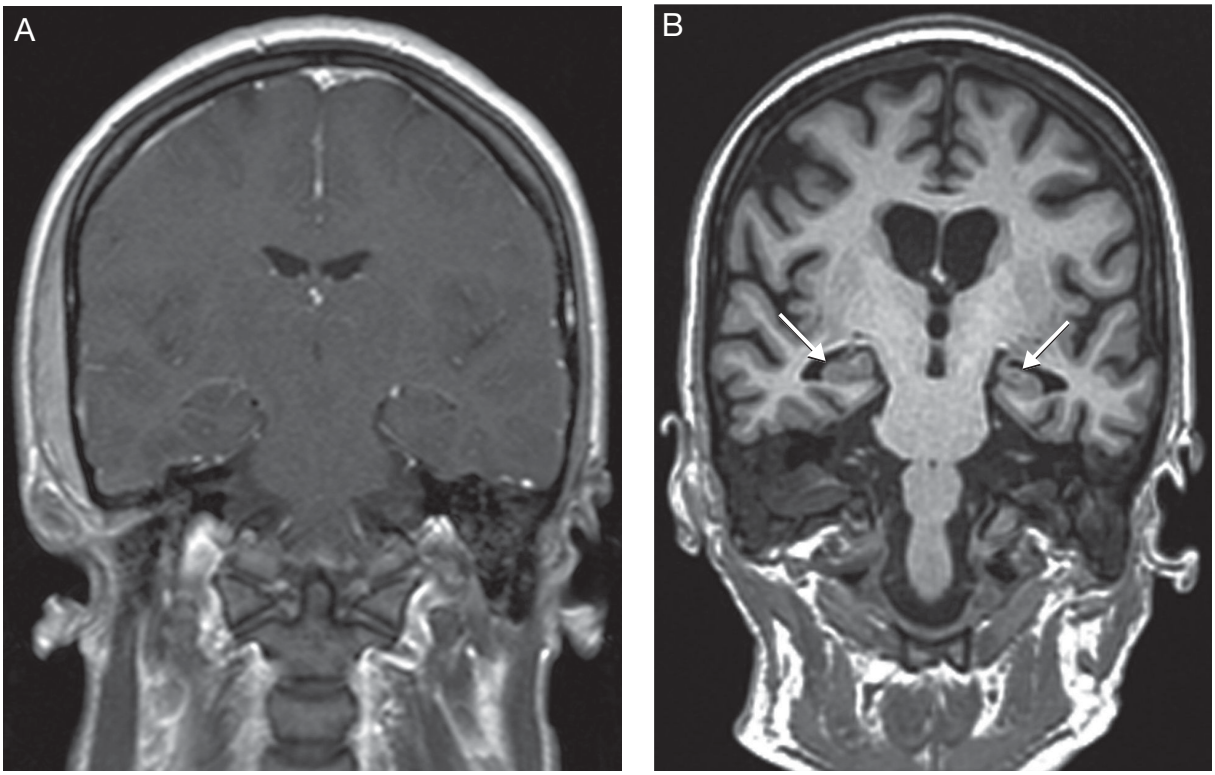


Figure 3.3 *Cortical Atrophy After Prolonged Status Epilepticus, as Shown on Magnetic Resonance Imaging. A, Brain of a 23-year-old woman at the onset of status epilepticus. B, Same patient after 4 months of continued status epilepticus despite aggressive treatment. Cortical atrophy is widespread and severe for age. Note especially the atrophy of the hippocampus (arrows).*

by several mechanisms: 1) mucous plugging, 2) pulmonary edema, 3) aspiration pneumonitis, or 4) apnea. Rhabdomyolysis may result from repeated contraction and breakdown of skeletal muscle tissue and can result in acute kidney injury without adequate hydration. Musculoskeletal trauma can occur in convulsive status epilepticus. Common injuries are lateral tongue bites, posterior fractures or dislocations of the shoulder, or falls resulting in various injuries.

Outcome and Prognosis

The strongest predictors of outcome in status epilepticus are cause and duration. Mortality is 10% to 20% in status epilepticus and is an average of 32% in refractory cases. Short-term complications include musculoskeletal trauma, rhabdomyolysis and acute kidney injury, aspiration pneumonitis or pneumonia, and cardiac dysrhythmias. Long-term complications may include the development of epilepsy (mesial temporal sclerosis in 20%-40% of patients) and cortical atrophy (Figure 3.3).

- The strongest predictors of outcome in status epilepticus are cause and duration.
- Mortality is 10% to 20% in status epilepticus and is an average of 32% in refractory cases.

4 Nontraumatic Subarachnoid Hemorrhage[a]

JENNIFER E. FUGATE, DO; EELCO F. M. WIJDICKS, MD, PHD

Introduction

Subarachnoid hemorrhage (SAH) is defined as introduction of blood in the subarachnoid space. Trauma is the most common cause of SAH. (Trauma is discussed in Chapter 6, "Traumatic Brain Injury.") The most common cause of nontraumatic SAH is aneurysm, typically located around the circle of Willis. Attention should be focused on finding a potential aneurysm, but several other conditions can cause SAH (Box 4.1).

- Trauma is the most common cause of SAH.
- The most common cause of nontraumatic SAH is aneurysm, typically located around the circle of Willis.

Box 4.1 • Causes of Subarachnoid Hemorrhage

Aneurysmal subarachnoid hemorrhage
Traumatic brain injury
Ruptured mycotic (distal) aneurysm
Use of tPA associated with treatment of STEMI
Arteriovenous malformation
Cavernous malformation
Vasculitis
Bleeding diathesis
Reversible cerebral vasoconstriction syndrome
Amyloid angiopathy

Abbreviations: STEMI, ST-segment elevation myocardial infarction; tPA, tissue plasminogen activator.

Epidemiology

The *incidence* of aneurysmal SAH (aSAH) is 7 to 9 per 100,000 person-years in most populations. The risk of aSAH increases with age, but about half of patients are younger than 55 years. Thus, aSAH may affect people in the prime of their life. Risk factors for aSAH are smoking, hypertension, and certain systemic medical illnesses such as polycystic kidney disease. Some families have several members with documented aneurysms without a yet identifiable genetic mutation. (See Chapter 15, "Unruptured Intracranial Aneurysms and Vascular Malformations," for a discussion of management of patients with unruptured intracranial aneurysms.)

Clinical Features

The clinical hallmark of aSAH is an instantaneous, unexpected, and overwhelmingly severe headache, which can be associated with loss of consciousness due to massively increased intracranial pressure (ICP). The headache is sometimes referred to as thunderclap because the pain is of maximal intensity at the onset. Some patients may refer to this pain subjectively as the "worst headache of my life" (and it often is), but this description is not specific to the condition. (See Chapter 53, "Secondary Headache Disorders," for the differential diagnosis of thunderclap

[a] Portions previously published in Fugate JE, Rabinstein AA. Intensive care unit management of aneurysmal subarachnoid hemorrhage. Curr Neurol Neurosci Rep. 2012 Feb;12(1):1–9. Used with permission.

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; DCI, delayed cerebral ischemia; ICP, intracranial pressure; SAH, subarachnoid hemorrhage

headache.) Other common associated symptoms include nausea and vomiting, neck pain, neck stiffness, and photophobia. Generalized tonic-clonic seizures can occur but are rare (<5%), but in comatose patients adventitious movements such as extensor posturing or myoclonus may be mistaken for seizure at the onset.

Intraparenchymal hematomas or arterial subdural hematomas caused by aneurysmal rupture may cause focal neurologic deficits. Ocular hemorrhages due to massively, suddenly increased ICP can be detected by a funduscopic examination, which should be performed in all patients with aSAH. Retinal subhyaloid hemorrhages are found in approximately one-quarter of patients. Patients may note severe visual loss, particularly if the hemorrhage ruptures into the vitreous (Terson syndrome), or they may be bothered by floating "blobs" that obstruct their vision (See Chapter 46, "Neuro-ophthalmology: Disorders of Visual Perception, Pupils, and Eyelids.") A pupil-involving third nerve palsy may occur from compression of the third nerve, which exits the brainstem and courses between the posterior communicating and posterior cerebral arteries.

In comatose patients, a downward gaze may indicate the presence of acute hydrocephalus. If coma is due to hydrocephalus, ventriculostomy could dramatically improve a patient's level of consciousness. Coma at presentation may be a result of an initial increase in ICP with consequently reduced cerebral perfusion, which, if prolonged, could cause diffuse bihemispheric ischemia.

The World Federation of Neurological Surgeons proposed a simple clinical grading system for SAH that has been found to correlate with outcome when used at presentation (Table 4.1). This simple scale is based on the sum score on the Glasgow Coma Scale and on the presence or absence of motor deficits. aSAH is typically dichotomized into a good grade (I-III) or poor grade (IV or V) based on the score at presentation.

Table 4.1 • World Federation of Neurologic Surgeons Grading Scale for Subarachnoid Hemorrhage

Grade	GCS Sum Score	Motor Deficit
I	15	Absent
II	13–14	Absent
III	13–14	Present
IV	7–12	Either absent or present
V	<7	Either absent or present

Abbreviation: GCS, Glasgow Coma Scale.

Adapted from Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg. 1988 June;68(6):985–6. Used with permission.

Diagnosis

A history of thunderclap headache should alert the clinician to the possibility of aSAH, and head computed tomography (CT) without contrast should be performed. With use of the latest CT techniques, the sensitivity for detecting SAH radiographically is 93% to 100% if scanning is done within 24 hours of symptom onset. An aneurysmal pattern of SAH consists of a diffuse distribution of blood in the basal cisterns. A more benign radiographic variant of SAH is the perimesencephalic (around the mesencephalon), or pretruncal (around the truncus cerebri or brainstem), pattern, which shows a focal hemorrhage anterior to the midbrain or upper pons (Figure 4.1). Whether a typical or pretruncal SAH is diagnosed, conventional 4-vessel arteriography is necessary to determine whether there is an aneurysm and to characterize its morphologic pattern (berry vs fusiform, neck size, presence of "daughter sacs") (Figure 4.2).

False-negative results on CT can occur in SAH. As time passes and cerebrospinal fluid (CSF) recirculates, the acute hemorrhage will be more difficult to detect, and the CT findings will "normalize" in up to 10% of patients by day 3 and in about 50% of patients by day 7. Thus, if the diagnosis of SAH is strongly suspected clinically, additional testing (eg, spinal fluid examination) is needed if head CT is unrevealing.

Next, if the suspicion for SAH is high and the results of CT are negative, a lumbar puncture should be performed to evaluate CSF for the presence of xanthochromia, a yellowish discoloration of CSF caused by bilirubin (a product of red blood cell breakdown). One needs to wait at least 6 hours after symptom onset to check reliably for the presence of xanthochromia. If CSF is obtained within 6 hours, it may yield false-negative results because that duration is insufficient for the breakdown of red blood cells. Laboratories have 2 methods by which to assess for xanthochromia: visual assessment of centrifuged CSF (by holding test tubes against a light source or white paper) or spectrophotometry. Most laboratories use the visual method. Relying merely on a decreasing red blood cell count between tubes 1 and 4 is not sufficient to distinguish SAH from a traumatic lumbar puncture. Xanthrochromia may also be present in the presence of high systemic bilirubin or a very increased CSF protein value.

• False-negative results on CT can occur in SAH. As time passes and CSF recirculates, the acute hemorrhage will be more difficult to detect, and the CT findings will "normalize" in up to 10% of patients by day 3 and in about 50% of patients by day 7. Thus, if the diagnosis of SAH is strongly suspected clinically, additional testing (eg, spinal fluid examination) is needed if head CT is unrevealing.

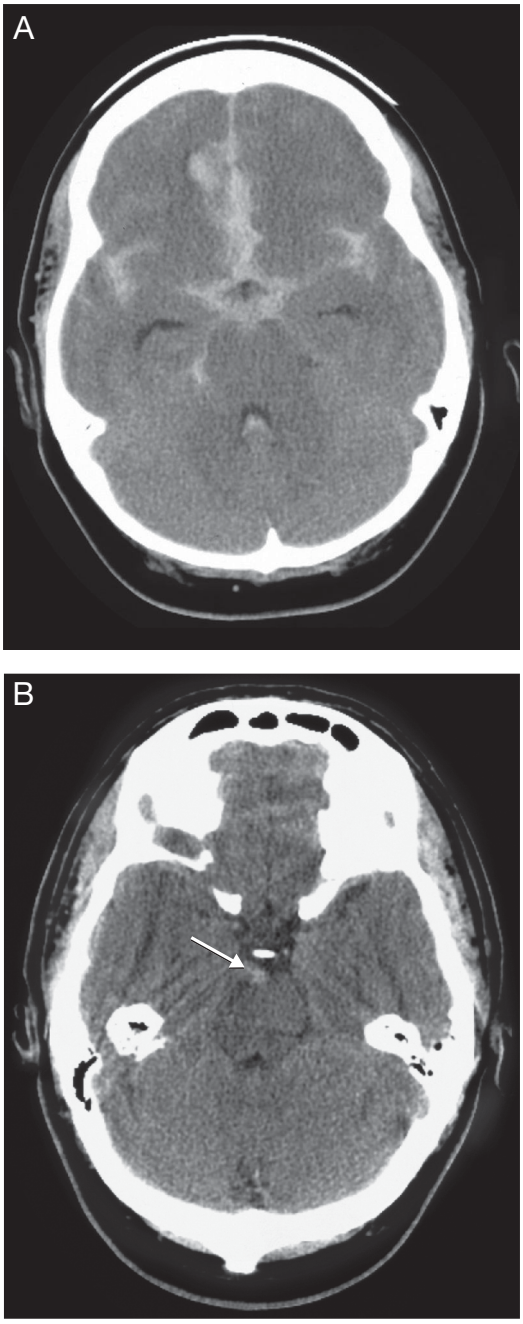


Figure 4.1 *Subarachnoid Hemorrhage on Noncontrast Computed Tomography in Different Patients.*
A, Subarachnoid blood is distributed diffusely in the cisterns and fissures, including sylvian fissure. B, Note small amount of perimesencephalic (pretruncal) (arrow) subarachnoid blood. This patient has a benign form of subarachnoid hemorrhage with a good prognosis.
(Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

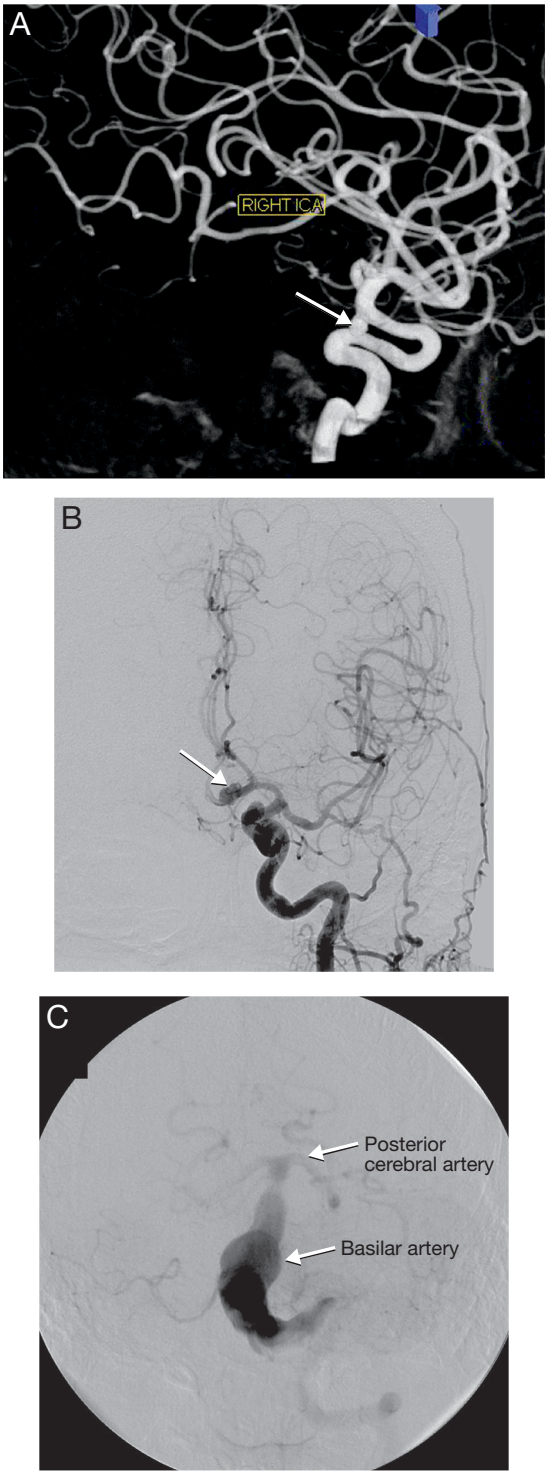


Figure 4.2 *Aneurysm Morphologic Patterns on Conventional Angiography.*
A, Common berry aneurysm of the posterior communicating artery (arrow). ICA indicates internal carotid artery. (Courtesy of Giuseppe Lanzino, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.) B, Wide-neck aneurysm of the anterior communicating segment (arrow). C, A less common fusiform aneurysm of the basilar artery on cerebral angiography.

Management

The primary initial goal in managing aSAH is to identify and treat the aneurysm early. Subsequently, the goal is to limit secondary brain injury, which can occur as a result of many complications, both cerebral and systemic (Table 4.2). The risk of aneurysmal rebleeding—a feared event with high risks of death or disability—is highest within 24 hours of SAH onset. The risk of rebleeding drives the emphasis on early treatment. Aneurysms can be secured either by percutaneous endovascular coiling (Figure 4.3) or by microsurgical clipping. The morphologic pattern and location of the aneurysm, in addition to individual patient characteristics, influence the treatment choice. Antifibrinolytics reduce the risk of rebleeding by about 40%, and their temporary use (<72 hours) should be considered for patients at high risk of rebleeding, particularly if there is any delay in securing the aneurysm.

Hydrocephalus is another common early complication of SAH, affecting approximately 20% of patients. Ventricular enlargement may first be evident only by mild dilatation of the temporal horns of the lateral ventricles. Hydrocephalus typically presents as gradual impairment of consciousness over hours, and patients may have limited vertical gaze, particularly when attempting to look upward. Alternatively, patients might present comatose at the initial evaluation because of massive hydrocephalus. Acute hydrocephalus responds rapidly to ventricular drainage and can be accompanied by striking clinical improvement.

Intracranial hypertension in comatose patients can be caused by hydrocephalus, global edema, or space-occupying hemorrhage. In patients with poor clinical grades, ICP and cerebral perfusion pressure (CPP) should be monitored. (Recall: CPP = mean arterial pressure – ICP.) Although the preferred CPP is not established with high-level evidence, most clinicians aim to keep it less than 60 mm Hg in patients with poor clinical grades. (For details on the management of ICP, see Chapter 2, "Principles and Management of Alterations in Intracranial Pressure.")

Table 4.2 • Prevention and Management of Complications Related to Subarachnoid Hemorrhage

Complication	Timing	Treatment Strategies
Rebleeding	Early	Secure aneurysm (coil, clip, flow-diverting stent) Antifibrinolytics if securing of aneurysm is delayed
Hydrocephalus	Often early, but may be delayed	External ventricular drain Ventriculoperitoneal shunt
Vasospasm	Delayed	Triple-H therapy (hydration, hypervolemia, hemodilution) Nimodipine 60 mg every 4 h
Hyponatremia	Delayed	Hypertonic saline Fludrocortisone
Seizure	Any time	Antiseizure medication No prophylaxis recommended

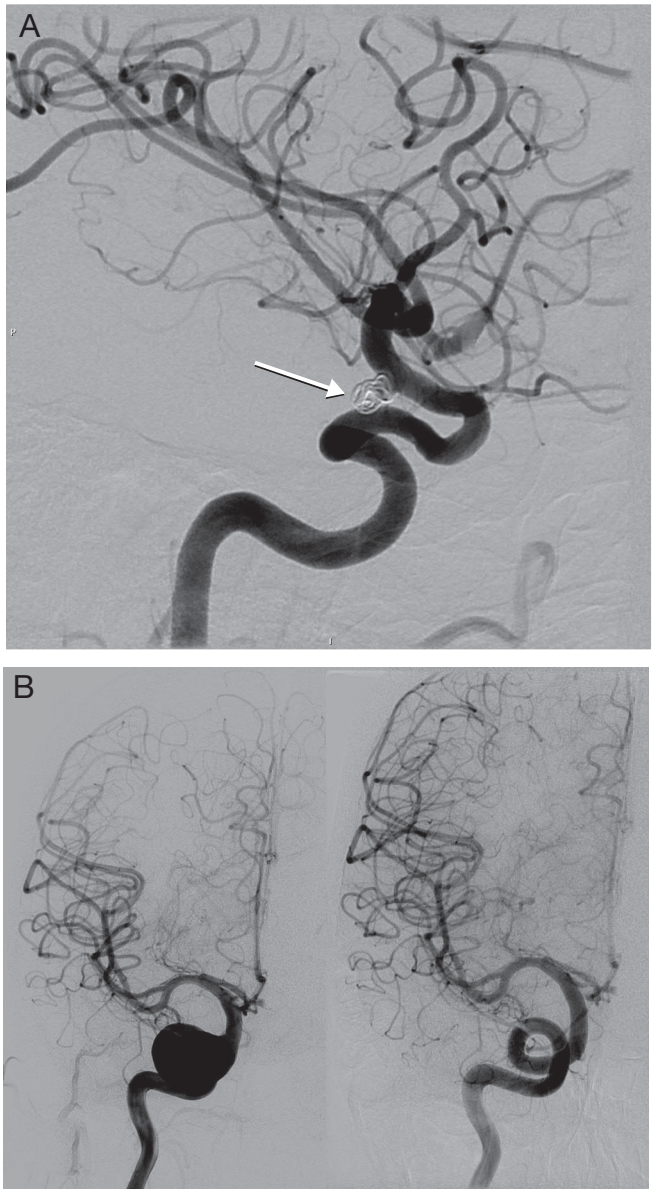


Figure 4.3 *Aneurysmal Endovascular Treatment, Shown on Angiography.*
A, Aneurysm of the posterior communicating segment treated with standard coiling (arrow). B, Aneurysm treated with a flow-diverting stent. Left, Before treatment. Right, After stent placement.
(Courtesy of Giuseppe Lanzino, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

After treatment of the aneurysm, one of the main goals of management of aSAH is to monitor for delayed vasospasm and delayed cerebral ischemia (DCI) and, potentially, to intervene to limit secondary brain injury. Enteral nimodipine, a calcium channel antagonist, reduces the frequency of DCI and poor functional outcome after aSAH. The standard treatment is to prescribe 60 mg enterally every 4 hours for 21 days. Intravenous calcium channel antagonists are expensive, unproven, and possibly even harmful if hypotension is precipitated. The precise mechanism by which nimodipine reduces DCI is not known, but it does *not* decrease angiographic vasospasm. The peak time for vasospasm and DCI is 4 to 14 days after aSAH. Angiographic vasospasm occurs in about two-thirds of patients, but only half of these are symptomatic. The best independent predictor for the development of vasospasm is the total volume of subarachnoid blood on the initial head CT. Patients with a poor clinical grade, intraventricular hemorrhage, and a history of cigarette smoking tend to have more severe vasospasm. DCI occurs in up to 33% of patients and is characterized by neurologic deficits that appear gradually over hours. This might manifest as focal deficits (25%), decreased level of consciousness (25%), or both (50%).

Transcranial Doppler ultrasonography is the most widely accepted method used to screen for vasospasm. Conventional cerebral angiography is the standard for diagnosing arterial vasospasm, but the procedure is costly and invasive. The routine use of serial conventional angiography to screen for vasospasm after aSAH is not recommended.

For treatment of vasospasm, it is crucial to ensure adequate intravascular volume and avoid hypovolemia. Triple-H therapy (hypertension, hypervolemia, and hemodilution) has been traditionally advocated, although it has never been tested in a randomized controlled trial. Hypervolemia, in particular, is questioned because of the propensity of inducing pulmonary edema. Induced hypertension (with use of vasopressors or inotropes) is the most effective of the 3 options. For patients with deficits that do not improve with hemodynamic augmentation, endovascular treatments for vasospasm (angioplasty or intra-arterial infusions of calcium channel blockers) should be considered.

- Enteral nimodipine, a calcium channel antagonist, reduces the frequency of DCI and poor functional outcome after aSAH.

Systemic Complications

The rupture of an intracranial aneurysm not only can cause dramatic neurologic symptoms and signs but also may produce serious systemic alterations.

Neurogenic Pulmonary Edema

In approximately 20% of patients (most with poor-grade aSAH), neurogenic pulmonary edema will develop; this is best treated with high levels of positive end-expiratory pressure.

Cardiac Complications

Myocardial stunning can also occur and is thought to be due to a massive release of catecholamines. Signs of cardiogenic shock—hypotension, cool skin, oliguria—should prompt this consideration, and transthoracic echocardiography and inotropes are likely needed. Electrocardiographic abnormalities such as T-wave inversions, ST-segment depression or elevation, prolonged QT interval, and mildly increased serum troponin levels may be present.

Hyponatremia

Hyponatremia occurs in 20% to 40% of patients with aSAH. This is most commonly caused by cerebral salt-wasting syndrome. Therapies consist of strict avoidance of free water and hydration with saline solutions (low rates of hypertonic saline may be needed). Oral fludrocortisone acetate up to 0.2 mg twice daily can be a useful adjunct therapy.

Seizures

Seizures occur in a minority of patients. Before the aneurysm is secured, seizures are often the expression of a rebleeding episode. After treatment of an aneurysm, the incidence of seizures is 3% to 5%. The frequency of seizures is twofold higher with surgical clipping than with endovascular treatment. Routine prophylactic antiepileptic treatment is controversial, and it probably is not necessary for most patients. If antiepileptics are prescribed, fosphenytoin should be avoided because it has been associated with worse functional outcomes and more cognitive impairment in patients with aSAH.

- After treatment of an aneurysm, the incidence of seizures is 3% to 5%. The frequency of seizures is twofold higher with surgical clipping than with endovascular treatment. Routine prophylactic antiepileptic treatment is controversial, and it probably is not necessary for most patients.

Prognosis

One of the most important predictors of clinical outcome is the patient's clinical condition at the time of hospital admission. Yet, 20% of patients who are comatose at admission recover without major cognitive or physical deficits. The chance of a patient surviving an aSAH has

increased by nearly 20% during the past 3 decades, an improvement that may be due to the emergence of dedicated neurologic-neurosurgical intensive care units, emphasis on early treatment of the aneurysm, and advances in endovascular therapies. However, survivors of aSAH commonly experience cognitive deficits, particularly with executive function and memory, which can lead to difficulties with activities of daily living and poorer quality of life. The percentage of patients who regain independence within the first year after aSAH is 30% to 50%.

- The percentage of patients who regain independence within the first year after aSAH is 30% to 50%.

5 Anoxic-Ischemic Encephalopathy[a]

JENNIFER E. FUGATE, DO; EELCO F. M. WIJDICKS, MD, PHD

Introduction

Anoxic-ischemic brain injury occurs when there is a complete lack of blood flow to the brain. Neurologists often find this in comatose patients who have had a cardiac arrest and prolonged attempts at cardiopulmonary resuscitation. Anoxic-ischemic injury also may occur in patients with primary respiratory arrest or severe hypoxemia (eg, asphyxia, anaphylaxis, drug intoxication), but it is less well understood in these circumstances.

Pathophysiology

The brain is very susceptible to ischemic damage because of its high metabolic demand and reliance on a continuous supply of oxygen and glucose from the circulation. Animal studies have shown that brain concentrations of glucose, adenosine triphosphate, and phosphocreatine decrease almost immediately after the cessation of blood flow to the brain and are nearly completely depleted within 10 minutes. Cell death occurs by the initiation of intracellular cascades involving modulatory and degradation signals. In addition, the excitotoxic neurotransmitter glutamate is released and destructive enzymes such as lipases, proteases, and nucleases are activated, processes that cause further tissue destruction.

Even after blood flow has been successfully restored, brain circulation continues to be impaired. A short-lived period of hyperemia is quickly replaced by a longer lasting period of hypoperfusion at the level of the microcirculation (the no-reflow phenomenon). Furthermore, reperfusion injury—which is characterized by excess free radical formation, nitric oxide toxicity, and further glutamate release—also occurs during this time. The restoration of blood flow can lead to worsening brain edema and microhemorrhages.

Currently, the only clinically beneficial intervention that has proved to be successful is the application of induced hypothermia, which inhibits apoptosis and reduces free radical formation and excitatory neurotransmitters.

Pathology

On gross examination of the brain affected by anoxic-ischemic injury, diffuse cerebral edema with loss of gray-white matter differentiation may be found. Cortical laminar necrosis, watershed infarctions, and hippocampal sclerosis are other abnormalities that may be found, particularly in the subacute or more chronic stages. On microscopic evaluation, neuronal loss and gliosis of vulnerable areas are seen. These areas include the CA1 region of the hippocampus (Sommer sector), the basal ganglia, thalami, cerebellar Purkinje cells, and the cortex. The vulnerability of these areas may be explained by the presence of receptors for excitatory neurotransmitters or the high metabolic demands of these neurons. Pyknotic nuclei and eosinophilic cytoplasm ("red, dead neurons") are early pathologic characteristics of ischemic neurons. Figure 5.1 shows exemplary features of anoxic-ischemic injury.

- Microscopic evaluation may show neuronal loss and gliosis of vulnerable areas; these include the CA1

[a] Portions previously published in Wijdicks EFM, Fugate JE. Anoxic-ischemic encephalopathy. In: Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors. Bradley's neurology in clinical practice, 6th ed. Philadelphia (PA): Elsevier/Saunders; c2012. p. 1314–20. Used with permission.

Abbreviation: EEG, electroencephalography

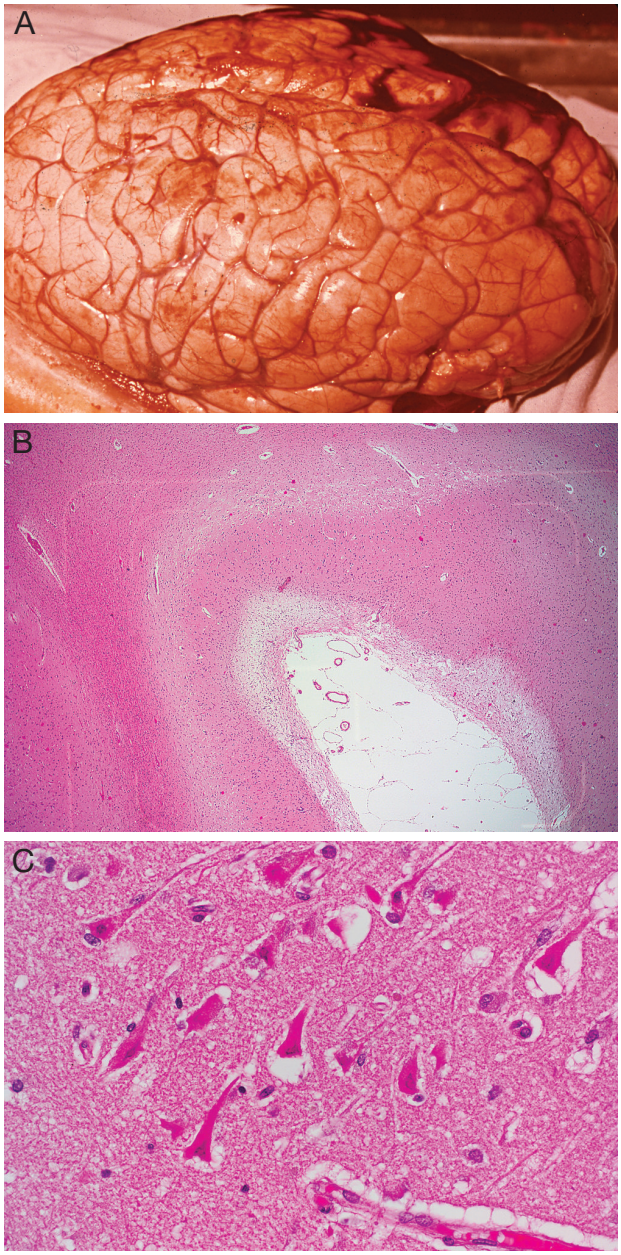


Figure 5.1 *Anoxic Brain Injury.*
A, Gross autopsy specimen shows diffuse global edema of the brain after a cardiac arrest. Microscopic examination showed laminar necrosis of the cerebral cortex (B) and ischemic neurons in CA1 sector of the hippocampus (C). Ischemic hippocampal neurons have pyknotic nuclei and densely eosinophilic cytoplasm; most of these neurons have nuclei that have become more eosinophilic and appear to be assimilated into the background of eosinophilic cytoplasm. (Adapted from Flemming KD. Cerebrovascular diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.)

region of the hippocampus (Sommer sector), the basal ganglia, thalami, cerebellar Purkinje cells, and the cortex.

Clinical Manifestations

The clinical manifestations of anoxic-ischemic encephalopathy are heterogeneous, and, in general, they correlate with the duration of the ischemic event. With very brief episodes, patients may present with only a syncopal episode, which can be associated with clonic movements ("convulsive syncope") and may be mistaken for seizure activity. With more significant episodes, seizures and altered consciousness occur.

Neurologists are often asked to evaluate patients who remain comatose after cardiopulmonary resuscitation and to provide a prognosis. In the most severe cases, patients remain comatose for days or weeks and never regain meaningful consciousness, transitioning to a persistent vegetative state or minimally conscious state. Other patients, however, awaken early (within 1–2 days) and can achieve a favorable functional outcome. The current literature does not provide criteria to predict a good outcome in patients who are comatose after cardiac arrest, but clinical signs that may be promising include localization of a pain stimulus or visual fixation and tracking. For patients who do not receive therapeutic hypothermia and do not awaken within the first 24 hours, the mortality rate is very high, approaching 80% to 90%.

The clinical examination is focused on brainstem reflexes, presence of generalized myoclonus, and motor responses to noxious stimuli.

Brainstem reflexes are often normal because the brainstem is relatively resistant to anoxic-ischemic injury compared with the cortex. Absent pupil responses or corneal reflexes within days 1 to 3 are invariably indicators of a poor prognosis. Eye movement abnormalities such as sustained upward gaze are also probably indicative of substantial global brain injury.

An important clinical sign is myoclonus status epilepticus, defined as continuous jerking that involves the facial muscles, limbs, and abdominal muscles. Myoclonic status can be considered an agonal phenomenon, a reflection of severe brain injury, rather than a treatable entity, and it indicates a very poor prognosis. Myoclonic status epilepticus should be differentiated from a few occasional myoclonic jerks, which can be seen on rewarming in patients who were treated with hypothermia and which do not preclude a favorable outcome.

In patients not treated with hypothermia, if the motor response to pain is extensor posturing or is absent at day 3 after resuscitation, the prognosis is poor. For those who underwent a hypothermia protocol, several studies have suggested that this motor response at day 3 is not reliable

for prognosticating, likely because of the greater amounts of sedatives and analgesics that accompany hypothermia protocols. During examination of a patient with anoxic-ischemic encephalopathy, regardless of whether hypothermia was used, it is imperative to exclude confounders before relying on the clinical examination for prognostication. One should keep in mind that a lack of motor response in the upper extremities can occur in the man-in-the-barrel syndrome that occurs after bilateral border zone infarction in the anterior and middle cerebral watershed regions. Involvement in this territory will result in prolonged weakness of the arms with normal findings in the lower limbs. Affected patients often have better outcomes than others with anoxic-ischemic injury. If the anoxic injury affects the watershed regions between the middle cerebral and posterior cerebral arterial territories, patients may be affected by Balint syndrome (asimultagnosia, optic ataxia, ocular apraxia) and a transcortical sensory aphasia.

Patients awakening from coma after resuscitation are not uncommonly agitated and may have cognitive impairment. An amnestic syndrome is the most common because of the sensitivity of the hippocampi to ischemic injury. Movement disorders may be present in patients who regain consciousness. In some, a significant action and stimulus-induced myoclonus develops that may be associated with ataxia (Lance-Adams syndrome). Damage to basal ganglia can cause dystonia or parkinsonism that is often resistant to pharmacologic treatments.

- Absent pupil responses or corneal reflexes within days 1 to 3 are invariably indicators of a poor prognosis.
- Myoclonic status can be considered an agonal phenomenon, a reflection of severe brain injury, rather than a treatable entity, and it indicates a very poor prognosis.

Treatment

Induced hypothermia has been shown to reduce mortality and improve neurologic outcomes in adults with cardiac arrest. The general practice involves cooling patients as soon as feasible to a target temperature of 32° to 34°C and maintaining it for 24 hours. This therapy has become the standard of care for patients with out-of-hospital cardiac arrests presenting with "shockable" rhythms (ventricular fibrillation or pulseless ventricular tachycardia), but it is less well proved in patients with cardiac arrests resulting from asystole or pulseless electrical activity.

- Induced hypothermia has been shown to reduce mortality and improve neurologic outcomes in adults with cardiac arrest.

Prognosis

Table 5.1 summarizes the factors associated with a poor prognosis for patients who are comatose after cardiac arrest.

The neurologic examination is crucial for determining prognosis. Two important factors indicating a poor prognosis in patients *not* receiving therapeutic hypothermia are absent or extensor motor response on day 3 and absent pupillary or corneal reflexes on day 3. However, examination in intensive care units within 72 hours can be confounded by multisystem organ failure, metabolic abnormalities, and lingering effects of sedating medications. Thus, interpreting clinical examination signs must be done with caution and, often, supplemented with further testing.

Several diagnostic tests may be useful to supplement the neurologic examination. Neuroimaging is potentially useful for prognosis in anoxic-ischemic injury; however, the literature is sparse, and available studies have been limited by relatively small sample sizes. Magnetic resonance imaging with diffusion-weighted sequences can determine the extent of anoxic-ischemic injury (Figure 5.2). Quantitative diffusion-weighted imaging and whole-brain apparent diffusion coefficient values have been shown to

Table 5.1 • Factors Associated With Poor Outcome in Patients With Anoxic-Ischemic Encephalopathy After Cardiac Arrest

Factor	Timeframe
Anoxia duration	>8–10 minutes
Duration of CPR	>30 minutes
Myoclonic status epilepticus	Day 1
Absent pupillary or corneal reflexes	Days 1–3
Motor response extensor or none	Day 3 for non-TH patients; possibly longer for TH patients
Absent N20 responses on SSEP bilaterally	Days 1–3
Serum NSE >33 μg/L	Days 1–3 for non-TH patients
EEG with nonreactive background	Not specified
EEG with burst-suppression and generalized epileptiform activity	Not specified
Loss of gray-white matter differentiation on head CT	Not specified
Widespread cortical restricted diffusion on brain MRI	Not specified

Abbreviations: CPR, cardiopulmonary resuscitation; CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; NSE, neuron-specific enolase; SSEP, somatosensory evoked potential; TH, therapeutic hypothermia.

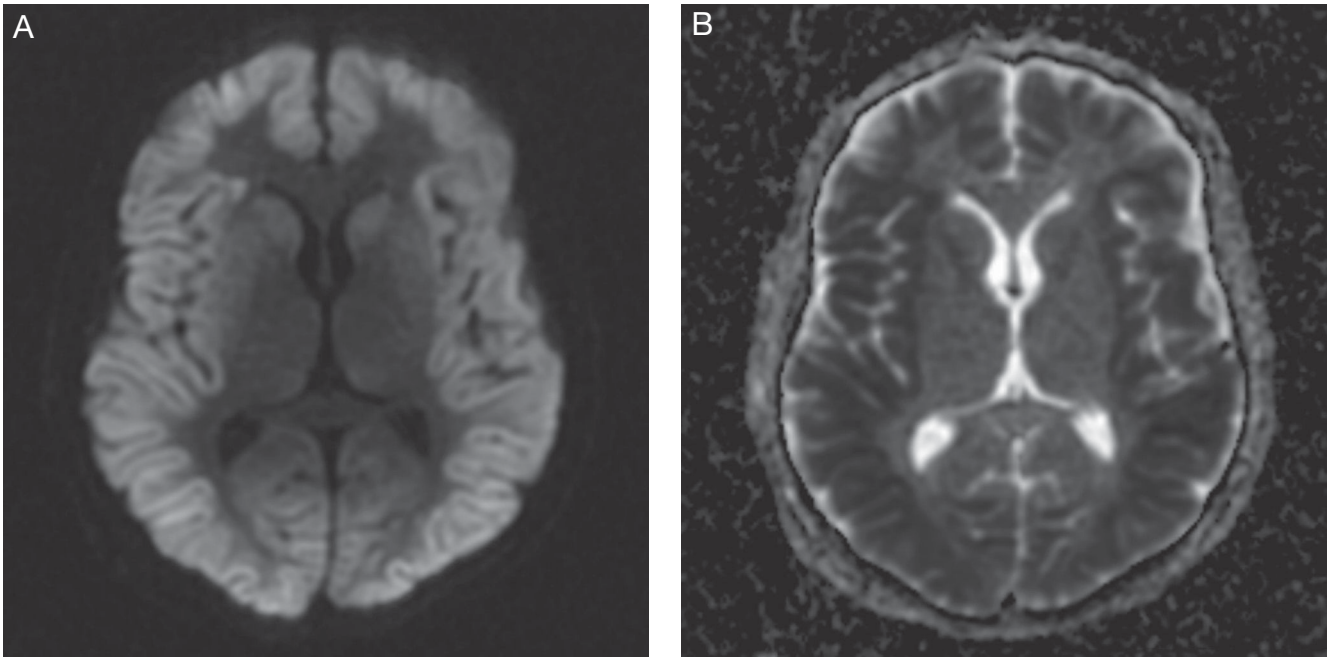


Figure 5.2 *Magnetic Resonance Imaging in Anoxic-Ischemic Encephalopathy.*
Diffusion-weighted (A) and apparent diffusion coefficient (B) sequences show diffuse restricted diffusion affecting the entire cortex, reflecting cortical laminar necrosis, in a patient with anoxic injury after cardiac arrest.

correlate with outcomes. Computed tomography results are often normal but may show cerebral edema in more extreme cases. Disappearance of the gray-white junction is associated with failure to awaken.

In addition to imaging, neurophysiologic studies such as electroencephalography (EEG) and somatosensory evoked potentials are often used for prognosis in anoxic-ischemic injury. The "malignant patterns" on EEG include burst suppression, alpha coma with periodic sharp waves and spikes, and isoelectric or a markedly suppressed EEG. Nonreactivity of the EEG background is associated with poor prognosis. With the increasing use of therapeutic hypothermia (which requires sedation and neuromuscular blockade), there has been interest in continuous EEG monitoring during cooling, but it is not clear whether this costly test provides additional information that cannot be gained with spot EEG. Although longer monitoring will almost certainly increase detection of epileptiform activity, there is no evidence that earlier detection and treatment of seizures in this setting alter outcome. Somatosensory evoked potentials are not influenced by drugs, temperature, or acute metabolic derangements and are often obtained in a comatose patient after cardiac resuscitation between days 1 and 3. Somatosensory evoked potentials require stimulation of the median nerve that then results in a potential at the brachial plexus, cervical spinal cord, and, finally, bilateral cortex potentials (N20). If both N20 components are absent, the prognosis is invariably poor and the patient will likely never regain consciousness.

There has been interest in finding a serum biomarker that could indicate the degree of brain injury and potentially assist in prognostication in comatose survivors. The most studied have been serum neuron-specific enolase and S100. In patients who were not treated with hypothermia, a serum neuron-specific enolase level more than 33 μ/L at days 1 to 3 after cardiac arrest is an accurate predictor of poor outcome. However, several studies have confirmed that this cutoff level is not reliable for patients who have undergone hypothermia protocols. Measuring serial neuron-specific enolase levels in these patients and following trends may be more informative than a single isolated value, but this approach has not been sufficiently studied to make firm recommendations.

- Table 5.1 summarizes the factors associated with a poor prognosis for patients who are comatose after cardiac arrest.
- Two important factors indicating a poor prognosis in patients *not* receiving therapeutic hypothermia are absent or extensor motor response on day 3 and absent pupillary or corneal reflexes on day 3.

6 Traumatic Brain Injury

JEFFREY T. JACOB, MD; EELCO F. M. WIJDICKS, MD, PHD

Introduction

Traumatic brain injury (TBI) remains the leading cause of death and long-term disability in people younger than 40 years worldwide. More than a million patients present to emergency departments with this condition in the United States each year; several hundred thousand are admitted for management. Fortunately, over the years the incidence of TBI has declined. Enforcing the use of seat belts and improved helmet laws have reduced the number of serious injuries. Although most TBIs occur as a result of motor vehicle accidents, falls, and gunshot or stab injuries, the increasing number of elderly patients taking anticoagulation or antiplatelet drugs has affected the outcome of TBI. Age is generally recognized as the strongest predictor of outcome after TBI, even after adjustment for potential confounders. Current evidence suggests a linear relationship between increasing age and worsening outcome after TBI. The mechanisms of injuries can be summarized as follows: 1) contact forces, 2) acceleration or deceleration forces, 3) cellular responses to injury, and 4) secondary insults from systemic complications.

This chapter reviews the diagnostic approach to head trauma and prognosis in brain injury and addresses specific conditions such as concussions and brain hemorrhage.

Traumatic Brain Injury

Diagnostic Approach to Patients With Head Trauma

Universal implementation of advanced trauma life support protocols has helped standardize trauma care and improve prehospital and primary evaluation and patient outcome. Rapid stabilization and transfer of a patient to a trauma care facility are critical to improve chances of survival. Initial management is based on advanced trauma life support guidelines from the American College of Surgeons, which include airway (creating or maintaining airway with neutral cervical spine precautions), breathing (assessing oxygen saturation and assessing and treating for chest injuries), circulation, disability, and exposure. Patients should also be evaluated for external signs of basal skull fractures such as periorbital ecchymoses (raccoon eyes), postauricular ecchymoses (Battle sign), cerebrospinal fluid rhinorrhea or otorrhea, facial fractures, and physical signs of spine trauma. Patients should be immobilized in a cervical collar, and evaluations should follow proper spine precautions until appropriate trauma providers determine the status of the cervical spine.

Radiographic imaging should be done on the basis of a patient's mechanism of injury or clinical condition and should include noncontrast computed tomography (CT) of the head and spinal radiography. Vascular imaging using CT angiography may be done depending on clinical or radiographic suspicion of a traumatic dissection or vascular channel injury.

All patients should undergo basic hematologic and electrolyte profile testing, specifically to assess hemoglobin, platelet count, and serum sodium values. Additionally, laboratory evaluation should include serum prothrombin time (international normalized ratio) and activated partial thromboplastin time. If a patient is receiving anticoagulants, reversal is necessary. Neurosurgical consultation should be obtained to guide decisions in conservative versus operative management.

Abbreviations: CT, computed tomography; DAI, diffuse axonal injury; EDH, epidural hematoma; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; SDH, subdural hematoma; TBI, traumatic brain injury

Management of Patients With Head Trauma

Comatose patients with severe head injury should have intracranial pressure monitoring (see Chapter 2, "Principles and Management of Alterations in Intracranial Pressure") in the presence of abnormal CT results and in the absence of a surgical lesion. Aggressive medical management of increased intracranial pressure includes head elevation to 30° or more, sedation and analgesia, short-term hyperventilation, and hyperosmolar therapy with mannitol or hypertonic saline. Corticosteroids do not improve outcome or reduce intracranial pressure in trauma.

Neurosurgical intervention is largely guided by the CT findings, and multiple CT scans are necessary to accurately judge an evolving contusion, epidural hematoma, or subdural hematoma or brain edema that may need decompression. Failure to aggressively control intracranial pressure to less than 20 mm Hg is common and, particularly in the first hours, could lead to early secondary brainstem injury. Decompressive surgery is often an adequate treatment for increasing the cranial pressure, and the threshold should be generally low.

Prognosis After TBI

Much research has been done to identify early predictors of mortality and functional outcome, as assessed by the Glasgow Outcome Scale on admission, after moderate or severe TBI. Studies have shown increased intracranial pressure, increased age, and hypotension among other factors that portend an unfavorable outcome. Recently, prognostic analysis and statistical modeling have shown great potential in TBI, both for diagnosis and prognosis (eg, International Mission for Prognosis and Clinical Trial, IMPACT). Although population-based studies can be a tremendous asset when counseling families, making treatment decisions, or allocating resources, neurotrauma patients can be very heterogeneous. Optimal management depends on a synthesis of the clinical findings for each individual patient and then refining according to the clinical judgment of the treating physician.

- Age is generally recognized as the strongest predictor of outcome after TBI, even after adjustment for potential confounders.
- Corticosteroids do not improve outcome or reduce intracranial pressure in trauma.
- Failure to aggressively control intracranial pressure to less than 20 mm Hg is common and, particularly in the first hours, could lead to early secondary brainstem injury.
- Studies have shown increased intracranial pressure, increased age, and hypotension among other factors that portend an unfavorable outcome.

Specific Conditions

Concussion

Definition

Concussion is the mildest form of injury (Glasgow Coma Scale [GCS] 13–15). In its classic form, patients experience a transient alteration of mental status, with or without loss of consciousness, followed by a rapid return to a normal state of alertness. Results of CT are generally negative. Repeated concussions can result in some degree of permanent neurologic impairment.

Symptoms

Patients with concussion may have headache, nausea, vomiting, seizures, or fixed neurologic deficits that can last for several hours to days, referred to as a postconcussion syndrome. Additionally, patients can experience dizziness, balance problems, fatigue, visual changes, insomnia, hypersomnia, photophobia, phonophobia, emotional lability, inattention, disorientation, and slowed reaction time, among other symptoms, as part of the postconcussion syndrome.

Diagnosis and Management

The nonspecific nature of these symptoms makes the diagnosis of concussion difficult and, perhaps, controversial. These sequelae have been tentatively attributed to a transient disturbance in neuronal function as the brain enters a hypermetabolic state, even up to 2 weeks after the initial injury. Although no specific therapy is advocated for postconcussion symptoms, most patients return to their baseline with reassurance and symptomatic treatment. For patients who experience a concussion, once the period of confusion has passed, the results of various investigations are negative, and someone reliable is available to observe the patient during the ensuing 24 hours, the patient may be dismissed from the emergency department. If the patient remains altered, there are positive radiographic findings, a reliable observer is not available, or additional problems occur, the patient should be admitted to the hospital for observation.

A major problem is to determine who needs CT; most patients, whether adult or children, will undergo CT and may not need it. The New Orleans criteria (Box 6.1) are highly sensitive and specific for identifying patients with what appears to be mild TBI but who have clinically important intracranial lesions. This model includes 7 variables; if all 7 are absent, CT is not needed. The absence of all 7 criteria has a sensitivity of 100% for detecting intracranial injury, defined as epidural hematoma, subdural hematoma, depressed skull fracture, cerebral contusion, or subarachnoid hemorrhage. However, if 1 factor is present, the specificity is only 24%.

Box 6.1 • Clinical Features in the New Orleans Criteria [a]

- Headache
- Vomiting
- Age >60 years
- Drug or alcohol intoxication
- Persistent anterograde amnesia (deficits in short-term memory)
- Evidence of traumatic soft-tissue or bone injury above clavicles
- Seizure (suspected or witnessed)

[a] If all 7 features are absent, head CT is not required.

- In the classic form of concussion, patients experience a transient alteration of mental status, with or without loss of consciousness, followed by a rapid return to a normal state of alertness. Results of CT are generally negative.
- If the patient remains altered, there are positive radiographic findings, a reliable observer is not available, or additional problems occur, the patient should be admitted to the hospital for observation.

Skull Fractures

Definition

Skull fractures are seen radiographically as linear fracture lines with distinct margins (Figure 6.1). Unlike vascular markings, the lines generally do not taper or branch. A fracture that produces multiple fragments of bone is termed *comminuted*. Skull fractures may result in tearing of the underlying dura and brain that causes extra-axial hemorrhages such as epidural or subdural hematomas or intra-axial hemorrhages such as focal contusions or traumatic subarachnoid hemorrhage.

Location and Potential Symptoms

Skull fractures may result in various symptoms depending on the location (Figure 6.2). Basilar skull fractures most commonly involve the petrous portion of the temporal bone, anterior cranial fossa, or posterior or lateral skull base. When there is violation of aerated sinuses in the skull along with dural lacerations, patients can experience cerebrospinal fluid otorrhea or rhinorrhea. Avulsion of olfactory fibrils from the cribriform plate by the shearing forces of a blunt impact rarely cause rhinorrhea in the absence of a fracture. Fracture of the posterior wall of the frontal sinus may allow cerebrospinal fluid to track through the frontonasal duct. Fractures through the petrous bone that extend to the middle ear may lead to otorrhea if the tympanic membrane is torn or to otorhinorrhea if leakage occurs via the eustachian tube into the nasopharynx. Cerebrospinal fluid can be assayed for β2-transferrin, which is unique to cerebrospinal fluid (and the vitreous of the eye).

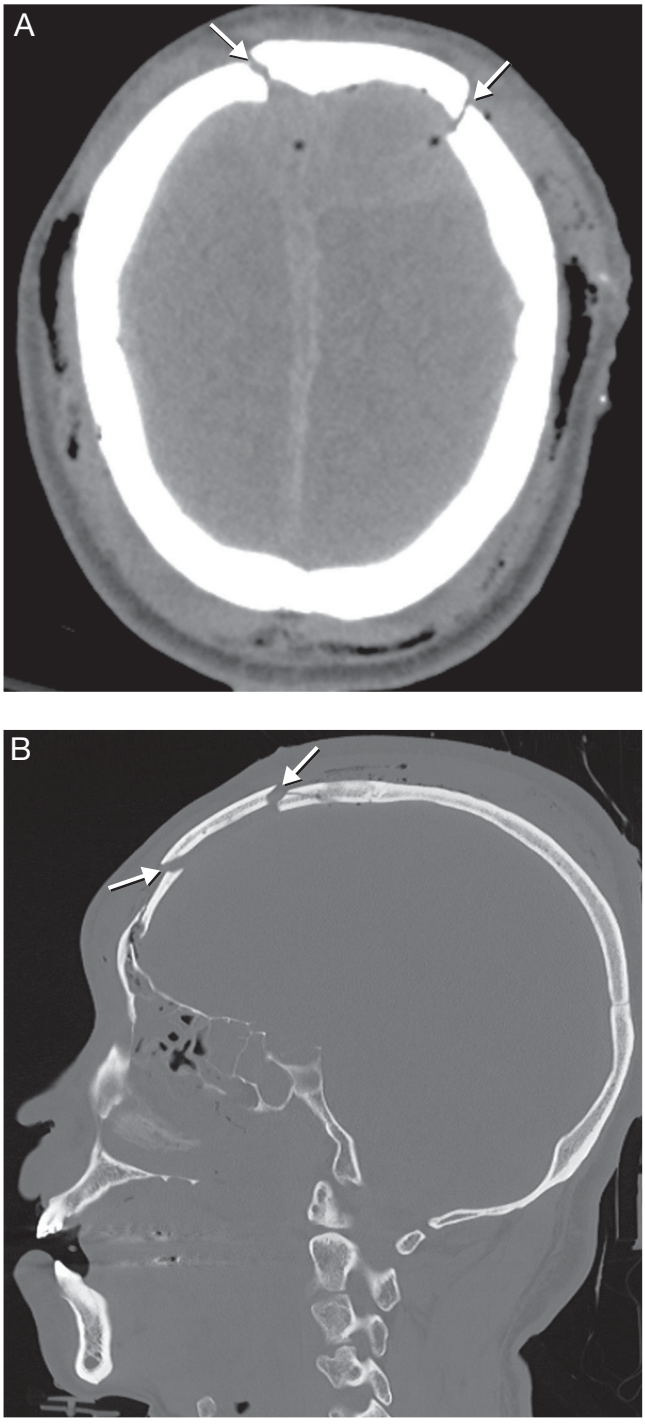


Figure 6.1 *Skull Fracture on CT.*
A and B, Anteriorly displaced fracture of the frontal bone with extension superiorly into the right coronal and sagittal sutures.

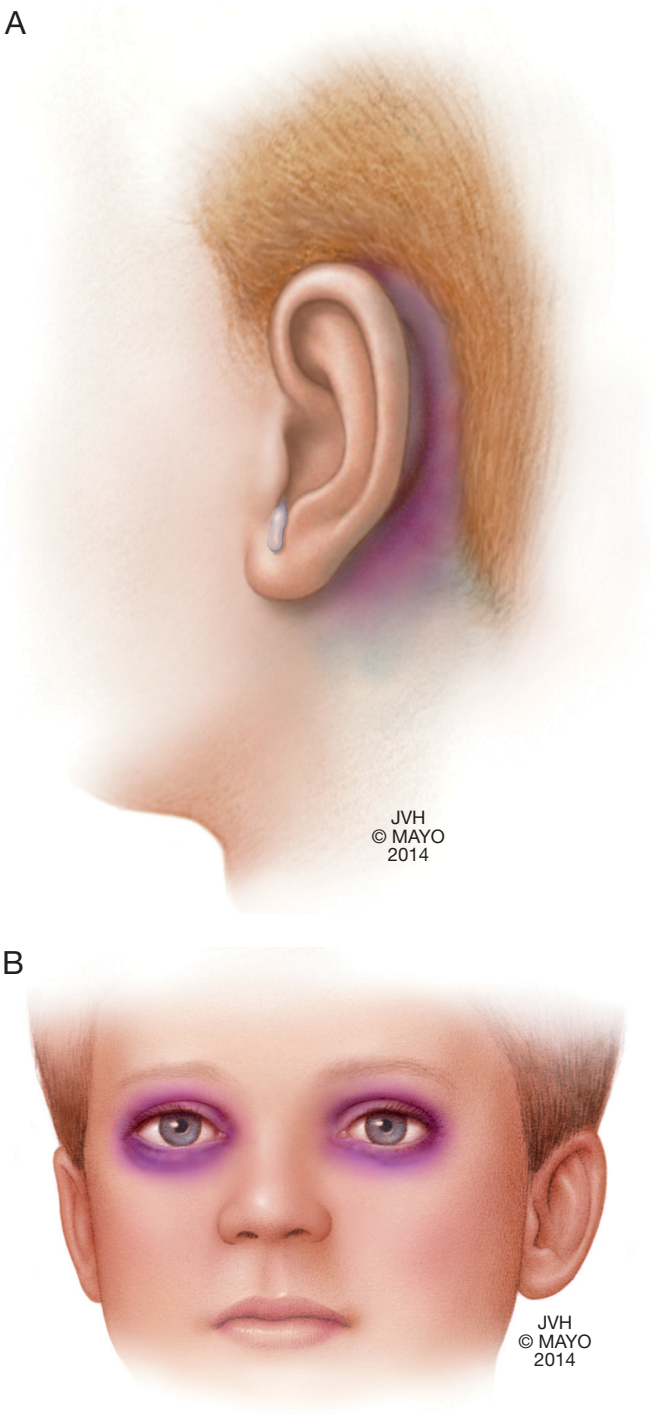


Figure 6.2 *Basilar skull fractures involve at least 1 of 5 bones that make up the skull base: cribriform plate, orbital plate of frontal bone, temporal bone, and sphenoid and occipital bones. Patients with a basilar skull fracture may have ecchymosis of the mastoid region (Battle sign) (A) or otorrhea (temporal bone fracture) (A). Patients with a basilar skull fracture or anterior or middle fossa facial trauma may also have periorbital ecchymosis (raccoon eyes) (B).*
(Used with permission of Mayo Foundation for Medical Education and Research.)

Management

Prophylactic antibiotics are no longer recommended in patients with cerebrospinal fluid leaks. Closed, nondisplaced fractures can be managed conservatively. Open, depressed fractures generally require open elevation and débridement.

- In skull fractures, cerebrospinal fluid can be assayed for β2-transferrin, which is unique to cerebrospinal fluid.
- Open, depressed fractures generally require open elevation and débridement.

Epidural Hematoma

Definition and Epidemiology

Epidural hematomas (EDHs) occur in the minority of major TBIs but do account for a large proportion of fatal head injuries. They are most common in patients younger than 50 years, particularly the pediatric population. EDHs result from vascular injuries to dural vessels or from skull fractures. The source is usually arterial (85%), but they may follow injury to meningeal veins, dural sinuses, or diploic vessels in the skull. The temporal fossa EDH is the most common and results from damage to the middle meningeal artery.

Symptoms

The injury causes an initial period of unconsciousness; subsequently, because the dura mater is quite adherent to the skull, accumulation of blood is delayed and a lucid interval follows, during which the patient's neurologic function is apparently normal. As the lesion enlarges, the level of consciousness rapidly deteriorates. This classic and long-recognized sequence of clinical signs occurs only in a minority of patients. As the hematoma enlarges, the temporal lobe is pushed medially, causing herniation of the uncus and mesial structures over and through the tentorial notch. The uncal herniation syndrome is characterized by a decreasing level of consciousness, early dilatation of the ipsilateral pupil, and hemiparesis. The hemiparesis is usually contralateral because of the decussation of the descending pyramidal tracts; however, if the opposite cerebral peduncle is compressed against the tentorial edge (Kernohan notch), ipsilateral hemiparesis may result.

Diagnosis and Management

CT of the head will show an EDH, often a convex shape that does not cross suture lines (Figure 6.3). Surgical evacuation is most often required after stabilization and reversal of a coexisting coagulopathy. Patients with small EDHs, often of venous type, who have normal results on neurologic examination, may be observed in a monitored setting.

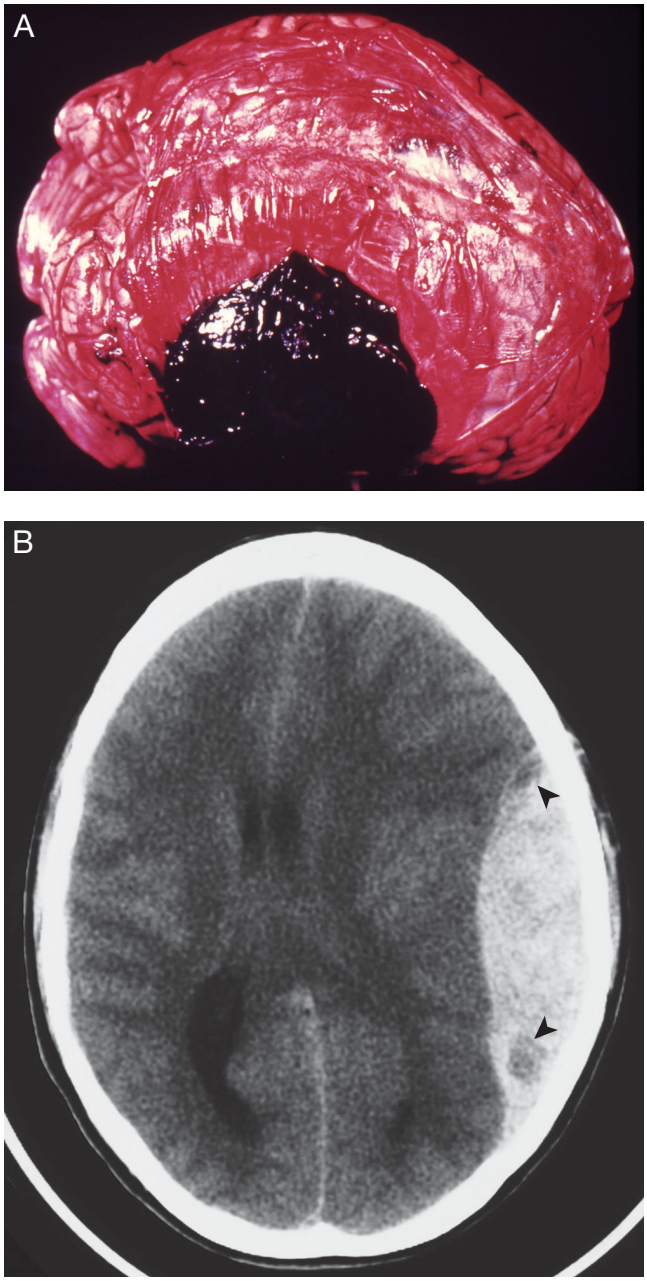


Figure 6.3 *Epidural Hematoma.*
A, Gross specimen. B, On computed tomography, epidural hematoma appears as a biconvex hyperdense lesion, often with substantial mass effect (as shown here). Small low-density areas within the hemorrhage (arrowheads) are likely hyperacute, unretracted, semiliquid blood building up rapidly.
(Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

- EDHs result from vascular injuries to dural vessels or from skull fractures.
- The temporal fossa EDH is the most common and results from damage to the middle meningeal artery.
- The injury causes an initial period of unconsciousness; subsequently, because the dura mater is quite adherent to the skull, accumulation of blood is delayed and a lucid interval follows, during which the patient's neurologic function is apparently normal. As the lesion enlarges, the level of consciousness rapidly deteriorates.
- Surgical evacuation is most often required after stabilization and reversal of a coexisting coagulopathy.

Acute Subdural Hemorrhage

Definition and Epidemiology

Subdural hemorrhage (SDH) refers to hemorrhage between the arachnoid and dura. Acute SDHs most commonly occur with assaults or falls and less commonly after motor vehicle accidents (Figure 6.4). Rarely, acute SDH may occur spontaneously (or after minor trauma) in patients receiving chronic anticoagulation therapy or after rupture of a cerebral aneurysm. Most acute SDHs result from venous vascular injury at the brain surface. Less commonly, they are in the interhemispheric fissure or along the tentorium.

Symptoms

Common presenting symptoms are similar to those of EDH. Frequently associated cerebral or brainstem contusions account for a very high rate of mortality (50%). Cerebral ischemia plays a critical role in the pathologic effects of SDH and has been demonstrated in postmortem studies. The mechanisms responsible for ischemia after SDH are poorly understood but are likely due to compressive effects of the hematoma and increased intracranial pressure with resultant compromised cerebral perfusion pressure.

Management

Symptomatic acute SDHs, with more than 1 cm at the thickest point and more than 5 mm of midline shift, should be given strong consideration for surgical evacuation after stabilization and reversal of coagulopathy, if present. Postoperative seizures are common.

- Symptomatic acute SDHs, with more than 1 cm at the thickest point and more than 5 mm of midline shift, should be given strong consideration for surgical evacuation.

Subacute and Chronic SDH

Definition

A subacute to chronic SDH is one that is delayed from the time of injury and shows subacute to chronic blood products

on imaging. Chronic SDH is most common in elderly patients and long-standing alcoholics, who usually have some degree of brain atrophy, with a resultant increase in size of the subdural space. Patients receiving chronic anticoagulation therapy or those who harbor blood dyscrasia are also at high risk. The precipitating trauma is often trivial.

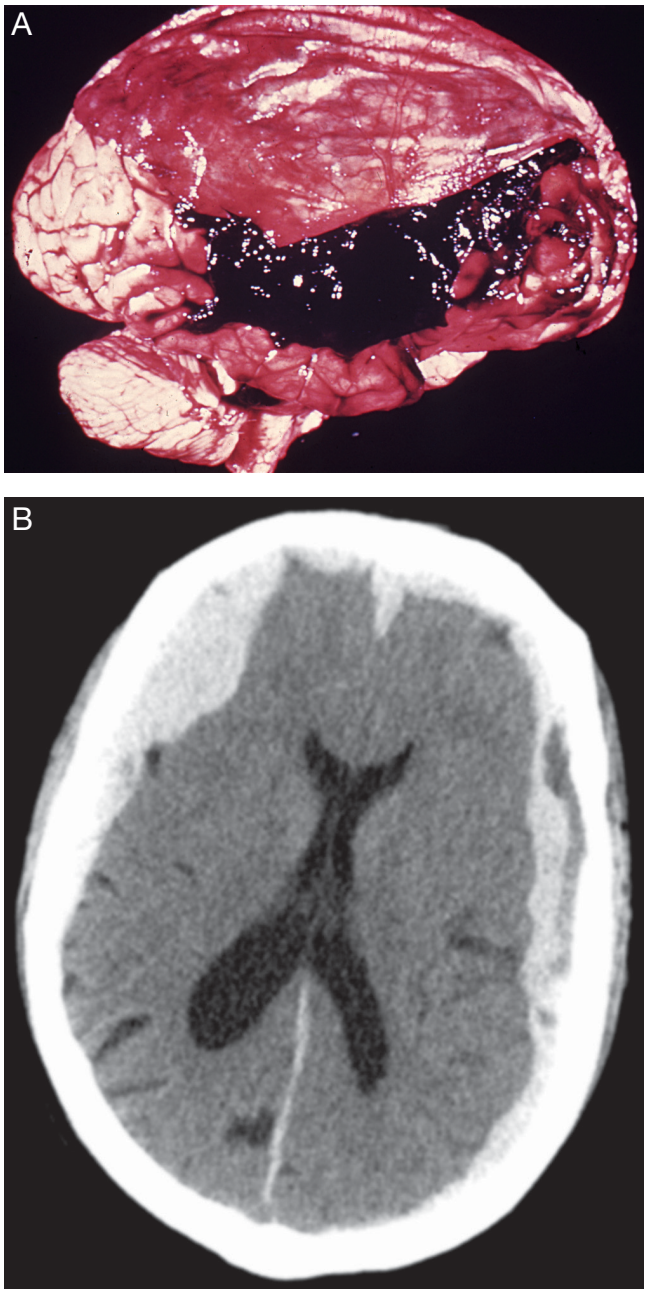


Figure 6.4 *Acute Subdural Hemorrhage.*
A, Gross specimen. B, On computed tomography, acute subdural hematoma appears as a hyperdense lesion over the convexity, as shown here bilaterally.
(A is adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

Symptoms and Presentation

Subacute or chronic SDHs generally develop within 7 to 10 days after injury. The signs and symptoms are similar to those of acute SDHs, but the course is generally slower and the mortality is correspondingly lower. The signs and symptoms of chronic SDH may be confused with ischemic phenomena or encephalopathy and can fluctuate. Patients also often experience seizures.

Diagnosis and Management

The definitive diagnosis can usually be made from the CT appearance of isodense or hypodense fluid collections along the cerebral convexity (Figure 6.5). A small hemorrhage fills the preexisting subdural space and, over several weeks, a vascular membrane forms around the collection.

In patients with subacute to chronic SDH, coagulation abnormalities should be corrected and pain control

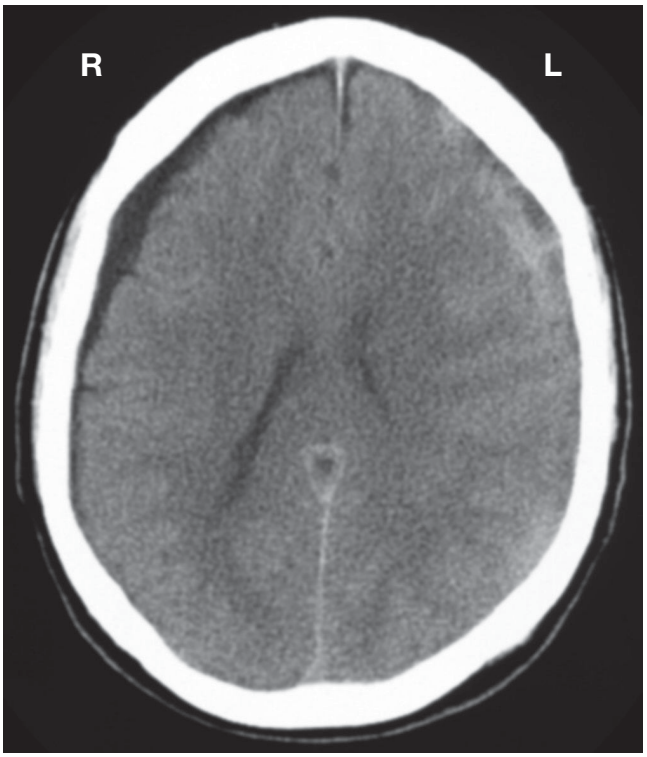


Figure 6.5 *Appearance of Chronic (R, right) and Subacute (L, left) Subdural Hematoma on Computed Tomography.*
The chronic hematoma appears hypodense to the brain, whereas the subacute hematoma is modestly isodense.
(Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

instituted. The severity of symptoms and amount of SDH may determine whether observation or surgical intervention is warranted. Both subacute and chronic SDH may be amenable to burr-hole drainage when symptomatic or the SDH is moderate to large.

- Subacute or chronic SDHs generally develop within 7 to 10 days after injury.
- The severity of symptoms and amount of SDH may determine whether observation or surgical intervention is warranted.

Traumatic Intracerebral Hemorrhage

Definition

Intracerebral hemorrhages (ICH) are hyperdense and usually develop within the temporal and frontal lobes after trauma (Figure 6.6). These focal brain injuries typically result in contusions or traumatic intracranial hematomas. Often they can be seen in conjunction with an overlying SDH. ICHs account for 20% of all traumatic intracranial hemorrhages.

Pathology and Pathophysiology

Brain contusions represent focal regions of subpial hemorrhage and swelling. Contusions are most common in regions that contact bony surfaces in the cranial vault during trauma: frontal and temporal poles, orbitofrontal gyri, perisylvian cortices, and inferolateral temporal lobe surfaces. These can be seen on the same side of impact (coup) or opposite side of impact (contrecoup). On CT, contusions are commonly associated with areas of relative hypodensity within the white matter structures, an indication of posttraumatic cerebral edema. They are associated with extensive lobar contusions, from which they are often difficult to distinguish.

ICHs differ from cerebral contusions in that a large proportion of these lesions are composed of blood, but they often result from growth or coalescence of smaller cerebral contusions. ICHs are more common in patients with skull fractures. About half of patients with severe TBI and skull fracture have a sizable ICH on initial head CT. Patients receiving chronic anticoagulation therapy are at increased risk for development of ICH, even after mild head injury.

Symptoms

Because the common location of contusions affects the bifrontal and temporal regions, symptoms are often behavioral and cognitive. Patients also may have headaches, nausea, vomiting, and seizures. Symptoms related to ICH depend on the location of the hemorrhage.

Management

Monitoring and treatment of increased intracranial pressure are essential. Symptomatic patients with large-volume clots (>50 cm^3) and more than 5-mm midline shift should be considered for clot evacuation.

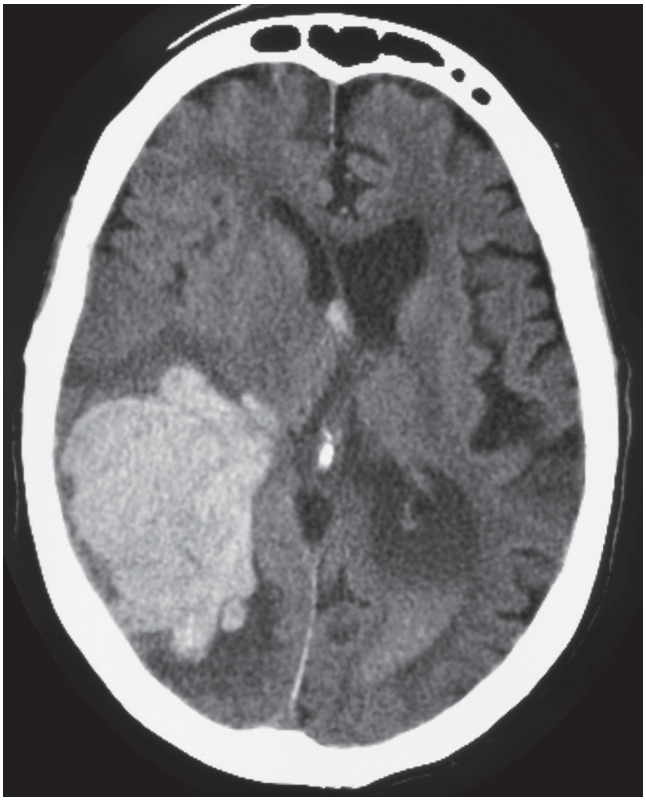


Figure 6.6 *Intracerebral Hemorrhage.*
Computed tomographic appearance of acute intracerebral hemorrhage with intraventricular extension.
(Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

- ICHs are hyperdense and usually develop within the temporal and frontal lobes after trauma (Figure 6.6).
- Contusions can be seen on the same side of impact (coup) or opposite side of impact (contrecoup).
- Traumatic ICHs are more common in patients with skull fractures.
- Symptomatic patients with large-volume clots (>50 cm^3) and more than 5-mm midline shift should be considered for clot evacuation.

Diffuse Axonal Injury

Definition

Diffuse axonal injury (DAI) results from severe acceleration-deceleration forces that deliver sheer and tensile forces to axons.

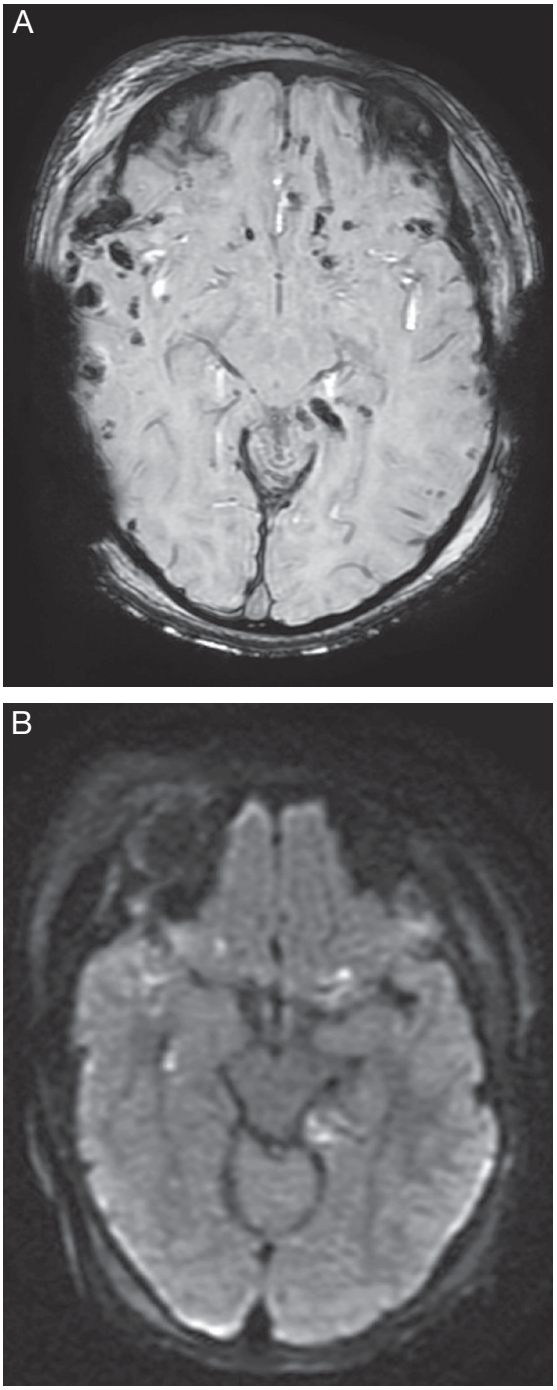


Figure 6.7 *Diffuse Axonal Injury on Magnetic Resonance Imaging.*
A, Susceptibility-weighted image shows extensive scattered foci of cortical and subcortical susceptibility effect compatible with microhemorrhages related to diffuse axonal injury. B, Diffusion-weighted image shows cortical and subcortical patchy areas of restricted diffusion consistent with diffuse axonal injury.

Pathology and Pathophysiology

The histologic findings of DAI include disruption and swelling of axons, retraction balls (swollen proximal ends of severed axons), and punctate hemorrhages in the pons, midbrain, and corpus callosum. As a result, DAI is responsible for most patients with TBI who are severely impaired despite lack of gross parenchymal contusions or hematomas. The location and severity of axonal injuries are important determinants of functional recovery.

Diagnosis

DAI lesions are often difficult to visualize on conventional CT and are better imaged using magnetic resonance imaging. T2-weighted gradient-echo imaging is particularly sensitive for hemorrhagic lesions after DAI (Figure 6.7).

Management

Monitoring and treating increased intracranial pressure are essential.

- Diffuse axonal injury (DAI) results from severe acceleration-deceleration forces that deliver sheer and tensile forces to axons.

Penetrating Injuries

Definition

Penetrating brain injuries are most commonly associated with gunshot wounds to the head. Projectiles can injure intracranial contents directly and indirectly through secondary pressure waves that can induce strength injuries in adjacent brain and vascular tissue from high-velocity projectiles.

Management

After initial resuscitation and imaging, the treatment of projectile injuries to the brain depends largely on the extent of injury and the results of neurologic examination. Management of penetrating injury is far more complicated, particularly if the diencephalic structures and mesencephalon is destroyed. Unfortunately, gunshots may also lacerate important arteries, including the vertebral artery with gunshots through the oropharynx. Bullet fragments will eventually migrate as a result of pulsation of cerebrospinal fluid and may also embolize into pulmonary arteries. Guidelines suggest that surgery should be reserved for patients with GCS 3 to 5 with concomitant large EDHs, GCS 6 to 8 without transventricular or bihemispheric injury, or GCS 9 to 15. Patients with transventricular, bihemispheric, or multilobar dominant hemisphere lesions, or GCS 3 to 5 without concomitant large EDHs, are generally not surgical candidates.

Box 6.2 • Injuries That May Raise Suspicion for Nonaccidental Causes

Injuries potentially related to traumatic abuse
- General
  - Spiral fracture of humerus
  - Metaphyseal fractures in infants
  - Duodenal hematomas
  - Frenulum tears in nonambulatory infants
  - Retinal hemorrhages
  - Immersion burns
  - Long bone injuries
  - Rib fractures
  - Cutaneous bruises
  - Patterned bruises
- Neurologic
  - Subgaleal hemorrhage
  - Subperiosteal hemorrhage
  - Skull fracture
  - Focal brain contusion

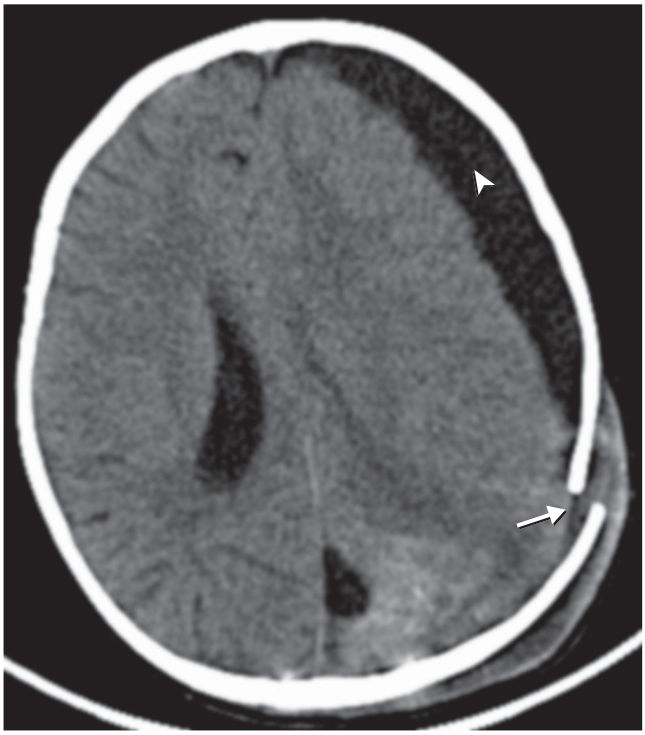


Figure 6.8 *Computed Tomogram With Evidence of Child Abuse.*
A left subdural hygroma (arrowhead) and depressed skull fracture (arrow) are seen in a 3-year-old patient.

Traumatic Abuse: Child Abuse

Child abuse is now recognized as a major cause of serious head injury in children and is second only to motor vehicle accidents as a cause of traumatic mortality in the pediatric population. In many institutions, a team approach to cases of suspected nonaccidental trauma provides an organized means of addressing the frequently complex issues involved in caring for these patients. A skeletal survey is a mandatory part of the evaluation of suspected nonaccidental injury in infants and young children, and bone scanning may be useful when results of plain radiography are equivocal. Anemia, thrombocytopenia, or other hematologic abnormalities are evaluated with standard laboratory tests. Toxicology screening is also mandatory.

Certain types of injuries that occur with greater frequency in the setting of physical abuse should raise a physician's level of suspicion for nonaccidental causation (Box 6.2). Characteristic findings in shaken baby syndrome include retinal hemorrhages, SDH (Figure 6.8), and cerebral edema. Other signs of abuse may or may not be present.

7 Acute Spinal Cord Compression, Spinal Cord Trauma, and Peripheral Neural Injury

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EELCO F. M. WIJDICKS, MD, PHD

Introduction

Acute spinal cord compression is a neurologic emergency. Recognition of spinal cord compression, urgent imaging, and treatment are important to preserve neurologic function.

This chapter reviews the causes and clinical approach to spinal cord compression. Spinal cord trauma, a common cause of spinal cord compression, is also reviewed in detail.

Spinal Cord Compression

Causes and Differential Diagnosis

Acute spinal cord compression is very often a neurologic and neurosurgical emergency. The most common primary cause is trauma, of which motor vehicle accidents, falls, and violence make up the largest share and in that order. Other, nontraumatic causes to consider include spontaneous or warfarin-induced epidural hematoma, epidural abscess, and expanding bone metastatic disease. The differential diagnosis of acute myelopathy, including compressive syndromes, is given in Table 7.1.

Clinical Presentation

Patients commonly present with acute paraparesis, which may be symmetric or asymmetric. Paraparesis from spinal cord compression should be distinguished from other causes. An acute bifrontal mass, cauda equina, or polyradiculopathy (Guillain-Barré syndrome) may manifest similarly with paraparesis, but clinical symptoms and examination findings (Table 7.2) may help to distinguish these causes and thereby help localize the problem. Features consistent with a spinal cord localization include paraparesis, Babinski sign present bilaterally, reflexes increased or normal acutely, urinary retention (check post-void residual volume), and decreased rectal tone. Respiratory compromise and dysautonomia (hypotension, bradycardia) may also be present.

Similarly, the examination may present clues to the cause. For example, an anterior cord syndrome sparing the dorsal columns may be suggestive of an ischemic cause. (For additional discussion and localization in cord syndromes, see Chapter 38, "Myelopathies.")

Diagnosis and Approach to Management

When cord compression is highly suspected and symptoms are acute, emergency magnetic resonance imaging (MRI) of the spine is necessary (Figure 7.1). In patients who cannot undergo MRI, computed tomographic (CT) myelography can be performed. If MRI does not show an obvious abnormality, lumbar puncture and laboratory studies are often performed to look for an inflammatory or infectious cause of the myelopathy. (See Chapter 38, "Myelopathies.")

Management often depends on the cause of compression. If the cause of the myelopathy is structural, emergency neurosurgical consultation is recommended. Certain

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SCI, spinal cord injury

Table 7.1 • Differential Diagnosis of Acute Myelopathy

Pathophysiologic Cause	Specific Cause
Vascular	Spinal cord ischemia
Inflammatory or infectious (transverse myelitis)	Inflammatory: systemic lupus erythematosus Infectious: HIV, HTLV-1, HSV-2, rabies, West Nile virus, TB (Pott disease), Lyme disease, syphilis, yaws, mycoplasma, leptospirosis, brucellosis, schistosomiasis, filariasis, eosinophilic meningitis Demyelinating: multiple sclerosis, neuromyelitis optica, acute demyelinating encephalomyelitis
Structural (cord compression)	Epidural compression: metastases, lymphoma, multiple myeloma, disk protrusion, epidural abscess or bleed, spondylolysis, atlantoaxial subluxation (rheumatoid arthritis) Extramedullary, intradural compression: meningioma, neurofibroma Intramedullary expansion: glioma, ependymoma, arteriovenous malformation
Paraneoplastic	Multiple antibodies and associated neoplasms
Toxic or metabolic	Arsenic Heroin Acute B_{12} deficiency (nitrous oxide exposure) Radiation
Trauma	. . .

Abbreviations: HIV, human immunodeficiency virus; HSV-2, herpes simplex virus type 2; HTLV-2, human T-lymphotropic virus 2; TB, tuberculosis.

structural lesions such as an epidural hematoma, large vertebral disk, or certain tumors may necessitate surgery. Radiation-responsive tumors may require emergency radiation.

The use of corticosteroids is not recommended in acute cord compression due to spinal cord injury. However, for cord compression due to neoplastic compression, corticosteroids are commonly used. (See Chapter 58, "Spinal Cord Tumors.")

No matter the cause, supportive management may include placement of a Foley catheter, monitoring and treating dysautonomia (abdominal binder for hypotension, atropine for bradycardia), and monitoring respiratory status (especially for a cervical or thoracic lesion).

Management of traumatic cord compression is discussed in the next section.

- The most common primary cause of acute spinal cord compression is trauma.

Table 7.2 • Distinguishing Causes of Paraparesis by Clinical Features and Examination (Cauda vs Conus)

Feature	Cauda Equina	Conus Medullaris
Onset/course	Gradual, asymmetric	Sudden, bilateral
Pain	Significant Radicular and low back	May or may not be present
Weakness	Often asymmetric Depending on chronicity, may have associated atrophy	Often symmetric weakness
Reflexes	Patellar and ankle reflexes reduced	May solely affect ankle reflexes
Sensory loss	Saddle numbness; may be asymmetric and dermatomal	Perianal, symmetric
Bowel/bladder	Urinary retention Impotence occasionally	Urinary retention Impotence common

- An acute bifrontal mass, cauda equina, or polyradiculopathy (Guillain-Barré syndrome) may manifest with paraparesis, similar to spinal cord compression, but clinical symptoms and examination findings (Table 7.2) may help to distinguish these causes and thereby help localize the problem.

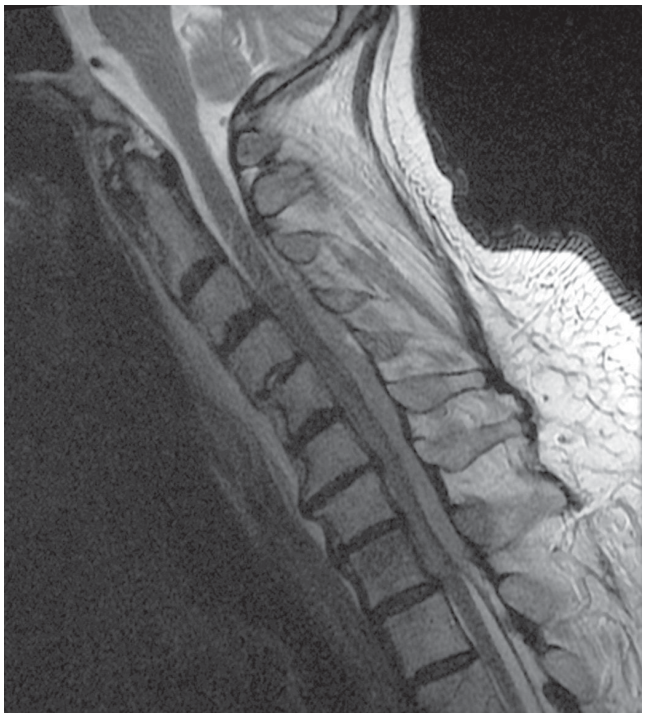

Figure 7.1 *Cord Compression on T2-Weighted Magnetic Resonance Imaging.*
A dorsal epidural extension of this patient's known right-sided Pancoast tumor extends from C2-C3 through T1-T2, with moderate associated cord compression from C4 through T1.

Spinal Cord Trauma

Epidemiology

The incidence of spinal cord injury (SCI) is approximately 40 cases per million, and it is primarily an injury of young men. The ratio of males to females is approximately 4:1.

Pathophysiology

SCI can be divided into primary and secondary types. Primary injury refers to an initial traumatic insult to the spinal cord that results in disruption of the long axons that provide effector and sensor function to the body. Secondary injury follows primary injury and can lead to progressive tissue damage for weeks and months after the initial injury. Secondary injury includes preventable causes such as hypotension and hypoxia, which can exacerbate tissue injury.

The loss of autoregulation in the microcirculation of the gray and white matter results in local ischemia, infarction, and hemorrhagic necrosis adjacent to the primary injury. These changes lead to disruption of cellular membrane potentials and ion-mediated cell damage with the influx of calcium. Neuronal dysfunction results in excitotoxicity due to glutamate release, oxidative stress, and eventually cell death. Macrophage invasion leads to cavitation, disruption of tissue architecture, and postinjury hydromyelia. Syrinxes can develop in up to 30% of patients after SCI, causing further neurologic deficits. Microglial cell activation initiates neuroinflammation, with glial scarring that can become a barrier to axonal regrowth. Myelin debris, including proteins such as Nogo-A, has been shown to inhibit axonal repair and has become a therapeutic target. Chondroitin sulfate proteoglycans are secreted by reactive astrocytes and have also been shown to be a barrier to axonal regrowth. Over time, this proinflammatory environment leads to wallerian degeneration and further loss of function.

Important Historical Features

Important history should be gathered as it relates to biomechanical and neurologic stability after an accident: speed of vehicle, loss of consciousness, use of seatbelt or airbag, position of patient before extraction, spontaneous or voluntary extremity movements, and other associated injuries.

Clinical Examination

A complete trauma evaluation under the Advanced Trauma Life Support protocol should be done for any patient who presents with a neurologic deficit in the setting of obvious or suspected trauma. The major causes of death in acute SCI are aspiration and shock. Therefore, initial evaluation should proceed according to protocol with the airway secured first, followed by respiration (breathing) and then circulation (ABCs). Intubation may be necessary in cervical or thoracic injury in which the diaphragm or thoracic musculature is compromised. Once these are secured, a neurologic evaluation takes place.

All patients being evaluated in the trauma bay should undergo total spine precautions with immobilization of the cervical spine in a cervical collar and log-rolling on a rigid board for the thoracic and lumbar spine until they can be cleared with careful examination and imaging.

A careful neurologic examination is important to document neurologic deficits and localize the problem. Clues from the examination may help determine the level of SCI. Important findings may include paradoxic breathing (abdominal breathing due to loss of thoracic musculature), reduced inspiratory capacity due to diaphragm involvement, autonomic instability, flaccid limbs with reduced reflexes (hyperreflexia and spasticity several days to weeks after the injury), sensory level, urinary retention, priapism, bowel or bladder incontinence, or sudden step-off of spinous processes. In the setting of SCI, rectal tone and perianal sensation are critical to document for appropriate management.

The American Spinal Cord Injury Association grading system should be used to document the extent of injury and localize the level of the lesion (Figure 7.2). The system grades from A (complete loss of sensory and motor function below the level of injury) to E (normal motor and sensory function below the level of injury). It is also useful for prognostication.

Depending on the location of the lesion, various spinal cord syndromes are appreciated (Figure 7.3). Central cord syndrome is an incomplete SCI with disproportionately greater motor deficits in the upper extremities than the lower extremities, thought to be caused by a hyperextension injury. Brown-Séquard syndrome involves half of the cord on one side, typically due to hemisection or injury to one lateral half of the spinal cord. It presents with ipsilateral motor deficit, proprioceptive and vibration deficit, and contralateral loss of pain and temperature sensation.

Initial Management of SCI

Spinal Shock

In the setting of SCI, hypotension could be due to interruption of sympathetic autonomic function resulting in loss of vasomotor tone, bradycardia due to unopposed parasympathetic action, and hypothermia, all of which contribute to secondary injury. The sympathetic chain travels in the intermediolateral column of the spinal cord from T1-L3.

Spinal shock is usually treated with vasoactive medication such as dopamine rather than non-ionotropic agents such as phenylephrine. Ideal vasoactive medications work toward counterbalancing vasodilatation (α-agonist) and impaired cardiac contractility (β-agonist). Other agents to consider are dobutamine, epinephrine, and

norepinephrine. Hydration is an important adjunct while avoiding volume overload and subsequent pulmonary edema. Hemodynamic augmentation should target a mean arterial pressure of 85 mm Hg or higher for the first 7 days after SCI.

Bowel and Bladder Management

A Foley catheter should be placed because urinary retention is common.

Use of Corticosteroids

Initial reports from the National Spinal Cord Injury Study showed improved functional outcome in acute SCI treated with high-dose methylprednisolone. Newer evidence based on randomized controlled trials shows no considerable benefit to the use of methylprednisolone in acute SCI.

Diagnostic Evaluation in Suspected SCI

Imaging should be tailored to the neurologic status and history of the patient. Patients who have had trauma but who have no neck pain, neurologic deficit, distracting injuries, or mental status changes do not require imaging. However, patients with SCI and traumatic encephalopathy should have imaging of the craniospinal axis. CT of the spine with thin cuts (1.5–3 mm) and 3-dimensional reconstruction can categorize the majority of fractures and dislocations. Patients who have a neurologic deficit not explained by CT alone should have MRI to characterize soft-tissue and ligamentous injury. MRI has the added benefit of capturing the degree of SCI by characterizing edema, hemorrhage, and demyelination. For patients in whom MRI is contraindicated, CT myelography can be considered, but caution should be used when introducing the needle because

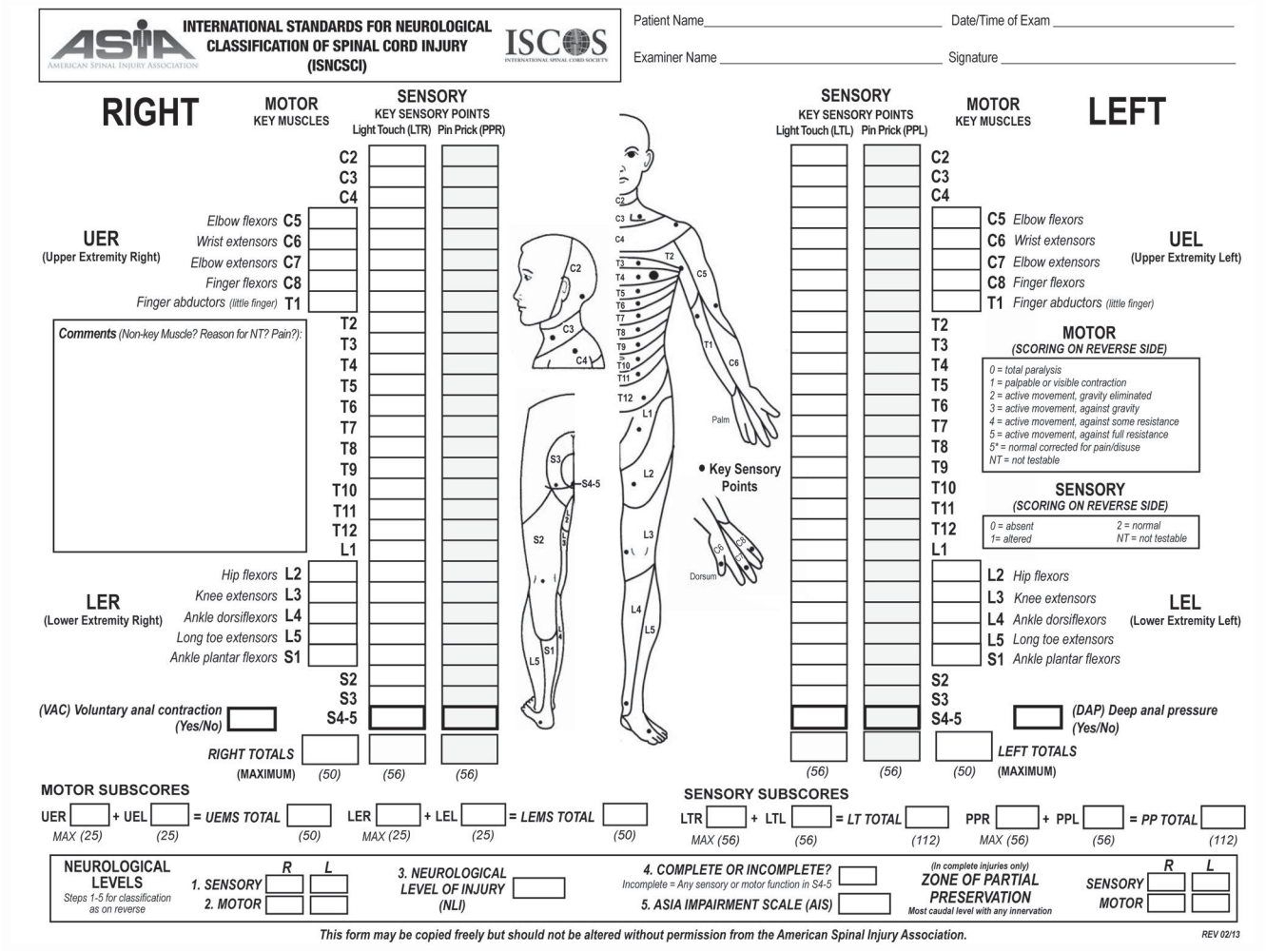

Figure 7.2 *American Spinal Injury Association Classification of Spinal Cord Injury.*
(Adapted from International Standards for Neurological Classification of Spinal Cord Injury [Internet]. Atlanta [GA]: American Spinal Injury Association. c2011—[cited 2014 Mar 24]. Available from: http://www.asia-spinalinjury.org/elearning/ISNCSCI_Exam_Sheet_r4.pdf. Used with permission.)

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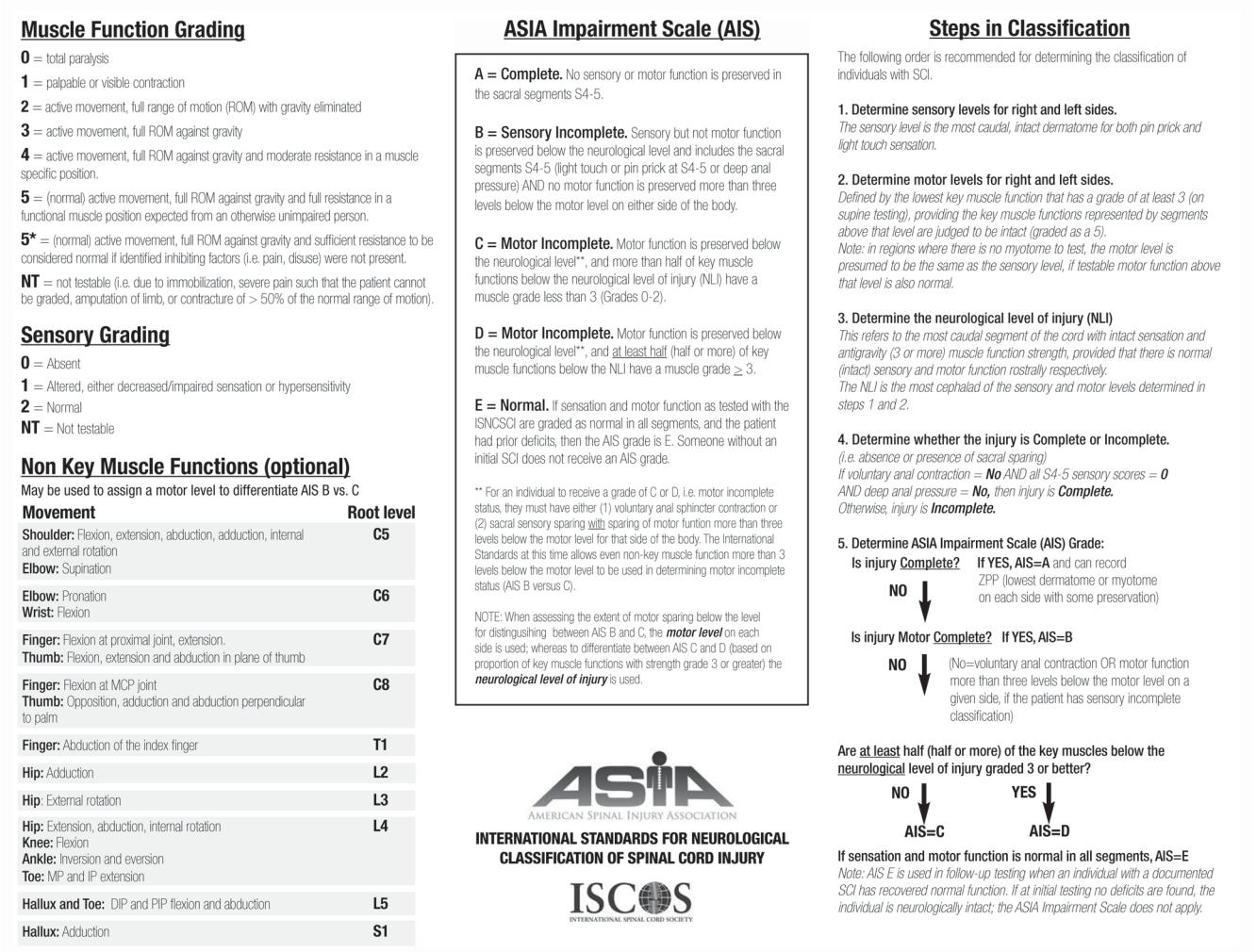

Muscle Function Grading

0 = total paralysis

1 = palpable or visible contraction

2 = active movement, full range of motion (ROM) with gravity eliminated

3 = active movement, full ROM against gravity

4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position.

5 = (normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person.

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present.

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal range of motion).

Sensory Grading

0 = Absent

1 = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal

NT = Not testable

Non Key Muscle Functions (optional)

May be used to assign a motor level to differentiate AIS B vs. C

Movement	Root level
Shoulder: Flexion, extension, abduction, adduction, internal and external rotation **Elbow:** Supination	C5
Elbow: Pronation **Wrist:** Flexion	C6
Finger: Flexion at proximal joint, extension. **Thumb:** Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved below the neurological level**, and more than half of key muscle functions below the neurological level of injury (NLI) have a muscle grade less than 3 (Grades 0-2).

D = Motor Incomplete. Motor function is preserved below the neurological level**, and at least half (half or more) of key muscle functions below the NLI have a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

** For an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor funtion more than three levels below the motor level for that side of the body. The International Standards at this time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS B versus C).

NOTE: When assessing the extent of motor sparing below the level for distinguishing between AIS B and C, the ***motor level*** on each side is used; whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the ***neurological level of injury*** is used.

ASIA
AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS
INTERNATIONAL SPINAL CORD SOCIETY

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI)
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0** AND deep anal pressure = **No,** then injury is **Complete.***
*Otherwise, injury is **Incomplete.***

5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? **If YES, AIS=A** and can record ZPP (lowest dermatome or myotome on each side with some preservation)

NO ↓

Is injury Motor Complete? **If YES, AIS=B**

NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?

NO ↓ **AIS=C**

YES ↓ **AIS=D**

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

Figure 7.2 *Continued*

pressure shifts have been shown to exacerbate neurologic deficits. Twenty percent of patients with a major SCI will have a second spine injury at a noncontiguous level and therefore should undergo a careful neurologic evaluation and may require more complete imaging of the entire spine, including both CT with 3-dimensional reconstruction and MRI.

Management of SCI After Imaging

Spine Trauma Clearance

In patients who are asymptomatic, alert, compliant, and nonintoxicated, are without a distracting injury or neurologic deficit, and are able to complete a functional range-of-motion examination, trained providers may safely clear the cervical spine from immobilization without radiographic evaluation. Patients who do not meet all of these criteria require a 3-view cervical x-ray series, adding a swimmer's view if the lateral view does not include the C7-T1 interface. In patients with degenerative disease of the cervical spine, a plain film series is often inadequate to assess for injury, and CT must be performed.

If a patient has a head injury with altered sensorium, is intoxicated, or has been given potent analgesics, then the cervical spine must remain immobilized until the clinical examination becomes possible.

In the obtunded trauma patient, the optimal approach to cervical spine clearance remains controversial. If the patient cannot be clinically evaluated in 48 hours, it is our practice to have cervical spine MRI done to assist with clearance. More recent studies suggest that high-quality thin-cut CT may be adequate in select patients; however, evaluation by a spine surgeon is essential to guide appropriate management in obtunded trauma patients.

There are currently no consensus guidelines for clearance of the thoracic and lumbar spine. Patients suspected of having thoracic or lumbar spine fractures should undergo radiographic and thorough neurologic evaluation and be maintained on total spine precautions until they

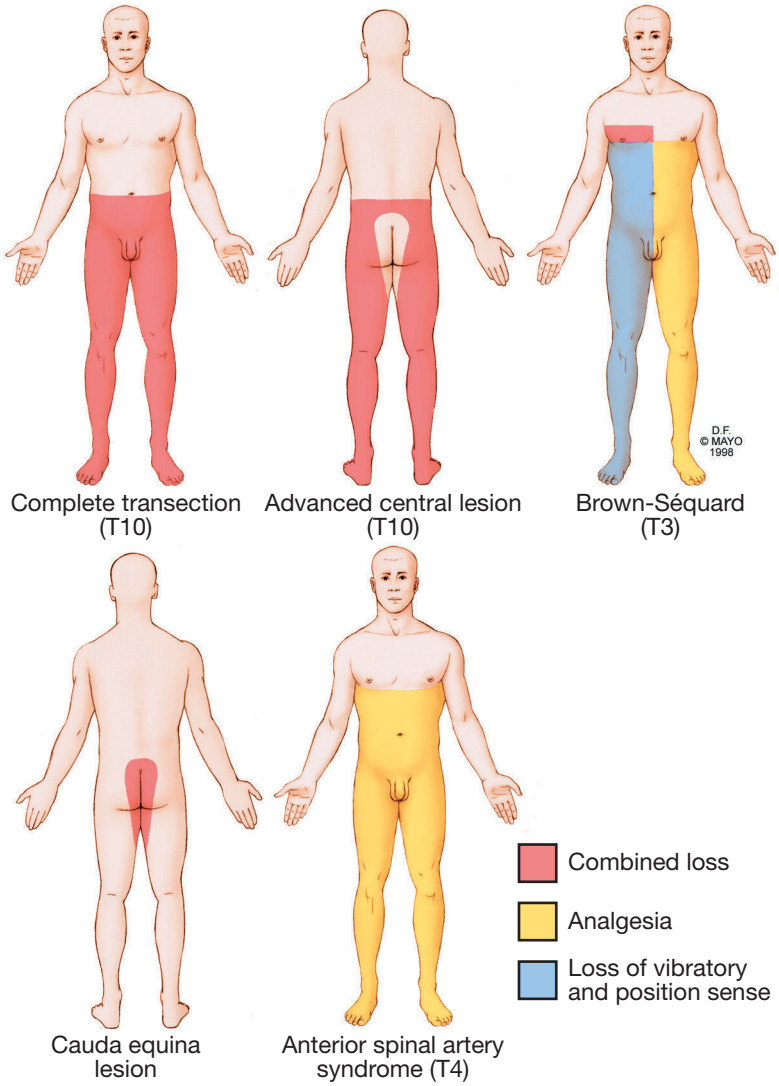

Figure 7.3 *The Major Spinal Cord Syndromes.*
(Adapted from Wijdicks EFM. The practice of emergency and critical care neurology. Oxford [UK]: Oxford University Press; c2010. Chapter 34, Acute spinal cord disorders; p. 494–512. Used with permission of Mayo Foundation for Medical Education and Research.)

are reviewed by trained personnel. Generally, patients who have polytrauma after high-impact trauma undergo full-spine reconstruction imaging with CT after undergoing primary and secondary surveys in the emergency department trauma bay.

Traction

Traction can be used initially for closed reduction in cases of fracture-dislocation. Contraindications to reduction include atlanto-occipital dislocation, traumatic disk herniation, and additional rostral injuries.

Surgical Management

Emergency neurosurgical evaluation for early decompression and stabilization should be performed in cases of epidural hematoma or bony canal compromise in the setting of an acute neurologic deficit. The timing of surgical intervention can be difficult to determine, particularly in polytrauma patients with other serious injuries. This is an area of ongoing research, but preliminary analysis suggests a greater benefit if surgery is performed within 12 hours of injury. Further evidence will have to be collected and tailored to individual cases before formal guidelines can be given.

Table 7.3 • Survival of Patients With Long-term Spinal Cord Injuries[a]

Age and Group	No. of Patients	Percent Surviving[b]				Median Survival, y
		10 years	20 years	30 years	40 years	
<30 y at injury						
Complete quad	66	86	77	64	NA[c]	
Incomplete quad	87	96	85	67	31	36
Complete para	233	91	79	63	47	36
Incomplete para	96	96	89	76	65	44[d]
30–49 y at injury						
Complete quad	33	71	42	34	NA[c]	17
Incomplete quad	50	70	63	33	0	26
Complete para	159	81	60	36	12	23
Incomplete para	64	84	69	47	16	29
50+ y at injury						
Complete quad	7	53	0	0	0	10
Incomplete quad	15	56	24	0	0	11
Complete para	14	50	17	0	0	12
Incomplete para	10	67	44	NA[c]	NA[c]	14

Abbreviations: NA, not applicable; para, paraplegia; quad, quadriplegia.
[a] First-year deaths were excluded from the study.
[b] Using standard life tables.
[c] No study cases in this group had been injured for 40 years.
[d] Estimated median survival.
Adapted from Whiteneck GG, Charlifue SW, Frankel HL, Fraser MH, Gardner BP, Gerhart KA, et al. Mortality, morbidity, and psychosocial outcomes of persons spinal cord injured more than 20 years ago. Paraplegia. 1992 Sep;30(9):617–30. Used with permission.

Nonsurgical Management

Treatment strategies other than surgery, such as halo stabilization and bracing, can also be considered.

Prevention of Complications

Common complications after SCI include bowel or bladder dysfunction, deep vein thrombosis, dysautonomia, and aspiration. Aggressive prevention of these complications is important.

Outcomes

The most important prognostic factors determining outcomes in patients with SCI are age and neurologic status (Table 7.3). Most of the recovery a patient achieves takes place within the first year of injury. Ongoing research of stem cell therapy, hypothermia, and other biologic approaches is attempting to improve the plasticity and regeneration capabilities within the spinal cord.

- Syrinxes can develop in up to 30% of patients after SCI, causing further neurologic deficits.
- The major causes of death in acute SCI are aspiration and shock.
- Twenty percent of patients with a major SCI will have a second spine injury at a noncontiguous level and therefore should undergo a careful neurologic evaluation and may require more complete imaging of the entire spine, including both CT with 3-dimensional reconstruction and MRI.
- If a patient with SCI has a head injury with altered sensorium, is intoxicated, or has been given potent analgesics, then the cervical spine must remain immobilized until the clinical examination becomes possible.
- The most important prognostic factors determining outcomes in patients with SCI are age and neurologic status (Table 7.3).

Peripheral Neural Trauma

Degenerative Spine Disease

Degenerative spine disease (spondylosis) has a high incidence and becomes more prevalent with age. Spondylosis involves hypertrophy of the facets, lamina, and ligaments, along with intervertebral disk degeneration, osteophyte formation, and loss of cervical and lumbar lordosis, resulting in multiple pain generators. In the absence of a progressive neurologic deficit, an initial course of nonoperative management is indicated in patients with spondylosis and minor neurologic deficits. These therapies include analgesics, epidural corticosteroid injections, oral

anti-inflammatory agents, physical therapy, weight loss, and muscle relaxants. Indications for surgery include cauda equina syndrome, progressive neurologic deficit, intractable pain, and spinal deformity.

Radiculopathy

Intervertebral disk herniations or facet narrowing resulting in nerve root compression (radiculopathy) can occur throughout the spine. MRI is the diagnostic imaging study of choice, although CT myelography may be useful. Cervical roots exit the corresponding neural foramen above the pedicle of the corresponding vertebral body, and herniated disks usually compress the nerve at this level. The majority of cervical disk herniations occur at C6–7 (C7 radiculopathy) and C5–6 (C6 radiculopathy).

Lumbar disk herniations often improve with nonsurgical therapies. Indications for surgery include persistent severe radicular pain despite a period of conservative management, progressive neurologic deficit, and cauda equina syndrome. Lumbar disk herniation most commonly occurs at L4–5 and L5-S1.

Brachial Plexus Injury

For evaluation of traumatic injury to the brachial plexus, the clinical history, physical examination, and adjuvant testing provide insight for localizing the injury and determining the extent of injury. Physical examination requires a detailed motor and sensory examination of the affected limb.

Regenerating nerve fibers develop mechanosensitivity. Percussion over the course of the nerve produces tingling paresthesia in the sensory distribution of the nerve (Tinel sign). Starting distally and progressing toward the lesion site, tingling is perceived as soon as the tip of the down-growing highly sensitive but not yet myelinated fibers is met. However, an advancing Tinel sign does not indicate the number or quality of regenerating axons and does not guarantee functional outcome. Conversely, lack of an advancing Tinel sign is indicative of a poor prognosis. Electrodiagnostic studies are useful in both the preoperative and the intraoperative evaluation of a brachial plexus injury. They can help determine the nerves injured, the location of the injury, and the presence of regeneration.

It is common practice to wait approximately 2 weeks after injury to perform the first electromyography and then, depending on the clinical scenario, either opt for early explorative surgery or perform serial electromyographic testing to look for early reinnervation. Recovery of electromyographic activity (new voluntary motor units) does not always predict a functional outcome. MRI as early as 4 days after injury (roughly 2 weeks before electromyographic changes become apparent) can document muscle changes caused by denervation. Once reinnervation has occurred, MRI muscle signals revert to normal.

- The majority of cervical disk herniations occur at C6–7 (C7 radiculopathy) and C5–6 (C6 radiculopathy).
- Lumbar disk herniation most commonly occurs at L4–5 and L5-S1.

8 Neuromuscular Disease in the Neuroscience Intensive Care Unit

PHILIPPE COUILLARD, MD; EELCO F. M. WIJDICKS, MD, PHD

Introduction

The neurologist invariably will be involved as primary caregiver for patients with neuromuscular diseases in the neuroscience intensive care unit or in consultation for patients with neuromuscular weakness in the general intensive care setting. This chapter describes general features of neuromuscular weakness and neuromuscular respiratory failure. Important aspects of Guillain-Barré syndrome, myasthenia gravis, and botulism are reviewed as they pertain to neurologic critical care. Critical illness neuropathy and myopathy are also briefly reviewed.

Neuromuscular Respiratory Failure

Cerebral hemispheres, brainstem respiratory centers, upper airway, phrenic nerve motoneurons, and respiratory muscles act in concert to provide adequate minute ventilation to maintain oxygenation and carbon dioxide clearance. Decreased respiratory drive, neuromuscular weakness, and pulmonary complications may lead to respiratory failure in the neurologic patient.

When respiratory muscle weakness occurs, chest wall mechanics are altered. An ineffective diaphragm action leads to accessory muscle contraction. This causes an upward displacement of the rib cage and a decrease in intra-abdominal pressure. As the chest rises, the abdomen is drawn inward, a phenomenon called paradoxic breathing. Scalene and sternocleidomastoid muscles are overactive and can be palpated. Weakness leads to smaller tidal volume breaths and poor cough. Despite increasing respiratory frequency, atelectasis ensues, causing pulmonary shunt and resultant hypoxemia. Poor secretion clearance may lead to upper airway obstruction and aspiration.

Early signs of respiratory failure include anxiety, restlessness, forehead sweating, tachycardia, tachypnea, and a tendency to sit upright (Box 8.1). Speech is hesitant and interrupted. Early on, patients may compensate and maintain a normal-appearing arterial blood gas value. Nocturnal hypoventilation and hypercapnia may be present at this stage as a result of relaxation of accessory muscles at night and worse diaphragmatic efficiency in the supine position. Hypercarbia is a late phenomenon.

Box 8.1 • Clinical Features of Imminent Neuromuscular Respiratory Failure

- Dyspnea at low levels of work
- Restlessness
- Tachycardia (heart rate >100 beats per minute)
- Tachypnea (respiratory rate >20 breaths per minute)
- Use of sternocleidomastoid, scalene muscles (by palpation alone)
- Forehead sweating
- Staccato speech
- Asynchronous (paradoxic) breathing

Adapted from Wijdicks EFM. The clinical practice of critical care neurology. 2nd ed. New York (NY): Oxford University Press; c2003. Chapter 5, Airway and mechanical ventilation; p. 38–67. Used with permission of Mayo Foundation for Medical Education and Research.

Abbreviations: GBS, Guillain-Barré syndrome; MG, myasthenia gravis

Table 8.1 • Laboratory Values Used in Monitoring Respiratory Failure

Factor	Normal Value	Critical Value
Vital capacity, mL/kg	40–70	<20
Maximal inspiratory pressure, cm H_2O	Male, >−100 Female, >−70	<−30
Maximal expiratory pressure, cm H_2O	Male, >200 Female, >140	<40

Adapted from Wijdicks EFM. The clinical practice of critical care neurology. 2nd ed. New York (NY): Oxford University Press; c2003. Chapter 5, Airway and mechanical ventilation; p. 38–67. Used with permission of Mayo Foundation for Medical Education and Research.

Bedside respiratory tests are important adjuncts to the physical examination and include measurement of vital capacity and maximal inspiratory and expiratory pressures. They are effort- and examiner-dependent. The 20/30/40 rule is a useful predictor of respiratory failure in Guillain-Barré syndrome: if vital capacity is less than 20 mL/kg, maximal inspiratory pressure is less than −30 cm H_2O, and maximal expiratory pressure is less than 40 cm H_2O, then the patient is likely to require endotracheal intubation (Table 8.1). A reduction of 30% of the baseline vital capacity is also worrisome. The predictive value of bugle pressures in myasthenia gravis is poor because of marked disease fluctuation. Study results may be normal in a patient with early myasthenic crises who later deteriorates to intubation.

- The 20/30/40 rule is a useful predictor of respiratory failure in Guillain-Barré syndrome: if vital capacity is less than 20 mL/kg, maximal inspiratory pressure is less than −30 cm H_2O, and maximal expiratory pressure is less than 40 cm H_2O, then the patient is likely to require endotracheal intubation (Table 8.1).

Guillain-Barré Syndrome

Overview and Epidemiology

Many patients with Guillain-Barré syndrome (GBS) present eventually with acute flaccid paralysis. The rapidly progressive weakness can lead to quadriplegia, bulbar and respiratory muscle involvement, and dysautonomia. The annual disease incidence is about 1 case per 100,000, and the syndrome is the most common cause of acute flaccid paralysis. For comparison, the annual incidence of neuroinvasive arbovirus infections, including West Nile virus, is 0.2 per 100,000.

Antecedent upper respiratory tract prodrome is present in two-thirds of patients, but other infectious agents are also associated with the illness. *Campylobacter jejuni* (30%) and cytomegalovirus (10%) are most common, followed by Epstein-Barr virus, varicella-zoster virus, and *Mycoplasma pneumoniae*. Other reported but rare precipitants include vaccination and surgery.

Pathophysiology

The general principle involves an immune response leading to myelin damage. Autoantibodies are thought to bind to myelin antigens and activate complement. Vesicular degeneration ensues as a result of the formation of membrane-attack complex on the outer surface of Schwann cells. Macrophages subsequently invade myelin and remove myelin debris. Molecular mimicry is a process whereby similarities between microbial and host proteins may result in cross-reacting immune responses and autoimmune disease. Gangliosides (an aggregate of sialic acid, oligosaccharides, and ceramide) are important components of the peripheral nerves. Some evidence supports molecular mimicry between gangliosides and antecedent infectious agents to explain demyelination in patients with GBS.

Clinical Presentation

Paresthesia in the feet is often the first manifestation of GBS. Nonspecific neck or back pain is frequently present and is dismissed as trivial by patients. These first symptoms occur mostly 2 weeks after a viral illness. Early in the process, the deep tendon reflexes are reduced or absent and often not evaluated in a patient presenting with tingling alone. Weakness in the proximal muscles soon follows and may appear ascending. The degree of proximal involvement often mirrors respiratory muscle weakness and should alarm the clinician to seek signs, subtle and overt, of respiratory failure preemptively. Weakness severity can be variable, from mild to a virtual locked-in state.

Because progression is expected to occur for 1 to 3 weeks after symptom onset, hospitalization is the rule for observation, monitoring, and treatment. Findings on physical examination are generally symmetric weakness, areflexia in weak muscles, and minimal loss of sensation despite paresthesias. Variable cranial nerve dysfunction in the form of ptosis, facial diplegia, and dysphagia can be present. Attention needs to be paid to abnormal vital signs to detect frequent involvement of the autonomic nervous system. Common autonomic symptoms include cardiac conduction arrhythmias, orthostatic hypotension, hypertension, and adynamic ileus. Early signs of respiratory failure are recognized from shortness of breath (often, pausing in sentences), mild tachypnea, and mild tachycardia.

Patients who have the Miller Fisher variant of GBS present with ophthalmoplegia, ataxia, and areflexia. Autoantibodies against GQ1b ganglioside are present in most patients with this syndrome. Other less common variants of GBS include acute motor axonal neuropathy,

acute motor and sensory axonal neuropathy, pandysautonomia, and pharyngeal-cervical-brachial involvement.

Diagnostic Approach to Suspected GBS

The differential diagnosis of GBS should include poliomyelitis in endemic regions, echovirus, coxsackievirus, West Nile virus, tick paralysis in children, rabies, lymphomatous or carcinomatous nerve infiltration, acute transverse myelitis and acute spinal cord compression, vasculitic neuropathy, and vascular myelopathy with spinal shock (Table 8.2). Major electrolyte imbalances such as hypophosphatemia or hypokalemia, myasthenia gravis, and botulism have few sensory features, and patients with acute myopathy have retained deep tendon reflexes.

Laboratory test results are mostly unremarkable except for normovolemic hyponatremia due to occasional syndrome of inappropriate antidiuretic hormone, moderate increase of the erythrocyte sedimentation rate, and occasional perturbations of liver function. If results of liver function tests are increased, a hepatitis panel should be obtained. Mild transient proteinuria can occur. Creatine kinase is in the normal range or slightly increased in patients with pain. In patients suspected to have respiratory failure, arterial blood gas testing and chest radiography are appropriate to look for atelectasis and features suggestive of aspiration in patients with dysphagia. Baseline electrocardiography is advisable. Brain and spinal imaging may also be useful to rule out a structural cause.

Electromyography most often shows slowed motor conduction velocities and distal latencies, motor conduction block, temporal dispersion (Figure 8.1), and slowed or absent F waves, but it can also have features of axonal degeneration. Cerebrospinal fluid analysis shows albuminocytologic dissociation. Most patients seen within the first week of symptoms have a protein concentration more than 50 mg/dL and few cells. A high leukocyte count in the cerebrospinal fluid prompts additional studies (cytologic and human immunodeficiency virus testing). Specific gangliosides can be found, for example, GQ1 in the Miller Fisher variant.

Management and Treatment

Respiratory failure and dysautonomia are important concerns and necessitate cardiac and respiratory monitoring. Admission to the intensive care unit is needed for patients with rapid disease progression, bulbar or facial dysfunction, severe dysautonomia, and respiratory failure. Preemptive elective intubation is preferred if the patient shows the initial signs of respiratory failure and will reduce emergency intubations. Electrocardiography, blood pressure, oxygen saturation, vital capacity, and swallowing should be checked regularly. The most common complications of GBS relate to disability incurred by the disease and the critical care environment: pneumonia, sepsis, severe dysrhythmias, adynamic ileus and bowel perforation, deep vein thrombosis with pulmonary embolism, gastrointestinal bleeding, pseudomembranous colitis, and complications of tracheostomy. Treatment intensity depends on patient needs but includes temporary cardiac pacing, mechanical ventilation, and orogastric or nasogastric enteral nutrition. Prophylaxis for gastrointestinal and venous thromboembolism and use of ventilator-associated pneumonia-reduction bundles are essential. Judicious antibiotic use is required for nosocomial infections.

Table 8.2 • Disorders Frequently Mimicking Guillain-Barré Syndrome

Disease	Relevant Clinical Features	Helpful Laboratory Tests
Transverse myelitis	Sensory level Urinary incontinence No facial or bulbar involvement	MRI of spine with gadolinium CSF: pleocytosis (>200 cells)
Myasthenia gravis	Marked fatiguing ptosis and ophthalmoplegia Intact tendon reflexes Masseter weakness No dysautonomia	EMG, NCV, repetitive stimulation CSF: normal Neostigmine test
Vasculitic neuropathy	History of PAN, SLE, WG, RA Pain without paresthesias Marked asymmetry of weakness	Chest and sinus radiography or CT of thorax Nerve and muscle biopsies
Carcinomatous or lymphomatous meningitis	Mental changes Radicular pain Asymmetric cranial nerve involvement	CSF cytology MRI with gadolinium MRI of spine or brain with gadolinium

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; EMG, electromyography; MRI, magnetic resonance imaging; NCV, nerve conduction velocity; PAN, polyarteritis nodosa; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; WG, Wegener granulomatosis.

Adapted from Wijdicks EFM. The clinical practice of critical care neurology. 2nd ed. New York (NY): Oxford University Press; c2003. Chapter 25, Guillain-Barré syndrome; p. 403–21. Used with permission of Mayo Foundation for Medical Education and Research.

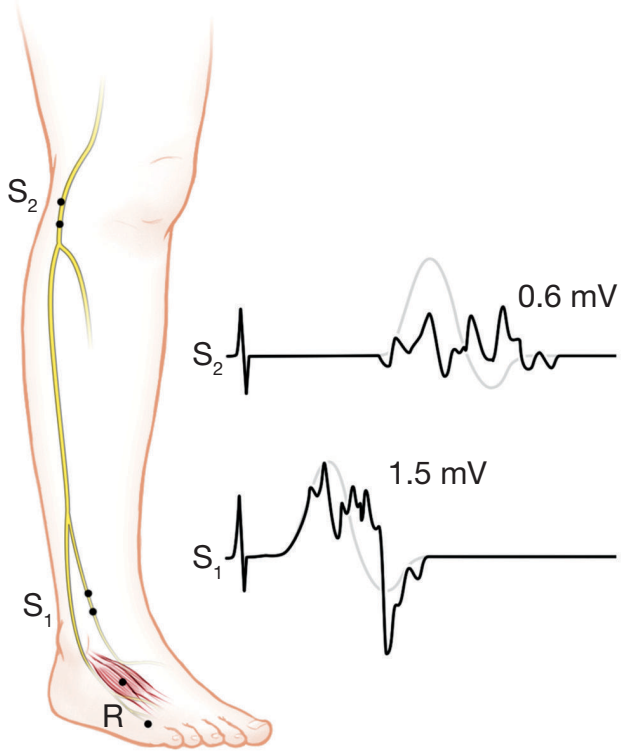

Figure 8.1 *Temporal Dispersion.*
Nerve conduction study in a patient with an immune-mediated demyelinating peripheral neuropathy shows considerable temporal dispersion of the peroneal compound muscle action potential (CMAP) (compared with the normally contoured [shaded] CMAP). This finding suggests differential degrees of slowing within the various fascicles of the affected nerve. Similar changes could be seen in the setting of Guillain-Barré syndrome. R indicates recording site; S_1, distal stimulation site; S_2, proximal stimulation site.
(Adapted from Jones LK. Nerve conduction studies: basic concepts and patterns of abnormalities. Neurol Clin. 2012;30(2):405–27. Used with permission.)

Intravenous immunoglobulin and plasma exchange are accepted treatment choices for patients who cannot walk unassisted. These can speed up strength recovery and reduce days of mechanical ventilation. Re-treatment can be considered if clinical symptoms progress after reaching a plateau with treatment. There is no role for corticosteroid therapy. Management of GBS is summarized in Table 8.3.

Outcome and Prognosis

Studies have shown that older age (>40 years), preceding diarrhea, and severe weakness (low Medical Research Counsel sum score) on admission and 1 week after onset predict lower probability of the ability to walk within 4 weeks but also at 3 and 6 months. Mortality has been estimated at 3%, but the rate doubles in long-term mechanically ventilated patients and may even approach 20%. Approximately 80% to 85% of patients will walk independently at 1 year after diagnosis, and full recovery occurs in approximately 60%.

Relapses are rare but can occur in up to 10% of patients.

Table 8.3 • Management of Guillian-Barré Syndrome

Type of Management	Treatment
Airway, respiratory	Intubate if vital capacity ≤20 mL/kg and maximal inspiratory pressure ≤30 mm Hg Monitor bugle pressures
Prophylaxis	DVT prophylaxis with subcutaneous heparin GI prophylaxis (critically ill patients)
Nursing/rehabilitation	Frequent turning to avoid decubitus ulcers Physical and occupational therapy
Nutrition	Enteral nutrition
Immunomodulation	IVIG, 0.4 g/kg for 5 days *or* Plasma exchange every other day for 5 days

Abbreviations: DVT, deep vein thrombosis; GI, gastrointestinal; IVIG, intravenous immunoglobulin.

- The rapidly progressive weakness of GBS can lead to quadriplegia, bulbar and respiratory muscle involvement, and dysautonomia.
- *Campylobacter jejuni* (30%) and cytomegalovirus (10%) are most common among the infectious agents associated with GBS.
- Paresthesia in the feet is often the first manifestation of GBS.
- Patients who have the Miller Fisher variant of GBS present with ophthalmoplegia, ataxia, and areflexia. Autoantibodies against GQ1b ganglioside are present in most patients with this syndrome.
- Cerebrospinal fluid analysis shows albuminocytologic dissociation in GBS.
- Intravenous immunoglobulin and plasma exchange are accepted treatment choices for patients with GBS who cannot walk unassisted.
- Approximately 80% to 85% of patients with GBS will walk independently at 1 year after diagnosis, and full recovery occurs in approximately 60%.

Myasthenic Crisis

Overview and Epidemiology

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder (see also Chapter 41, "Neuromuscular Junction Disorders"). Anti–acetylcholine receptor and

anti–muscle-specific kinase are the 2 most common causative antibodies. The disorder manifests as fluctuating extraocular, bulbar, cervical, or proximal weakness. Marked respiratory muscle weakness can lead to respiratory failure, whereas profound bulbar weakness can lead to marked difficulty with secretion clearance, diminish airway tone, and hinder normal deglutition. Taken together, these life-threatening manifestations are termed *myasthenic crisis*.

Etiology

Two clinical scenarios should raise suspicion: a patient with known myasthenia presenting with an intercurrent infection and a patient who has had thymectomy and cannot be weaned off mechanical ventilation. Exacerbation of underlying MG has also been associated with certain drugs (eg, aminoglycosides, magnesium, quinine), surgery, fever, pregnancy, and other systemic illnesses (Box 8.2) (see also Chapter 41, "Neuromuscular Junction Disorders"). Myasthenic crisis can develop abruptly with few clinical signs as a result of chronic immunosuppression or muscle weakness masking the usual signs of respiratory failure. Moreover, oxygen desaturation is expected late, sometimes shortly before respiratory arrest.

Diagnosis

The diagnosis is typically made on the basis of clinical symptoms in the setting of a patient with known MG. However, patients may present with their first significant crisis undiagnosed, in which case other acute neurologic conditions resulting in diffuse weakness or tetraplegia (eg, GBS, botulism, stroke) must be considered. In addition, a myasthenic crisis must be distinguished from a cholinergic crisis because often they both may present with weakness (Table 8.4).

Management of Myasthenic Crisis

Cholinesterase inhibitors are not sufficient to treat patients with myasthenic crisis. In fact, their use is often stopped during mechanical ventilation to improve secretion management. Patients are best managed with several courses of plasma exchange. Corticosteroids are given concurrently with plasma exchange therapy.

Box 8.2 • Potential Risk Factors for Development of Myasthenic Crisis

- Concurrent infection or fever
- Thymectomy or other surgery
- Medications (see also Chapter 41, "Neuromuscular Junction Disorders")
- Pregnancy
- Systemic illness

Table 8.4 • Differentiation of Cholinergic and Myasthenic Crises

Factor	Cholinergic Crises	Myasthenic Crises
Frequency[a]	Rare	Common
Trigger	Overdose, drug therapy for MG	Infection, certain drugs, corticosteroids
Pupils	Miosis	Mydriasis
Respiration	Bronchus plugging and spasm, marked salivation	Diaphragm failure
Fasciculations, cramps	Present	Absent
Diarrhea	Present	Absent

Abbreviation: MG, myasthenia gravis.
[a] Combination of both crises is often clinically encountered.
Adapted from Wijdicks EFM. The clinical practice of critical care neurology. 2nd ed. New York (NY): Oxford University Press; c2003. Chapter 26, Myasthenia gravis; p. 422–36. Used with permission of Mayo Foundation for Medical Education and Research.

Frequent clinical assessments and bedside pulmonary function testing and blood gas analysis are essential in a monitored setting. Endotracheal intubation should be considered with deteriorating vital capacity or bugle pressures, atelectasis on chest radiography, or inability to handle secretions. However, a trial of biphasic positive airway pressure before the development of hypercapnia has been shown to prevent intubation in certain cases.

Outcome and Prognosis

About 40% of the patients with generalized MG may have a severe crisis at some point that requires endotracheal intubation and mechanical ventilation, mostly in the first 2 years from onset. The quality of life after MG is largely determined by the severity of muscle weakness (which may include weakness of neck muscles and constant head drop), dysphagia and chewing problems, ptosis, diplopia, and a speech impediment.

- A myasthenic crisis must be distinguished from a cholinergic crisis because often they both may present with weakness (Table 8.4).
- Patients with myasthenic crisis are best managed with several courses of plasma exchange.

Botulism

Overview and Epidemiology

Clostridium botulinum is part of a family of bacteria that are gram positive, spore forming, and anaerobic. After spore germination, the organisms produce toxins.

The light chain of botulinum toxin produces a proteolytic enzyme directed at the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors) complex. This cleavage prevents acetylcholine exocytosis from the motor nerve terminals and autonomic ganglia. The toxin may be food borne, the toxin may be produced by bacteria in an open wound, or the spores may be ingested and toxin released in the gastrointestinal tract (often the case in infants).

Botulism is extremely rare in the developed world. Infant botulism has occasionally been associated with ingestion of raw honey.

Clinical Manifestations

Autonomic manifestations include loss of pupillary accommodation and ophthalmoplegia leading to blurred vision, dilated pupils (Figure 8.2), bradycardia, hypotension, dry mouth, decreased sweating, and urinary retention. Decreased presynaptic acetylcholine leads to bilateral cranial nerve palsies with incumbent diplopia, ptosis, dysarthria, and dysphagia. Descending flaccid paralysis involving all muscles, including respiratory, is typical. Sensory symptoms are absent. Incremental response is found on rapid repetitive nerve stimulation.

Diagnosis

Detection of the toxin in serum can make the diagnosis. However, the result can be negative in infantile botulism, in which isolating the *Clostridium* spore in the stool is more useful. Electromyography can also be useful, but it may not be necessary if the clinical picture and other study results are positive.

Treatment

Supportive measures and careful assessment of respiratory status is important. Antitoxin can be delivered to patients who are older than 1 year and to adults. Botulism immunoglobulin can be given to infants younger than 1 year.

- The light chain of botulinum toxin produces a proteolytic enzyme directed at the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors) complex. This cleavage prevents acetylcholine exocytosis from the motor nerve terminals and autonomic ganglia.
- Botulism is extremely rare in the developed world.
- Infant botulism has occasionally been associated with ingestion of raw honey.
- Autonomic manifestations of botulism include loss of pupillary accommodation and ophthalmoplegia leading to blurred vision, dilated pupils, bradycardia, hypotension, dry mouth, decreased sweating, and urinary retention (Figure 8.2).

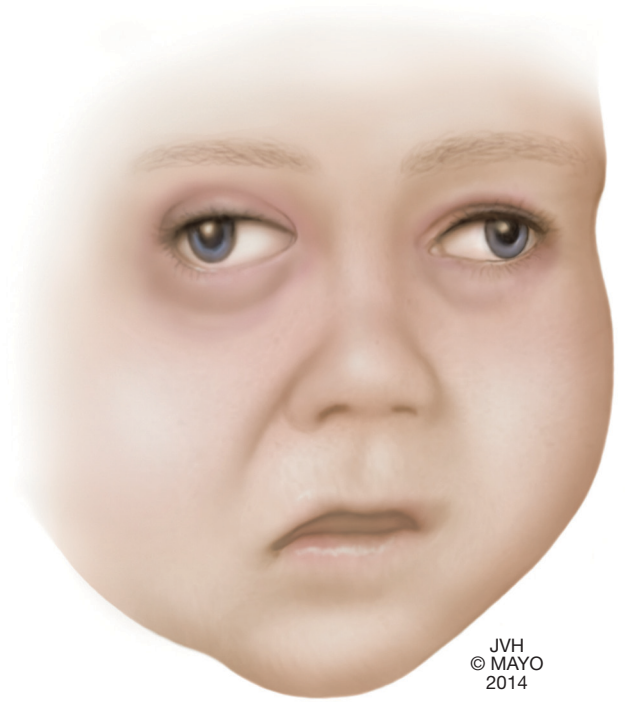

Figure 8.2 *Dysconjugate Gaze and Dilated Pupils of Botulism.*
In infants, ingestion of raw honey may lead to botulism poisoning manifested as dysconjugate gaze, bulbar and limb weakness, and dilatation of pupils.
(Used with permission of Mayo Foundation for Medical Education and Research.)

Critical Illness Neuropathy

Overview and Epidemiology

Critical illness neuropathy is rare, but it may occur in up to 50% to 70% of patients with systemic inflammatory response syndrome. This syndrome may occur in patients with severe infection, septic shock, or severe trauma.

Clinical Manifestations

Because patients are critically ill, often the earliest indicator of the disease is difficulty weaning from the ventilator. Significant muscle weakness, often of all 4 limbs, and respiratory muscle weakness develop. Tendon reflexes are reduced, and distal sensation is lost. The loss of distal sensation is sometimes difficult to test in a critically ill patient. Cranial nerves are often normal.

Diagnosis

The diagnosis is made with electromyography and laboratory studies. Nerve conduction studies show reduced amplitude of sensory nerve action potentials and

compound muscle action potentials with relatively preserved distal latencies and conduction velocities, findings suggesting an axonal pattern. Sensory nerve responses can be normal in the early stages. Needle examination shows fibrillation potentials and reduced recruitment. A concomitant myopathy sometimes occurs, as evidenced by rapid recruiting and short-duration motor unit potentials. Creatine kinase and cerebrospinal fluid values are usually normal. Rarely, the cerebrospinal fluid protein value is mildly increased.

Pathologic examination, when done, shows axonal degeneration of motor and sensory fibers. There are no inflammatory infiltrates.

Treatment and Prognosis

Treatment is supportive. Recovery occurs over weeks to months and may not be complete.

- Critical illness neuropathy is rare, but it may occur in up to 50% to 70% of patients with systemic inflammatory response syndrome.
- Often the earliest indicator of the disease is difficulty weaning from the ventilator.

Critical Illness Myopathy

Overview and Epidemiology

Critical illness myopathy is often recognized in the intensive care unit as diffuse flaccid paresis and difficulty weaning from the ventilator. It can occur in isolation or concomitantly with critical illness neuropathy. It often occurs in the setting of multiorgan failure (renal) and sepsis or systemic inflammatory response. Additional risk factors include corticosteroid use, use of neuromuscular junction blocking agents, chronic obstructive pulmonary disease, and liver failure.

Clinical Manifestations

Patients typically have diffuse weakness of all 4 limbs, proximal more than distal, and difficulty weaning from the ventilator. Facial weakness, but rarely oculomotor weakness, can occur. Sensory changes, if able to be tested, are typically absent. However, not uncommonly, critical illness myopathy and neuropathy overlap, and thus sensory abnormalties may occur in the latter.

Diagnosis

The diagnosis is made with electromyography. Nerve conduction studies often show low-amplitude, long-duration compound muscle action potentials with relative preservation of sensory responses. Needle electromyography shows increased insertional activity with fibrillation potentials and positive sharp waves. The creatine kinase value may be increased.

Treatment and Prognosis

Supportive treatment and prevention of complications are the mainstays of management.

- Critical illness myopathy is often recognized in the intensive care unit as diffuse flaccid paresis and difficulty weaning from the ventilator.
- Additional risk factors include corticosteroid use, use of neuromuscular junction blocking agents, chronic obstructive pulmonary disease, and liver failure.

9 Acute Hyperthermic Syndromes

PHILIPPE COUILLARD, MD; EELCO F. M. WIJDICKS, MD, PHD

Introduction

A **high core body** temperature is a medical emergency. Neuronal mitochondria and plasma membranes are thought to experience protein changes at temperatures higher than 40°C and lead to brain damage or dysfunction. In hyperthermia, the thermoregulatory control mechanisms are impaired or overwhelmed, as opposed to fever, in which the hypothalamic set point is increased. Hyperthermia can be caused by conditions such as thyrotoxicosis, pheochromocytoma, or meningitis. Heat stroke is another important example of hyperthermia. Drugs that impair thermoregulation can also play a role and include amphetamines, cocaine, opiates, antihistamines, selective serotonin reuptake inhibitors, β-blockers, and diuretics. There are several acute hyperthermia syndromes (Table 9.1).

Serotonin Syndrome

Epidemiology

5-Hydroxytryptamine (5-HT) is a monoamine derived from tryptophan. Serotoninergic neurons are located in the brainstem raphe nuclei. This system assists in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, nociception, and motor tone. Serotonin syndrome may occur after combining medications that block serotonin metabolism, an effect leading to excess extracellular 5-HT. In most patients, the syndrome develops within 6 hours after initial use of medication, an overdose, or a change in dosing.

Several drugs and drug combinations have been associated with serotonin syndrome. A thorough review of medications is essential for use of selective serotonin reuptake inhibitors, triptans, opioids, metoclopramide, ondansetron, or inhibitors of cytochrome P450 2D6 and 3A4. Severe cases often involve unsuspected use of monoamine oxidase inhibitors such as linezolid or methylene blue (Box 9.1).

Clinical Manifestations

Mild cases present with tachycardia, shivering, diaphoresis, and mydriasis. Tremor, myoclonus, and hyperreflexia are common. Hypertension, hyperthermia, and hyperactive bowel sounds complicate moderate cases. Hyperreflexia, myoclonus, rigidity, and clonus are striking features that may occur in this disorder, in addition to agitated delirium. In life-threatening cases, seizures, shock, metabolic acidosis, rhabdomyolysis, renal failure, and disseminated intravascular coagulation develop, due in part to uncontrolled hyperthermia.

Treatment

Treatment is supportive and includes discontinuing use of the precipitating drugs—a simple fact that is often forgotten. In addition, aggressive control of cardiorespiratory and thermal abnormalities is needed. The 5-HT_{2A} antagonist cyproheptadine is often used for intubated patients, along with sedation and neuromuscular paralysis. Seizures are treated with intravenous benzodiazepines, which also may help control agitation.

- Serotoninergic neurons are located in the brainstem raphe nuclei.

Abbreviation: 5-HT, 5-hydroxytriptamine

Table 9.1 • Comparison of the Acute Hyperthermia Syndromes

Condition	Precipitants	Clinical Features	Treatment
Serotonin syndrome	Drugs resulting in increased serotonin (Box 9.1)	Hyperthermia Hyperreflexia Tremor, clonus Myoclonus Mental status changes	Removal of offending agent Supportive 5-hydroxytriptamine$_{2A}$ antagonist Cyproheptadine or sedation for intubated patients
Neuroleptic malignant syndrome	Neuroleptic agents or sudden withdrawal of dopamine agent	Hyperthermia Tachycardia, diaphoresis Rigidity, tremor Mental status changes Dysphagia Mutism	Removal of offending agent Supportive Bromocriptine, dantrolene, or amantadine can be considered
Paroxysmal sympathetic hyperactivity	Brain trauma Severe brain injury (stroke)	Hyperthermia Tachycardia Hypertension Tachypnea Excessive sweating Dystonic posturing	Supportive treatment Morphine, β-blockers, gabapentin
Malignant hyperthermia	Succinylcholine in the setting of an abnormal ryanodine receptor	Hyperthermia Muscle spasms Trismus	Removal of offending agent Cooling Dantrolene

Neuroleptic Malignant Syndrome

Clinical Manifestations

Neuroleptic malignant syndrome is suspected in a patient who has sudden acute rigidity and increased core temperature and has used a dopaminergic agent (or abruptly withdrawn use of dopamine). The onset may not always be abrupt, and milder forms have been described. Various changes in level of consciousness, ranging from confusion to coma, are often present. Basal ganglia dysfunction takes the form of tremor, dystonia, and bradykinetic features such as dysphagia, sialorrhea, and mutism. When severe, autonomic dysfunction is present with diaphoresis, tachycardia, and labile blood pressure. Neuroleptic malignant syndrome may mimic shock. Leukocytosis and hyperCKemia are present. The occurrence of neuroleptic malignant syndrome is unpredictable, and its pathophysiologic mechanism may be unresolved.

Treatment

Treatment is supportive: cooling, hydration, and discontinuing use of the offending drugs. Bromocriptine, dantrolene, and amantadine have been shown to improve outcome over supportive care alone. Neuromuscular blockade in life-threatening cases prevents heat generation. Malignant catatonia is a rare condition that shares many similar features and culminates in life-threatening autonomic dysregulation. Lorazepam, clonidine, and electroconvulsive therapy are possible approaches, coupled with discontinuation of drug use and aggressive supportive care.

- Neuroleptic malignant syndrome is suspected in a patient who has sudden acute rigidity and increased core temperature and has used a dopaminergic agent (or abruptly withdrawn use of dopamine).
- For neuroleptic malignant syndrome, bromocriptine, dantrolene, and amantadine have been shown to improve outcome over supportive care alone.

Paroxysmal Sympathetic Hyperactivity

Clinical Manifestations

Episodes of paroxysmal sympathetic hyperactivity generally occur in patients with severe traumatic brain injury or, less frequently, hypoxic-ischemic encephalopathy or stroke. Whether triggered by stimulation or not, manifestations include hyperthermia, tachycardia, hypertension, tachypnea, excessive sweating, and dystonic posturing. Because of the condition's sudden onset, episodes may be mislabeled as seizure or simply considered a manifestation of the primary brain disorder.

Treatment

Management of paroxysmal sympathetic hyperactivity includes adequate hydration, effective analgesia, and avoidance of triggers such as frequent positioning and frequent tracheal suctioning. Morphine sulfate, nonselective β-blockers, and gabapentin are first-line therapy.

Box 9.1 • Medications Sometimes Associated With Serotonin Syndrome

Drugs of abuse
- Amphetamines
- Cocaine
- 3,4-Methylenedioxymethamphetamine (Ecstasy)
- Lysergic acid diethylamide (LSD)

Pain medications
- Tramadol
- Meperidine
- Pentazocine
- Fentanyl

Psychiatric medications
- Selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
- Serotonin norepinephrine reuptake inhibitors (desvenlafaxine, duloxetine, venlafaxine)
- Dopamine norepinephrine reuptake inhibitors (bupropion)
- Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine)
- Serotonin modulating agents (nefazodone, trazodone, vilazodone)
- Monoamine oxidase inhibitors
- Lithium
- Amphetamines

Antiseizure medications
- Valproate
- Carbamazepine

Other neurologic medications
- Levodopa/carbidopa
- Triptans
- Ergotamine
- Cyclobenzaprine
- Dextromethorphan

Gastrointestinal medications
- Metaclopramide
- Ondansetron

Over-the-counter medications or supplements
- St. John's wort

Second-line agents include baclofen, bromocriptine, and clonidine.

- Episodes of paroxysmal sympathetic hyperactivity generally occur in patients with severe traumatic brain injury or, less frequently, hypoxic-ischemic encephalopathy or stroke.

Malignant Hyperthermia

Pathophysiology

Malignant hyperthermia is a muscle disorder caused by a mutation in the ryanodine receptor. An increased tendency for excessive calcium release from the sarcoplasmic reticulum is the key response to exposure to a trigger such as inhaled anesthetics or the muscle relaxant succinylcholine. Calcium excess leads to muscle hyperactivity and hypermetabolism followed by fever and rhabdomyolysis. Uncoupling of oxidative phosphorylation with metabolic breakdown activates the sympathetic nervous system and causes catecholamine release.

Clinical Manifestations

Generalized muscle spasms, trismus, cutaneous vasoconstriction, and increased systemic vascular resistance, cardiac output, and minute ventilation are presenting symptoms and signs. Overwhelmed, ATP production ceases, the result of which is failure of membrane pumps, leakage of electrolytes, increased creatine kinase value, myoglobinuria with cardiac arrhythmia, and death.

Treatment

The mainstay of treatment is discontinuing use of the offending agent, cooling, cardiovascular support, renal and electrolyte management, and administration of dantrolene. This disorder is more often seen by anesthesiologists than neurologists because of its association with certain types of anesthetic agents.

- Malignant hyperthermia is a muscle disorder caused by a mutation in the ryanodine receptor.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

I.1. A 56-year-old man is found unresponsive in his home. He was noted to be pulseless, but a perfusing rhythm was restored in the field. Three days later in the intensive care unit, he remains unresponsive and on a ventilator. Which of the following statements is most correct regarding his case?

a. After this period of time, a diagnosis of brain death can be established despite continued use of intravenous propofol
b. The presence of an apneustic pattern of breathing after pausing the ventilator is strongly suggestive of clinical brain death
c. If brainstem reflexes are absent, including no oculocephalic responses to head movement, cold-caloric testing should be performed
d. A clinical diagnosis of brain death cannot be made if the patient's family believes the patient is responding to their voices
e. During the apnea test the patient has no spontaneous respiration despite an increase in his Pco_2 from 35 to 50 mm Hg, a finding confirming the diagnosis of brain death

I.2. An unbelted 21-year-old woman is ejected from the backseat of a car during a high-velocity multivehicle collision. On evaluation in the emergency department she is stuporous and has multiple scalp lacerations and abrasions. Which of the following statements regarding her evaluation is most correct?

a. If her neurologic examination does not show any focal abnormalities, urgent computed tomography can be deferred
b. Acute subarachnoid hemorrhage noted on head computed tomography would likely reflect traumatic rupture of a saccular intracranial aneurysm
c. An epidural hematoma is very unlikely unless she had a lucid interval after her injury
d. A persistent bloody nasal discharge can be assayed for β_2-transferrin to exclude cerebrospinal fluid rhinorrhea
e. A small subdural hematoma noted on head computed tomography would require evacuation rather than observation given her mechanism of injury

I.3. A 40-year-old man is admitted to the hospital after a motorcycle accident. He was helmeted and there was no loss of consciousness, but he has noted neck pain and left upper limb weakness since the accident. On examination, he has no voluntary movement of left upper limb muscles, and there is moderate weakness of lower limb muscles in an upper motor neuron pattern. Which of the following is most correct regarding his evaluation and management?

a. If plain radiographs of his cervical spine have normal results, no further spine imaging is indicated
b. Urinary catheterization is required to prevent bladder injury in the setting of possible urinary retention
c. Electromyography performed more than 3 weeks after the accident would be unlikely to detect axonal injury to the left brachial plexus
d. Low-dose intravenous corticosteroids are required to minimize any deficit related to cervical spinal cord injury
e. If results of spine magnetic resonance imaging are normal, prophylaxis for deep vein thrombosis with subcutaneous heparin must still be avoided given the risk for delayed spinal epidural hematoma

I.4. A 52-year-old woman with a history of poorly controlled focal seizures with dyscognitive features is brought to the emergency department with a prolonged generalized convulsive seizure lasting more than 40 minutes. She was intubated and ventilated in the field and has not responded to lorazepam 4 mg intravenously. Which of the following statements regarding her management is most accurate?

a. Serum glucose and electrolytes should be checked and abnormalities corrected urgently
b. She should immediately be given lamotrigine 25 mg twice daily, with a plan to increase to 50 mg twice daily in 3 days
c. Fosphenytoin intravenously is contraindicated given the risk of hemodynamic instability
d. Loading valproic acid intravenously cannot be performed unless the patient had previously tolerated the oral form in the outpatient setting
e. Infusions of propofol or pentobarbital are contraindicated if the seizures do not respond to initial intravenous benzodiazepines

I.5. An 81-year-old woman with long-standing idiopathic Parkinson disease is brought to the emergency department by her family for progressive confusion. On examination she has a temperature of 38.6°C and is diffusely rigid. Her family believes she may have recently run out of her carbidopa/levodopa medication. Which of the following treatments is most likely to be helpful in her case?

a. Haloperidol
b. Quetiapine
c. Morphine
d. Tramadol
e. Dantrolene

I.6. A 32-year-old smoker is admitted to the neurointensive care unit after an abrupt, severe headache and progressive obtundation. Evaluation in the emergency department included head computed tomography, which showed diffuse subarachnoid hyperdensity. Which of the following statements regarding the patient's evaluation and management is most correct?

a. Transcranial Doppler ultrasonography must be performed to identify the presumably ruptured intracranial aneurysm

b. Vasospasm is unlikely to develop if the aneurysm is secured within the first 24 hours
c. Aggressive hydration with 5% dextrose solutions is indicated to reduce the risk of hyponatremia
d. Dual antiepileptic therapy is required to prevent seizures in most patients
e. If treatment of the aneurysm is delayed, consideration of antifibrinolytic agents to reduce the risk of rebleeding should be considered

I.7. A 64-year-old man with a history of coronary artery disease experiences an out-of-hospital cardiac arrest. He is resuscitated in the emergency department but did not have a perfusing rhythm for approximately 25 minutes. On examination he does not respond to external stimuli but has preserved brainstem reflexes. Which of the following electroencephalographic patterns is associated with the best prognosis?
a. Burst-suppression
b. Slowed background responsive to external stimuli
c. Persistent alpha rhythm
d. Diffusely suppressed background amplitude
e. Periodic sharp waves

I.8. A 22-year-old woman presents with 4 days of progressively diffuse cutaneous paresthesia, beginning in her feet and now involving all limbs. For the past day she has had trouble climbing stairs. On examination she has a moderate flaccid quadriparesis with neck flexor weakness and absent muscle stretch reflexes throughout. Which of the following statements regarding her case is most accurate?
a. A maximal inspiratory pressure of −20 mm Hg is reassuring against the need for urgent ventilatory support
b. Immediate treatment with methylprednisolone 1,000 mg daily should be initiated
c. Given her high risk of autonomic instability, close hemodynamic monitoring is required
d. Her electromyogram is likely to show decrement of compound muscle action potential amplitude with slow repetitive stimulation
e. A low cerebrospinal fluid protein value would confirm the suspected diagnosis in her case

I.9. An 84-year-old man is found unresponsive on the floor of his bathroom. Evaluation in the emergency department found a large, acute, putaminal hemorrhage and moderate obstructive hydrocephalus. His blood pressure is 220/115 mm Hg and his heart rate is 50 beats per minute. Which of the following statements regarding his case is most accurate?
a. His intracranial pressure is likely to be between 10 and 20 mm Hg
b. Reducing his intracranial pressure would likely be best achieved with cerebrospinal fluid diversion through a ventriculostomy
c. Lumbar puncture and cerebrospinal fluid examination are required to exclude intraventricular extension of the hemorrhage
d. A cerebral blood flow of 50 mL/100 g tissue per minute would indicate a poor prognosis
e. If the patient is intubated, hyperventilation for several days may prevent the need for invasive means of reducing his intracranial pressure

I.10. Pharmacoresistence in status epilepticus occurs because of which of the following?
a. Increased γ-aminobutyric acid inhibition
b. Decreased availability of γ-aminobutyric acid receptors
c. Cessation of change in gene expression
d. Cytochrome inhibition
e. Decreased serum medication protein binding

I.11. Which of the following are common physiologic manifestations of status epilepticus?
a. Cardiac dysrhythmias
b. Metabolic alkalosis
c. Hypoglycemia
d. Hypocapnea
e. Hypothermia

Answers

I.1. Answer c.
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Section
II

Cerebrovascular Diseases

Kevin M. Barrett, MD, *editor*

10 Ischemic Stroke: Common Causes and Diagnosis

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Introduction

Ischemic stroke is the fifth leading cause of death and a major condition feared by older adults. Clinically identifying patients with cerebral ischemia is important so that appropriate, immediate treatment can be provided and stroke preventive strategies initiated. This chapter presents an overview of the more common causes and mechanisms of stroke. Uncommon causes of stroke and stroke in specific situations are covered in Chapter 11 ("Ischemic Stroke: Uncommon and Special Situations").

Clinical Ischemic Stroke Syndromes

Basic anatomy and physiology are reviewed in Volume 1. Large-artery clinical syndromes are summarized in Table 10.1. Vascular brainstem syndromes are described in Table 10.2 and illustrated in Figure 10.1. More than 20 lacunar syndromes have been described; however, the most common clinical lacunar syndromes are listed in Table 10.3.

Overview of Ischemic Stroke

Mechanisms of Cerebral Ischemia

Ischemic stroke has been classically defined as a fixed focal neurologic deficit attributable to an arterial or venous territory and lasting longer than 24 hours. *Transient ischemic attack* (TIA) has been classically defined as a transient focal neurologic deficit attributable to an arterial territory lasting less than 24 hours. However, diffusion-weighted imaging (DWI) has shown that many TIAs are associated with tissue damage. Therefore, a tissue-based diagnosis of stroke and TIA has been proposed. The proposed definition of *TIA* is a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. A patient who has symptoms lasting less than 24 hours but who has an abnormality on DWI would be considered to have had an ischemic stroke.

Cerebral ischemia may result from several mechanisms, including hypoperfusion, thrombosis, and embolism. Hypoperfusion may cause either global deficits or focal deficits depending on the severity and length of hypoperfusion and whether it occurs with a fixed-vessel stenosis. Watershed or borderzone infarctions often result from hypoperfusion. Thrombosis often occurs at the site of a vessel stenosis or at a site of plaque rupture. Embolism may result from a cardiac embolus (thrombus, myxomatous emboli, or vegetation), from artery-to-artery emboli, or, rarely, from air, fat, or amniotic fluid.

Causes of Cerebral Ischemia

Causes of arterial cerebral ischemia can be classified simply into roughly 6 categories: cardioembolic disease; large-vessel extracranial disease (aorta, carotid, and vertebral arteries); large-vessel intracranial disease (intracranial internal carotid,

Abbreviations: ADC, apparent diffusion coefficient; $CHADS_2$, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and prior stroke or transient ischemic attack; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 65 to 74 years, age 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack, female sex, and vascular disease; CREST, Carotid Revascularization Endarterectomy vs Stenting Trial; CT, computed tomography; CTA, computed tomographic angiography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; ICSS, International Carotid Stenting Study; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NASCET, North American Symptomatic Carotid Endarterectomy Trial; PFO, patent foramen ovale; SAMMPRIS, Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; TIA, transient ischemic attack

Table 10.1 • Large-Vessel Clinical Syndromes

Vessel	Clinical Presentation
Internal carotid artery	Ipsilateral retinal ischemia (amaurosis) Sensorimotor dysfunction similar to involvement of middle and anterior cerebral artery territories
Middle cerebral artery, M1 segment	Contralateral facial and arm weakness more than leg weakness Aphasia (dominant hemisphere) Contralateral sensory loss Cortical sensory loss (nondominant hemisphere) Contralateral visual field defect Gaze deviation ipsilateral to lesion
Middle cerebral artery, anterior division	Contralateral facial and arm weakness more than leg weakness Broca aphasia (dominant hemisphere)
Middle cerebral artery, posterior division	Contralateral sensory loss Wernicke aphasia (dominant hemisphere) Gerstmann syndrome (dominant hemisphere) Cortical sensory loss or neglect (nondominant hemisphere) Contralateral visual field defect
Anterior cerebral artery	Contralateral leg weakness Contralateral leg sensory loss Apraxia Abulia (bilateral)
Anterior choroidal artery	Contralateral homonymous hemianopia (lateral geniculate body) Contralateral facial, arm, leg weakness (posterior limb internal capsule) Contralateral facial, arm, leg sensory loss (thalamus)
Posterior cerebral artery, precommunicating part	Contralateral sensory loss (thalamus) Cognitive dysfunction (thalamus) Thalamic aphasia (rarely) Visual dysfunction as for postcommunicating segment
Posterior cerebral artery, postcommunicating part	Contralateral homonymous hemianopia Visual agnosias
Posterior inferior cerebellar artery	Horner syndrome Ipsilateral hemiataxia Ipsilateral palatal weakness Hoarse voice Decreased pain and temperature on ipsilateral portion of face and contralateral limbs
Anterior inferior cerebellar artery	Ipsilateral deafness Ipsilateral facial weakness (lower motor neuron) Ipsilateral hemiataxia Contralateral sensory loss in limbs
Superior cerebellar artery	Ipsilateral ataxia Decreased sensation contralaterally Diplopia
Basilar perforators, median and paramedian pontine perforators	Contralateral limb weakness if unilateral; quadriparesis if bilateral Hemiataxia may develop (crossing pontocerebellar fibers) CN VI and VII (affecting nuclei or nerve fibers) palsies Internuclear ophthalmoplegia
Midbrain basilar, posterior cerebral artery perforators	Ipsilateral nuclear or fascicular CN III palsy Contralateral facial, arm, leg weakness (corticospinal tracts) Rubral tremor (red nucleus) may develop Ataxia (decussation of superior cerebellar peduncle) may occur
Anterior spinal and vertebral perforators to median and paramedian medulla	Ipsilateral tongue weakness (CN XII nucleus or nerve fibers) Contralateral arm and leg have reduced vibration sensation and proprioception (medial lemniscus) Contralateral arm and leg weakness (medullary pyramids)

Abbreviation: CN, cranial nerve.
Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.

middle cerebral, anterior cerebral, vertebrobasilar, and posterior cerebral arteries); small-vessel disease; abnormalities intrinsic to the blood (eg, prothrombotic disorders); and other diseases. Despite patients undergoing thorough evaluations, the cause of 20% to 30% of ischemic stroke remains cryptogenic (ie, without a defined cause). Cryptogenic stroke has been hypothesized to be due to nonstenotic plaque rupture, paroxysmal atrial fibrillation, or undefined coagulation disorders. Venous infarction is also important, and further details of venous thrombosis are in Chapter 11, ("Ischemic Stroke: Uncommon and Special Situations"). A more extensive differential diagnosis of cerebral ischemia based on those simplified categories is listed in Box 10.1. Cardioembolic disease (30%–40%) is most prevalent, followed by lacunar disease (20%–30%), cryptogenic disease (20%–30%), large-vessel disease (10%–15%), and coagulation disorders (<5%). It is important to keep in mind that there are conditions that may mimic cerebral ischemia (Box 10.2).

- The proposed definition of *TIA* is a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. A patient who has symptoms lasting <24 hours but who has an abnormality on DWI would be considered to have had an ischemic stroke.

Box 10.1 • Differential Diagnosis of Ischemic Stroke

Cardiac disorder
- Atrial fibrillation
- Mitral stenosis
- Left ventricular thrombus
- Atrial myoma
- Dilated cardiomyopathy
- Anterior wall myocardial infarction
- Prosthetic valves
- Endocarditis (bacterial, nonbacterial, marantic)
- Patent foramen ovale
- Atrial septal aneurysm
- Mitral valve calcification
- Fibroelastoma
- Pulmonary fistula (Osler-Weber-Rendu disease)
- Air or fat emboli (rare)

Large-vessel extracranial disorder
- Atherosclerosis
- Dissection
- Radiation vasculopathy
- Fibromuscular dysplasia
- Vasculitis
  - Takayasu vasculitis
  - Giant cell arteritis

Large-vessel intracranial disorder
- Atherosclerosis
- Dissection
- Inflammatory vasculitis
  - Isolated CNS angiitis
  - Necrotizing vasculitides (Wegener granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, lymphomatoid granulomatosis)
  - Hypersensitivity angiitis with connective tissue disease (sarcoidosis, systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis)
  - Susac syndrome (retinocochleocerebral arteriopathy)
  - Kohlmeier-Degos disease
  - Behçet syndrome
- Infectious vasculitis
  - Varicella zoster virus
  - Human immunodeficiency virus
  - Hepatitis B and C
  - Epstein-Barr virus
  - Cytomegalovirus
- Noninflammatory vasculopathies
  - Moyamoya disease
  - Drug-induced (cocaine, methamphetamine, phenylpropanolamine, ergotamines)
  - Postpartum cerebral angiopathy
  - Radiation-induced
  - Eales disease
  - Arterial dolichoectasia
  - Endovascular lymphoma
- Thrombosed aneurysm with emboli

Small-vessel disease
- Lipohyalinosis or atherosclerosis
- Vasculitis
  - Varicella zoster vasculitis
  - Cryoglobulin-related angiitis
  - Angiitis related to lymphomatoid malignancies
  - Henoch-Schönlein purpura

Hematologic and coagulation disorders
- Disorders of coagulation factors
  - Protein C or protein S deficiency
  - Antithrombin III deficiency
  - Activated protein C resistance or factor V Leiden mutation
  - Prothrombin 20210 mutation
- Disorders of red blood cells
  - Sickle cell anemia
  - Polycythemia (primary or secondary)
  - Paroxysmal nocturnal hemoglobinuria
- Disorders of white blood cells
  - Lymphoma
  - Leukemia
- Disorders of platelets
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenic purpura
  - Idiopathic thrombocytopenic purpura
  - Essential thrombocythemia
  - Thrombocytosis
  - Paraproteinemia
  - Uremia
- Disorders of plasma cells
  - Myeloma
  - Cryoglobulinemia
- Other
  - Antiphospholipid antibody syndrome
  - Hyperhomocystinemia
- Malignancy-associated coagulopathy

Other
- CADASIL
- Sneddon syndrome
- Fabry disease
- MELAS
- Homocystinuria
- Organic acidemias

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes.

Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.

Table 10.2 • Brainstem Clinical Syndromes

Name	Corresponding Illustration	Localization	Vascular Supply	Clinical Symptoms (Anatomy)
Midbrain syndromes				
Weber syndrome	Figure 10.1A	Medial midbrain	PCA perforators	Contralateral hemiparesis (cerebral peduncle) Ipsilateral CN III palsy (fascicles of CN III) Impaired ipsilateral pupillary reflex (CN III) and dilated pupil
Benedikt syndrome	Figure 10.1B	Midbrain tegmentum	PCA perforators	Ipsilateral CN III palsy, usually with dilated pupil (CN III fascicles) Contralateral involuntary movements (red nucleus, subthalamic nucleus)
Claude syndrome	Figure 10.1C	Midbrain tegmentum (dorsal)	PCA perforators	Ipsilateral CN III palsy (CN III fascicles) Contralateral hemiataxia and dysmetria (dentatothalamic fibers within the superior cerebellar peduncle) Contralateral tremor (red nucleus)
Nothnagel syndrome	Figure 10.1D	Midbrain	PCA perforators	Ipsilateral CN III palsy (CN III fascicles) Contralateral hemiataxia (dentatothalamic fibers in superior cerebellar peduncle)
Pontine syndromes				
Millard-Gubler syndrome	Figure 10.1E	Ventral pons	Basilar artery perforators, median and paramedian perforators	Ipsilateral lower motor neuron facial paralysis (CN VII) Ipsilateral abducens paralysis (CN VI fibers) Contralateral hemiparesis (corticospinal tract in basis pontis)
Foville syndrome	Figure 10.1F	Dorsal pons tegmentum	Basilar artery perforators	Ipsilateral lower motor neuron facial paralysis (nucleus or fascicles of CN VII) Ipsilateral gaze paralysis (nucleus abducens palsy) Contralateral hemiparesis (corticospinal tract in basis pontis)
Ventral pontine syndrome	Figure 10.1G	Ventral pons	Basilar artery, paramedian perforators	Ipsilateral CN VI palsy (CN VI fascicles) Contralateral hemiparesis (corticospinal tract in basis pontis)
Marie-Foix syndrome	Figure 10.1H	Base of pons	Basilar artery perforators	Ipsilateral cerebellar ataxia (corticopontocerebellar fibers) Contralateral hemiparesis (corticospinal tract in basis pontis) Variable contralateral decrease in pain and temperature sensation (spinothalamic tract involvement)
Medullary syndromes				
Wallenberg syndrome	Figure 10.1I	Lateral medulla	PICA	Ipsilateral hemiataxia (inferior cerebellar peduncle) Dysphagia, hoarseness, ipsilateral palatal weakness (nucleus ambiguus) Horner syndrome (sympathetic) Decrease in pain and temperature sensation (spinal tract and nucleus of CN V and lateral spinothalamic tract) on ipsilateral portion of face, contralateral portion of body
Dejerine syndrome (medial medullary syndrome)	Figure 10.1J	Medial medulla	Vertebral artery perforators, anterior spinal artery	Contralateral hemiparesis (medullary pyramid) Contralateral decrease in vibration or proprioception sensation in limbs (medial lemniscus) Ipsilateral CN XII palsy

Abbreviations: CN, cranial nerve; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery.

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

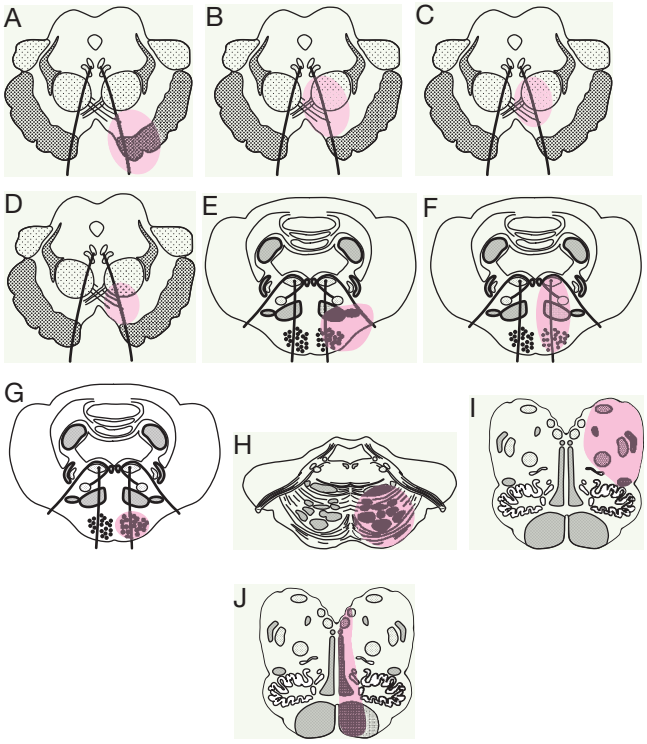

Figure 10.1 *Brainstem Clinical Syndromes. See Table 10.3 for details. A, Weber syndrome. B, Benedikt syndrome. C, Claude syndrome. D, Nothnagel syndrome. E, Millard-Gubler syndrome. F, Foville syndrome. G, Ventral pontine syndrome. H, Marie-Foix syndrome. I, Wallenberg syndrome. J, Dejerine syndrome.*

(Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 10.3 • Lacunar Syndromes

Syndrome	Typical Clinical Presentation	Typical Localization
Pure motor hemiparesis	Contralateral facial, arm, leg weakness	Internal capsule Corona radiata
Pure sensory stroke	Contralateral facial, arm, leg sensory loss	Thalamus (ventral posterolateral and posteromedial nuclei)
Sensorimotor stroke	Contralateral facial, arm, leg weakness Contralateral facial, arm, leg sensory loss	Thalamocapsular
Ataxic-hemiparesis	Hemiataxia and hemiparesis on same side of body	Basis pontis Thalamocapsular Corona radiata
Clumsy hand dysarthria	Facial weakness Dysarthria Slight hemiparesis Cerebellar dysmetria	Basis pontis

Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.

General Approach to Evaluation of a Patient With Arterial Cerebral Ischemia

Evaluation of a patient with suspected arterial cerebral ischemia should begin with an evaluation to identify whether the patient is a candidate for intervention (intravenous tissue plasminogen activator, intra-arterial thrombolytics, or mechanical thrombectomy). This evaluation is covered in detail in Chapter 12 ("Acute Ischemic Stroke Evaluation and Treatment"). The National Institutes of Health Stroke Scale score (often calculated at hospital admission) helps determine the risk of hemorrhage with intravenous tissue plasminogen activator and also predicts the outcome after cerebral ischemia.

If a patient is a candidate for acute intervention, the patient undergoes further evaluation. One goal is to identify the potential cause of cerebral ischemia, so that the appropriate antithrombotic for secondary prevention is selected, and to identify patients who need surgical or endovascular treatment. The second goal of evaluation is to identify and modify contributing risk factors. The third goal is to identify and prevent complications related to cerebral ischemia (aspiration pneumonia, urinary tract infections, deep vein thrombosis or pulmonary embolism, myocardial infarction, arrhythmias, and depression). Rehabilitation is an important aspect of treatment as well (see Chapter 16, "Neurorehabilitation").

A general approach to stroke evaluation (Figure 10.2) is based on the pretest probability (ie, prevalence) of causes in addition to the identification of causes that change management. The approach varies depending on other factors influencing the pretest probability of individual causes collected in the initial history, physical examination, laboratory studies, and imaging (Box 10.3). Additional recommendations for diagnostic evaluation are noted in individual sections below.

Computed tomography (CT) and magnetic resonance imaging (MRI) are common tools used in the evaluation of cerebral ischemia. CT of the head should be performed for all patients presenting with suspected stroke. This aids in the distinction between hemorrhage and ischemia. The CT may be negative for stroke in the first 24 hours, but early signs of ischemia include sulcal effacement, loss of the gray-white junction, and a hyperdense artery (eg, basilar or middle cerebral artery).

The most useful brain MRI sequences for cerebral ischemia are fluid-attenuated inversion recovery (FLAIR),

Box 10.2 • Mimics of Cerebral Ischemia

Differential diagnosis of transient neurologic deficits
- Transient ischemic attack
- Seizure
- Migraine
- Metabolic disturbance (hypoglycemia, hypocalcemia, or hypercalcemia)
- Myasthenia gravis
- Paroxysmal symptoms in multiple sclerosis
- SMART syndrome
- Reversible cerebrovasoconstrictive syndrome
- Psychogenic

Differential diagnosis of acute fixed focal neurologic deficit
- Ischemic stroke
- Cerebral hemorrhage
- Bell palsy
- Peripheral mononeuropathy
- Encephalitis
- SMART syndrome
- Reversible cerebrovasoconstrictive syndrome
- PRES
- Unmasking of prior stroke due to infection or metabolic derangement
- Psychogenic

Abbreviations: PRES, posterior reversible encephalopathy syndrome; SMART, strokelike migraine attacks after radiotherapy.

DWI, and apparent diffusion coefficient (ADC) map (Figure 10.3). DWI measures the random diffusion of water molecules. Random diffusion of water is relatively free in the extracellular space and more restricted in the intracellular space. When cytotoxic edema forms early in cerebral ischemia, water shifts from the extracellular space to the intracellular space, and diffusion is restricted. In general, the DWI signal is bright and the ADC map dark with acute cerebral ischemia. These sequences both normalize over 2 to 3 weeks; thus, DWI is useful in determining the acuity of the lesion and confirming the diagnosis and tissue damage. The DWI signal must be evaluated with the ADC map and the clinical history since a DWI signal abnormality can also be present with acute demyelinating lesions, neoplasms, infection, Creutzfeldt-Jakob disease, and other processes.

Ischemic Stroke by Etiologic Factor

Cardioembolic Source

Approximately 30% to 40% of ischemic strokes or TIAs are due to a cardioembolic source; thus, the pretest probability for any patient is high. Major cardioembolic sources are those for which the medical literature clearly shows a causal relationship with cerebral ischemia and for which clinical trials for treatment exist (Box 10.4). Minor cardioembolic sources are those for which the medical literature presents controversial or inconclusive findings related to the relationship to cerebral ischemia.

A cardiac examination, chest radiography, and electrocardiography are recommended for all patients with cerebral ischemia. Selected patients may benefit from echocardiography or extended cardiac monitoring (Holter, event recorder, or extended cardiac monitoring). Suspicions of cardiac disease that would warrant such tests include multiple arterial territory ischemic stroke, palpitations, large left atrium, mitral valve disease, and history of cardiac disease.

Nonvalvular atrial fibrillation is one of the most common causes of cerebral ischemia. Atrial fibrillation affects 1% of the general population but 10% of persons older than 75 years. Both paroxysmal and chronic atrial fibrillation are risk factors for ischemia, but paroxysmal atrial fibrillation is often difficult to prove. Factors that increase the risk of thromboembolism in the presence of atrial fibrillation include age older than 75 years, hypertension, diabetes mellitus, history of thromboembolism, and congestive heart failure. The $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or TIA) score (Table 10.4) and the CHA_2DS_2-VASc (congestive heart failure, hypertension, age 65–74 years, age ≥75 years, diabetes mellitus, prior stroke or TIA, female sex, and vascular disease) score can be used to predict the risk of recurrent thromboembolism (Table 10.5). The risk may be as high as 10% to 12% per year for patients with multiple risk factors. Paroxysmal atrial fibrillation can be missed with 24-hour telemetry or Holter monitoring. Extended monitoring should be considered for patients with multiple arterial territory strokes, enlarged left atrium by echocardiography, advanced age, or cryptogenic disease.

Warfarin (international normalized ratio goal, 2–3) is superior to aspirin and superior to clopidogrel plus aspirin for prevention of thromboembolism. Three novel anticoagulants, dabigatran (a direct thrombin inhibitor), rivaroxaban (a factor Xa inhibitor), and apixaban (a factor Xa inhibitor), have been compared with warfarin and are

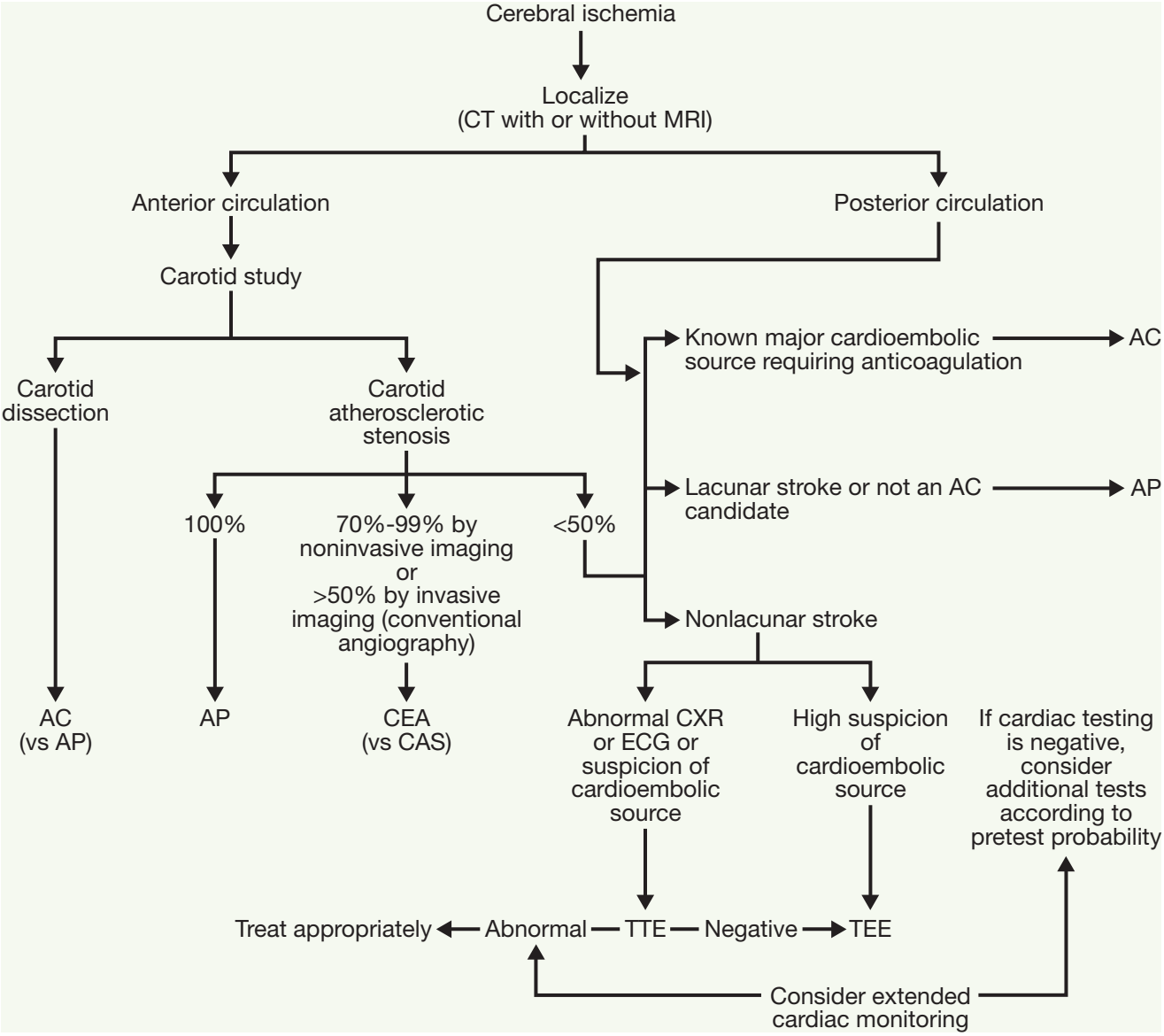

Figure 10.2 *General Approach to Stroke Evaluation.*
Factors that influence the pretest probability of individual causes of stroke are listed in Box 10.3. AC indicates anticoagulation; AP, antiplatelet agent; CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; CXR, chest radiograph; CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.
(Adapted from Flemming KD. Diagnosis of stroke mechanisms and secondary prevention. In: Barrett KM, Meschia JF, editors. Stroke. Chichester [West Sussex]: Wiley-Blackwell; c2013. p. 55–77. Used with permission.)

alternatives to warfarin. See also Chapter 13 ("Secondary Prevention of Ischemic Stroke").

Patients who have cardiomyopathy and a left ventricular ejection fraction less than 35% have an increased risk of thromboembolic events. Clinical trial findings are conflicting, but findings from combined primary and secondary prevention trials suggest that warfarin therapy and antiplatelet agent therapy are equivalent, but warfarin therapy carries a higher bleeding risk. However, most patients in these studies did not have a thromboembolic event.

Stroke in the presence of myocardial infarction is more common in patients who have 1 or more of the following risk factors: older age, apical or anterior wall myocardial infarction, left ventricular dysfunction or atrial fibrillation, mural thrombi or severe wall motion abnormality by echocardiography, prior history of stroke, hypertension, or history of systemic or pulmonary embolism. The stroke risk is

Box 10.3 • Factors Related to the Pretest Probability of Individual Stroke Mechanisms

- Cardioembolic
  - History of atrial fibrillation, congestive heart failure, or myocardial infarction
  - Abnormal chest examination
  - Abnormal electrocardiogram
  - Cortical stroke or multiple arterial territories
- Large-vessel extracranial
  - Atherosclerotic risk factors
  - Bruit on examination
  - Systemic symptoms or elevated sedimentation rate (giant cell arteritis) or both
  - History of head or neck injury (dissection)
- Large-vessel intracranial
  - Atherosclerotic risk factors
  - Multiple stereotyped transient ischemic attacks
  - Systemic symptoms, seizures, young patient (vasculitis)
  - Illicit drug use
- Small vessel
  - Atherosclerotic risk factors
  - Classic clinical lacunar syndrome
  - Waxing and waning symptoms
- Coagulation
  - Personal or family history of clotting disorder
  - Multiple miscarriages
  - Age, race (sickle cell disease)
  - Young age
  - Multiple arterial territories
  - Venous thrombosis

Adapted from Flemming KD. Diagnosis of stroke mechanisms and secondary prevention. In: Barrett KM, Meschia JF, editors. Stroke. Chichester (West Sussex): Wiley-Blackwell; c2013. p. 55–77. Used with permission.

highest in the first week after myocardial infarction, but the increased risk persists for up to 6 months. Short-term anticoagulation in addition to aspirin may be recommended for high-risk patients with a recent myocardial infarction.

Infectious endocarditis and nonbacterial thrombotic endocarditis are uncommon causes of cerebral ischemia. Infectious endocarditis often occurs with intravenous drug use (generally involving the right-sided heart valves) and in patients with prosthetic valves or structural heart valve disease. *Staphylococcus aureus* and the viridans streptococci group are the most typical sources. Neurologic complications of infectious endocarditis include cerebral ischemia, mycotic aneurysms, and intracranial abscesses.

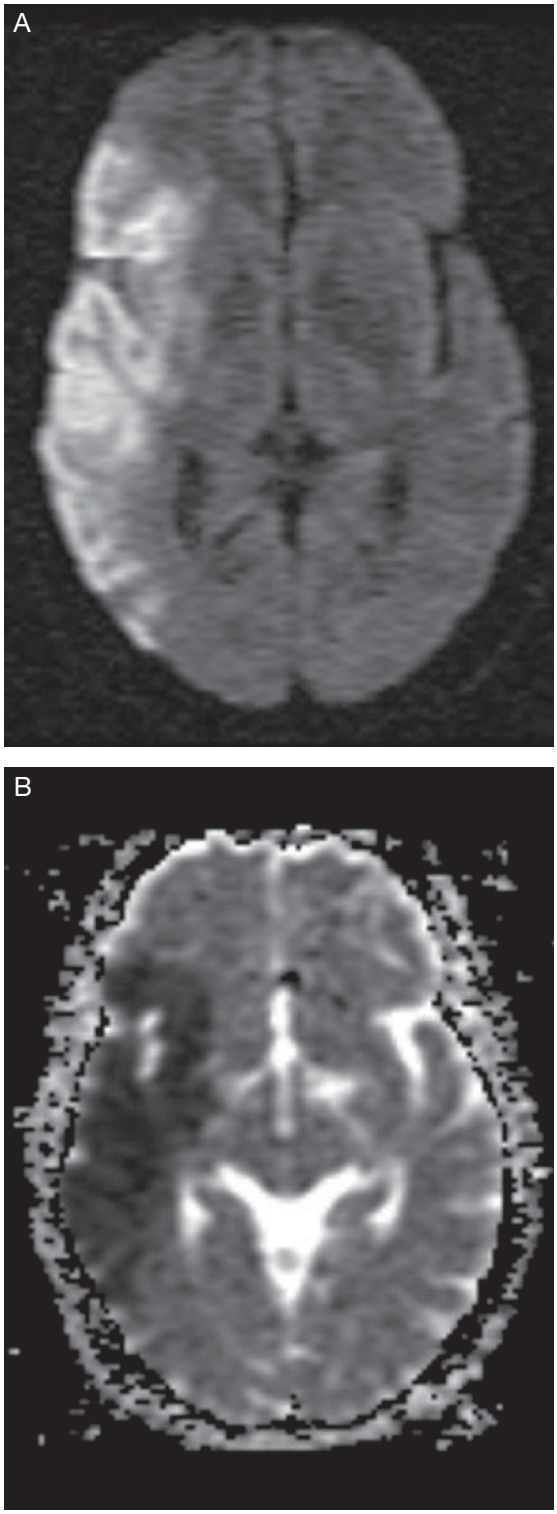

Figure 10.3 *Cerebral Ischemia.*
A, Diffusion-weighted image demonstrates restriction of diffusion in the distribution of the right middle cerebral artery. B, Apparent diffusion coefficient (ADC) map demonstrates corresponding ADC hypointensity, confirming ischemia as the reason for the diffusion hyperintensity.

Box 10.4 • Major and Minor Cardiac Risk Sources

Major risk sources	Minor risk sources
Atrial fibrillation	Mitral valve prolapse
Mitral valve stenosis	Severe mitral annular calcification
Prosthetic cardiac valve	Patent foramen ovale
Recent myocardial infarction	Atrial septal aneurysm
Left ventricular or left atrial thrombus	Calcific aortic stenosis
Atrial myxoma	Left ventricular regional wall motion abnormalities
Infectious endocarditis	Mitral valve strands
Dilated cardiomyopathy	
Marantic endocarditis	

Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.

Other clinical clues to the diagnosis may include a new heart murmur, fever, Janeway lesions, Osler nodes, and Roth spots. Diagnosis is typically made with blood cultures and echocardiography. Treatment is to identify the source of the endocarditis and treat with appropriate antibiotics. Surgery may be necessary for ruptured or enlarging mycotic aneurysms.

Nonbacterial thrombotic endocarditis may be associated with systemic lupus erythematosus (Libman-Sacks endocarditis) or malignancy (marantic endocarditis). In both forms of endocarditis, the valvular vegetations consist of immune complexes, white blood cells, fibrin and platelet thrombi, and fibrosis. Mitral, aortic, and tricuspid valves are commonly involved in Libman-Sacks endocarditis, and the mitral and aortic valves are involved with malignancies. In addition to malignancies and systemic lupus erythematosus, human immunodeficiency virus and antiphospholipid antibody syndrome can be associated with nonbacterial thrombotic endocarditis. The diagnosis is made with echocardiography. Blood cultures are used to rule out infection, and systemic laboratory tests are performed to identify contributing causes. Treatment often involves consideration of anticoagulation and potential surgery or valvuloplasty if the heart valve has been damaged.

Table 10.4 • $CHADS_2$ Score

Historical Feature	Points
History of congestive heart failure	1
Hypertension (any history)	1
Age ≥75 y	1
Diabetes mellitus	1
Secondary prevention for patient with prior cerebral ischemia or systemic thromboembolism	2

Abbreviation: $CHADS_2$, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and prior stroke or transient ischemic attack.

Data from Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001 Jun 13;285(22):2864–70.

Table 10.5 • Stroke Risk per 100 Person-Years

$CHADS_2$ Score	With Warfarin	Without Warfarin	NNT
0	0.25	0.49	417
1	0.72	1.52	125
2	1.27	2.50	81
3	2.20	5.27	33
4	2.35	6.02	27
5 or 6	4.60	6.88	44

Abbreviations: $CHADS_2$, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and prior stroke or transient ischemic attack; NNT, number needed to treat.

Valvular heart disease and mechanical heart valves increase the risk of stroke. The thromboembolic risk increases with multiple mechanical valves, associated left ventricular dysfunction, associated atrial fibrillation, associated left atrial thrombus, advanced age, previous thromboembolic event, mitral position of the valve, and certain types of mechanical valves. Anticoagulation is preferred over antiplatelet agents, and the level of anticoagulation depends on the type and position of the mechanical valve.

The discovery of a patent foramen ovale (PFO) in the evaluation for causes of stroke presents considerable controversy. Approximately 25% of the general population has a PFO. Some epidemiologic studies suggest a relationship to cerebral ischemia and others refute the concept. Purported risk factors that are thought to increase the probability that a PFO is related include size, shunting characteristics (right to left), associated atrial septal aneurysm, known deep vein thrombosis, and cortical stroke. However, even for a patient with 1 of these risk factors, the best treatment is unclear. To date, results have been largely negative or conflicting from clinical trials involving PFO device closure in patients who have ischemic stroke. In general, therapy with an antiplatelet agent is recommended, and PFO device closure is often reserved for patients with a second cryptogenic stroke.

While not technically a cardiac source, pulmonary shunts are often discovered on echocardiography and thus are discussed here. Pulmonary shunts are most commonly seen in Osler-Weber-Rendu disease. Also known as hereditary hemorrhagic telangiectasia, this is an autosomal dominant condition characterized by telangiectasias in multiple organs. Patients may also have vascular

malformations of the brain, but more commonly they are evaluated for cerebral ischemia relevant to pulmonary fistulae. Treatment is embolization of the fistulae. Antithrombotics are generally contraindicated because of the high risk of bleeding from nasal and gastrointestinal tract telangiectasias.

- The $CHADS_2$ score and the CHA_2DS_2-VASc score can be used to predict the risk of recurrent thromboembolism in patients with atrial fibrillation.
- Extended monitoring (longer than 24-hour telemetry or Holter monitoring) should be considered for patients with multiple arterial territory strokes, enlarged left atrium by echocardiography, advanced age, or cryptogenic disease.

Extracranial Large-Vessel Disease

Approximately 15% to 20% of strokes are due to large-vessel extracranial disease with the majority (10%–12%) due to carotid atherosclerosis.

All patients with cerebral ischemia relevant to the anterior circulation should have carotid imaging. Magnetic resonance angiography (MRA), CT angiography (CTA), or carotid ultrasonography could be performed. Compared with carotid ultrasonography, MRA and CTA are superior in sensitivity and specificity for high-grade internal carotid artery stenosis (Figure 10.4), but they may be less available and more costly, and they generally require use of a contrast agent. CTA of the neck is useful for reviewing the anatomy of the bifurcation in relation to the cervical spine; however, if the plaque is heavily calcified, the degree of stenosis may be difficult to discern. The usefulness of carotid ultrasonography is limited for showing dissection, which generally occurs distally toward the skull base. In patients with posterior circulation cerebral ischemia where dissection is a suspicion, CTA or MRA could be considered.

The aorta may be a source of stroke when severe atherosclerosis is present and if there is an associated dissection. Epidemiologic studies have produced conflicting data on the relationship of severe (>4 mm) aortic plaque and cerebral ischemia. Treatment recommendations are also conflicting, but currently an antiplatelet agent and a statin are commonly used.

Clues to a stroke due to aortic dissection may include associated chest or back pain, an aortic regurgitation murmur, hypotension, reduced peripheral pulses, and a difference in blood pressure between the 2 arms. Diagnosis is suggested by a widened mediastinum on chest radiography, but if suspicion is high, CT of the chest or transesophageal echocardiography can be performed to confirm the diagnosis. Management of aortic dissection complicated by cerebral ischemia is controversial. The prognosis is often poor with either medical or surgical management.

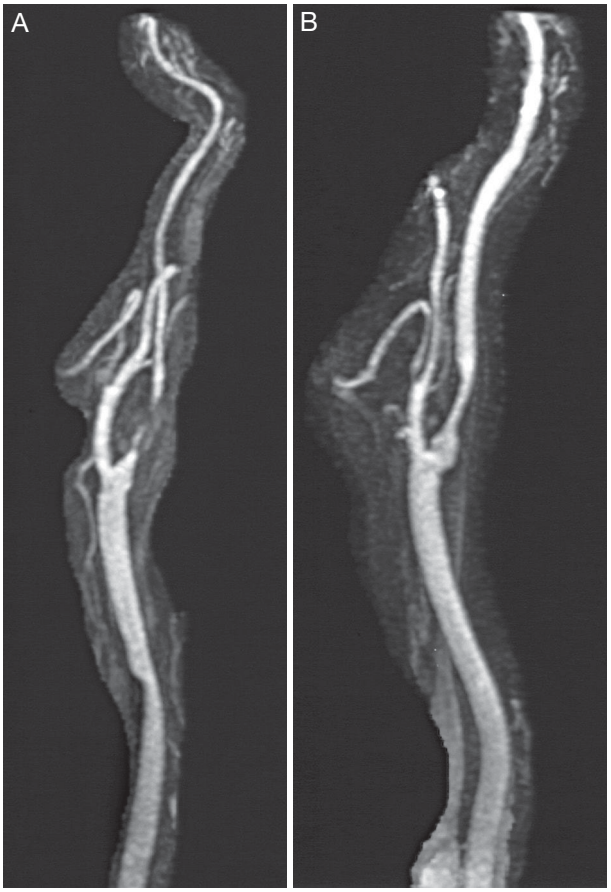

Figure 10.4 *Magnetic Resonance Angiography of Carotid Stenosis.*
A, Very high-grade stenosis (near occlusion) of the proximal left internal carotid artery with reduced caliber of the distal internal carotid artery. B, Moderately severe stenosis (50%–70%) in the area of the right carotid bulb.
(Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.)

Carotid atherosclerosis at the bifurcation accounts for 10% to 12% of ischemic strokes and is more common than intracranial stenosis. Clinical syndromes associated with carotid stenosis are discussed at the beginning of this chapter. The treatment of asymptomatic carotid stenosis is discussed in Chapter 13 ("Secondary Prevention of Ischemic Stroke"). It is important to distinguish symptomatic from asymptomatic carotid stenosis since the treatment differs significantly. *Symptomatic* refers to a cerebral infarction or TIA in the anterior circulation ipsilateral to the atheromatous diseased internal carotid artery.

The treatment of symptomatic carotid stenosis has evolved over time, guided originally by the North American

Symptomatic Carotid Endarterectomy Trial (NASCET) and, more recently, by the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) and the International Carotid Stenting Study (ICSS). The current recommendations of the American Heart Association are as follows: For patients with recent cerebral ischemia (within the past 6 months) due to ipsilateral stenosis of 70% to 99%, carotid endarterectomy is recommended if the perioperative morbidity is less than 6%. Selected patients with moderate-grade stenosis could be considered for carotid endarterectomy if perioperative morbidity and mortality are less than 6%. Carotid angioplasty and stenting could be considered as an alternative to carotid endarterectomy for symptomatic patients with an average or low risk of complications if the stenosis is more than 50% by conventional angiography or more than 70% by noninvasive imaging. In patients with symptomatic carotid artery occlusion, medical management is superior to surgical considerations such as superficial temporal artery–to–middle cerebral artery bypass. After carotid intervention, antiplatelet therapy and risk factor management are recommended (low-density lipoprotein cholesterol goal <70 mg/dL).

Extracranial dissection can affect either the carotid arteries or the vertebral arteries. This is a common cause of stroke in patients younger than 45 years (causing 2% of strokes in the general population, but 10%–25% of strokes in the young). About 50% of dissections result from identifiable trauma, and 50% occur without an identifiable predisposing event. Conditions that may predispose to dissection include fibromuscular dysplasia, the vascular type of Ehlers-Danlos syndrome (formerly type IV), Marfan syndrome, polycystic kidney disease, pseudoxanthoma elasticum, and osteogenesis imperfecta.

Dissection typically occurs at extracranial sites. In the internal carotid arteries, dissection often occurs 2 to 3 cm distal to the bifurcation and may have a flamelike tapering on angiography (Figure 10.5). Dissections of the vertebral arteries typically occur at C1–2, where the artery courses posteriorly and enters the foramen magnum. The intimal tear results in a false lumen and occasionally an associated pseudoaneurysm.

Clinically, patients may have anterolateral cervical and retro-orbital pain with carotid dissection or posterior head pain with vertebral dissection. A carotid dissection may be associated with an ipsilateral Horner syndrome due to the sympathetics traveling near the carotid artery. Rarely, other cranial nerves (eg, cranial nerves X and XII) can be affected. Patients with carotid dissection have typical anterior circulation symptoms. Patients with vertebral artery dissection commonly have Wallenberg syndrome (also called lateral medullary syndrome).

Carotid ultrasonography has a low sensitivity for dissection, especially if the vessel is nonstenotic. MRA or CTA is the test of choice. Conventional angiography is reserved for patients in whom dissection is highly suspected, but noninvasive tests are unrevealing. Radiographic findings may include a tapered, flamelike appearance; a double lumen; and an intimal flap.

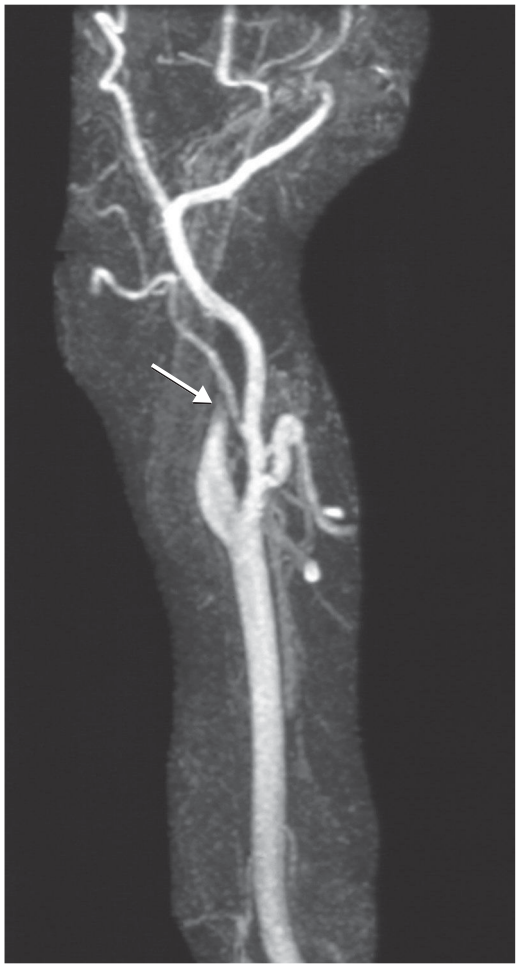

Figure 10.5 *Magnetic Resonance Angiography of Carotid Dissection.*
The flamelike tapering (arrow) of the internal carotid artery suggests dissection.
(Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.)

Optimal treatment for dissection is unclear. Most clinicians typically recommend anticoagulation for 3 to 6 months and then another imaging study. Recent observational studies suggest that antiplatelet therapy may be equivalent to anticoagulation, but a comparative clinical trial has not yet been performed. Angioplasty and stenting can be considered if the patient has no response to medical therapy, but there is a risk of further extension of the dissection.

Fibromuscular dysplasia is a nonatherosclerotic, noninflammatory arteriopathy. The tunica media vasorum is characterized by disorganized smooth muscle cells, loss of smooth muscle cells, and general disorganization of the arterial wall. The internal elastic lamina is disrupted (Figure 10.6). This condition is more common in women and whites. It affects the renal vessels most commonly (60%–75%); the extracranial carotid or vertebral arteries are the second most common site (20%–30%). Intracranial vessels and the iliac, femoral, subclavian, and visceral arteries may also be affected. Patients may be asymptomatic, have pulsatile tinnitus, or present with focal cerebral ischemia. Fibromuscular dysplasia predisposes patients to arterial dissection. Patients may also have hypertension due to involvement of the renal arteries. The diagnosis is based on the angiographic appearance of a "string of beads" or "beading" (ie, alternating constricted and dilated segments generally of the distal cervical carotid). Conventional angiography is superior to MRA; however, gadolinium-enhanced

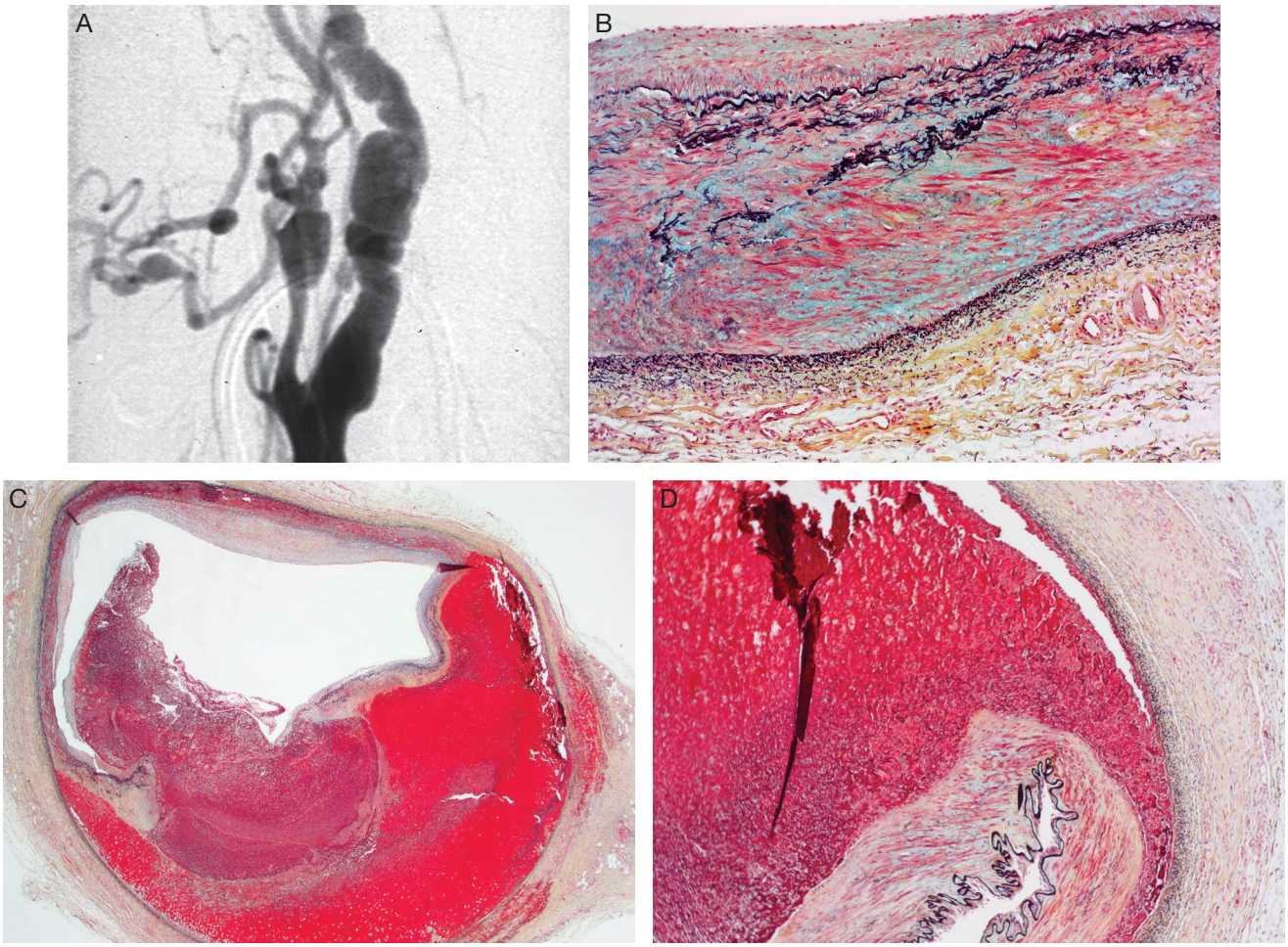

Figure 10.6 *Fibromuscular Dysplasia.*
A, Appearance of severe fibromuscular dysplasia in extracranial internal and external carotid arteries on conventional angiography. Note the "string of beads" appearance with the characteristic luminal narrowing alternating with aneurysmal dilatation. B, Histopathologic features include a thin tunica media and disorganized smooth muscle cells, disarranged laminae, and a disrupted internal elastic lamina. This disruption of the structure of the thin media predisposes the artery to dissection. C, Arterial dissection secondary to fibromuscular dysplasia in the same patient as in panel A. The intimal tear in the center allows the formation of a hematoma in the media, with more blood tearing through and expanding the media. D, Higher magnification of a different arterial dissection in the same patient, showing the plane of dissection between the adventitia and tunica media.
(Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.)

MRA may show changes as well. Treatment involves antiplatelet agents and management of concomitant hypertension if present.

Vasculitides affecting the large-vessel extracranial arteries include giant cell arteritis (see Chapter 53, "Secondary Headache Disorders") and Takayasu arteritis (also called pulseless disease).

- For the treatment of symptomatic carotid stenosis, the current recommendations of the American Heart Association are as follows: For patients with recent cerebral ischemia (within the past 6 months) due to ipsilateral stenosis of 70%–99%, carotid endarterectomy is recommended if the perioperative morbidity is <6%. Selected patients with moderate-grade stenosis could be considered for carotid endarterectomy if perioperative morbidity and mortality are <6%.
- After carotid intervention, antiplatelet therapy and risk factor management (including high-intensity statin therapy) are recommended.

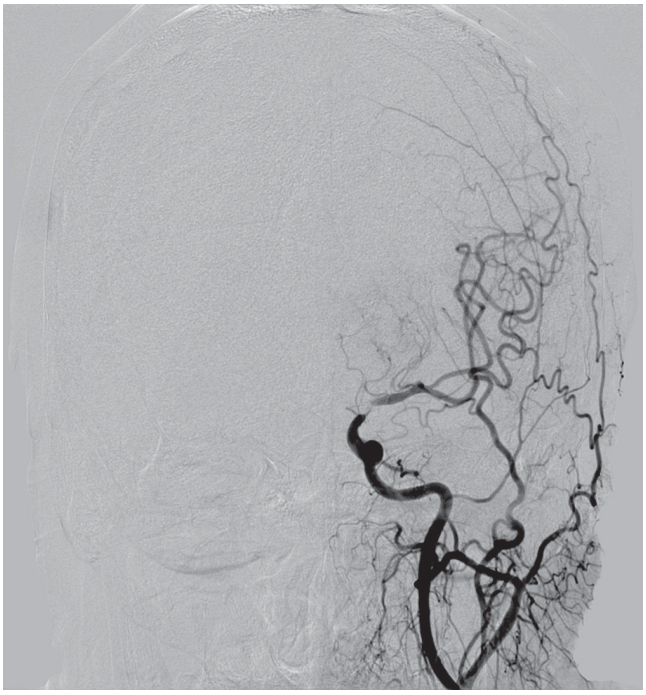

Figure 10.7 *Intracranial Atherosclerosis. Conventional angiography demonstrates severe atherosclerotic narrowing of the left intracranial distal internal carotid artery.*

Intracranial Large-Vessel Disease

Intracranial large-vessel disease accounts for approximately 5% to 10% of all strokes, most commonly strokes due to atherosclerosis. The differential diagnosis is listed in Box 10.1. Intracranial vasculature can be visualized noninvasively with MRA or CTA. Conventional angiography is the gold standard and is reserved for patients in whom small-vessel vasculitides are of concern.

Intracranial atherosclerosis accounts for 5% of strokes and is more common in African Americans and Asian Americans than whites. Clinical suspicion for intracranial atherosclerosis may arise if a patient is having stereotyped episodes of cerebral ischemia. The episodes may be postural, suggesting hypoperfusion, and they often have typical vascular risk factors as well (Figure 10.7). Treatment is generally an antiplatelet agent and risk factor management, including a statin. The American Heart Association recommends aspirin daily. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial compared patients receiving medical treatment (aspirin and clopidogrel for 90 days and risk factor management) with patients undergoing angioplasty and stenting. The group that underwent angioplasty and stenting had a higher rate of stroke, often perioperatively. Thus, for this group of patients, angioplasty and stenting offer unclear benefit and are generally reserved for patients after medical management has failed.

Moyamoya disease is a rare disorder resulting in distal intracranial internal carotid artery stenosis with unusual collateral formation of the lenticulostriate arteries. The lenticulostriate arteries resemble puffs of smoke on conventional angiography—hence, the term *moyamoya* (*foggy* or *smoky* in Japanese) (Figure 10.8). The cause of moyamoya disease has not been determined, but the disease has been associated with several conditions, including autoimmune disease, sickle cell anemia, neurofibromatosis type 1, cranial irradiation, and Down syndrome. Patients often present in childhood (mean age, 5 years) or in their 30s, and they most commonly present with cerebral ischemia. In children, the symptoms may be provoked by hyperventilation or crying because of decreased cerebral perfusion. Adult patients may also present with hemorrhage due to the friability of the collaterals. It is estimated that two-thirds of patients have progressive disease. In patients with cerebral ischemia, a "direct" procedure, such as a superficial temporal artery–to–middle cerebral artery bypass, is often performed in combination with an "indirect" procedure such as encephaloduroarteriosynangiosis.

Isolated central nervous system vasculitis or systemic vasculitides (polyarteritis nodosa, Wegener granulomatosis, systemic lupus erythematosus, Churg-Strauss syndrome, and cryoglobulinemia) may affect the intracranial large vessels. Isolated central nervous system (granulomatous) angiitis may involve the arteries of the brain

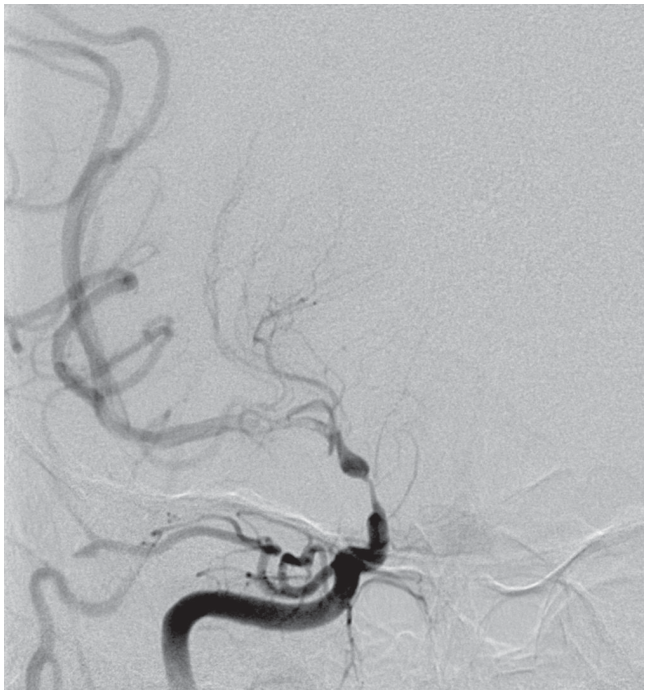

Figure 10.8 *Moyamoya Disease. Conventional angiography of the right internal carotid artery (ICA) demonstrates the characteristic distal ICA stenosis and the lenticulostriate collaterals ("puff of smoke").*

and spinal cord. Pathologically, the blood vessels show evidence of inflammation, consisting of granulomas with multinucleated giant cells and lymphocytes (Figure 10.9). Patients may present with cerebral ischemia, hemorrhage (rarely), seizures, encephalopathy, and headache.

Systemic markers, such as sedimentation rate and C-reactive protein level, are often normal. MRI may show areas of ischemia in multiple territories and may show meningeal enhancement. MRA may show diffuse irregularity of the large vessels, but conventional angiography is superior. Angiography often shows beading of the vessels, with alternating stenosis and dilatation. While the beading appearance is classic, it is not diagnostic, and the differential diagnosis may also include vasospasm (migraine, sympathomimetics, hypertensive crisis, or reversible cerebrovasoconstrictive syndrome), sarcoid angiopathy, infectious arteritis, radiation vasculopathy, atherosclerosis, fibromuscular dysplasia, intravascular lymphoma, and leptomeningitis. Brain biopsy in combination with leptomeningeal biopsy is the gold standard for diagnosis, but the findings can be negative because of patchy involvement. Thus, negative biopsy findings do not completely exclude the diagnosis. Treatment is generally with immunosuppressants, most commonly cyclophosphamide and corticosteroids.

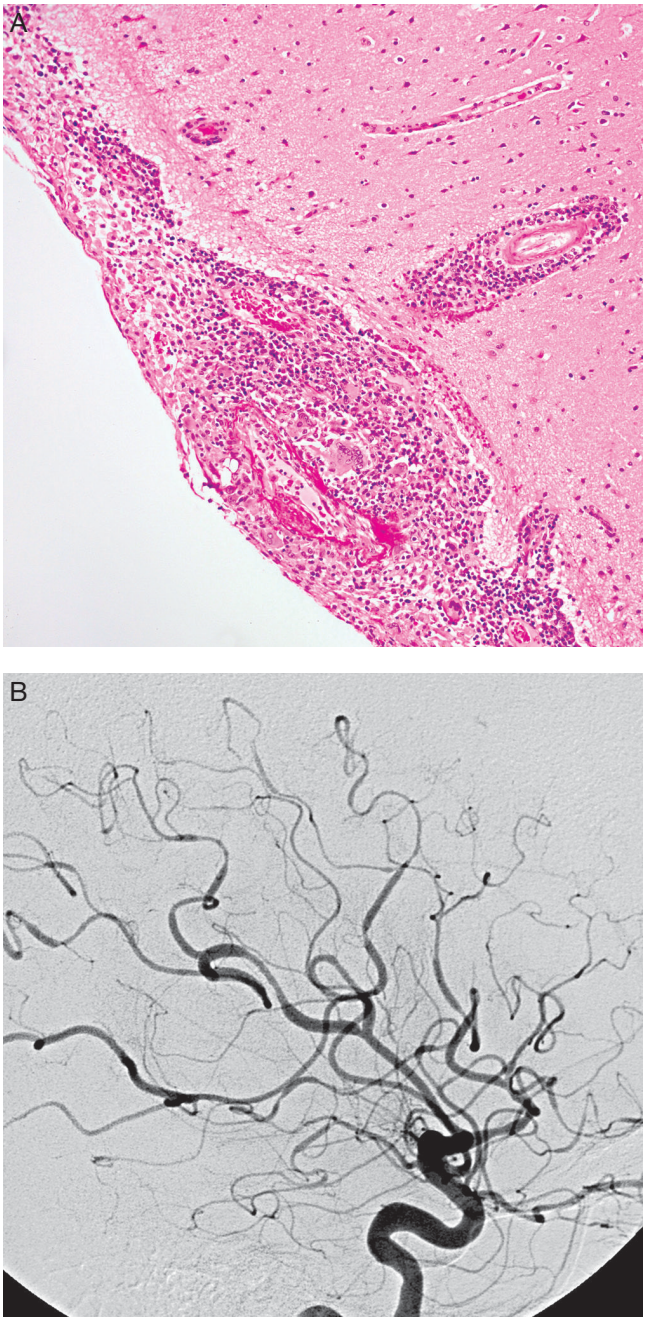

Figure 10.9 *Primary Central Nervous System Vasculitis. A, Extensive leptomeningeal acute and chronic cellular infiltrates and necrotizing vasculitis of small leptomeningeal and parenchymal arteries. B, Classic angiographic appearance of primary central nervous system vasculitis, with characteristic "beading" of vessels, with alternating stenosis and dilatation, although this is not diagnostic by itself.*
(Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.)

Reversible cerebrovasoconstrictive syndrome is characterized by thunderclap headaches, vasospasm, cerebral ischemia, and, sometimes, sulcal subarachnoid hemorrhage. Predisposing factors include the postpartum state, use of vasoactive substances (selective serotonin reuptake inhibitors, cannabis, and sympathomimetics), and catecholamine-secreting tumors. Angiography typically shows diffuse vasospasm (see Chapter 53, "Secondary Headache Disorders").

Infectious arteritis is rare. It has been associated with herpes zoster ophthalmicus, hepatitis B and C, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, bacterial aortitis, and syphilis. Herpes zoster ophthalmicus can be associated with ipsilateral stenosis of the M1 segment of the middle cerebral artery. Cerebrospinal fluid studies may confirm the presence of virus, and treatment may be a combination of acyclovir with or without corticosteroids and antiplatelet agents.

- The SAMMPRIS trial compared patients receiving medical treatment (aspirin and clopidogrel for 90 days and risk factor management) with patients undergoing angioplasty and stenting for intracranial artery atherosclerosis. The group that underwent angioplasty and stenting had a higher rate of stroke, often perioperatively.

Small-Vessel Disease

Lacunar stroke (20% of strokes) refers to a small subcortical infarction (<1.5 cm) resulting from the occlusion of a penetrating end artery. Examples of penetrating end arteries include basilar perforating vessels, lenticulostriate arteries, and thalamoperforate arteries. Thus, common locations of lacunar strokes include the basal ganglia, thalamus, pons, and internal capsule. Pathologic findings are microatheroma, lipohyalinosis, and fibrinoid necrosis. However, in about 10% of persons with lacunar stroke, these pathologic findings are absent, raising the possibility of an embolic source.

The most common risk factors are hypertension, smoking, and diabetes mellitus. There are numerous clinical lacunar syndromes; however, even the most experienced clinicians cannot always predict the localization based on the clinical syndrome alone. Thus, MRI may be useful to confirm the localization and topography. Treatment of typical lacunar disease is an antiplatelet agent and risk factor management.

Other disorders may result in strokes that appear to be small-vessel strokes. These disorders include certain vasculitides, phospholipid antibody syndrome, and Behçet syndrome.

- Common locations of lacunar strokes include the basal ganglia, thalamus, pons, and internal capsule.

Coagulation Disorders

The overall pretest probability (ie, the prevalence) of a coagulation disorder as the cause of stroke is less than 5%. The pretest probability may increase among younger patients, patients with malignancies, patients who are pregnant or are taking a contraceptive, patients who have a history of miscarriages, patients with a personal or family history of a clotting disorder, or patients with cryptogenic stroke. The differential diagnosis of clotting disorders is noted in Box 10.1. Testing for all patients

Box 10.5 • Sapporo Criteria for Antiphospholipid Syndrome (APS)

Definite APS is considered if ≥1 of the following clinical criteria *and* ≥1 of the following laboratory criteria are satisfied:

- Clinical criteria—the presence of either vascular thrombosis *or* pregnancy morbidity, defined as follows:
  - *Vascular thrombosis* is defined as ≥1 episodes of venous, arterial, or small-vessel thrombosis, with unequivocal imaging or histologic evidence of thrombosis in any tissue or organ. Superficial venous thrombosis does *not* satisfy the criteria for thrombosis for APS.
  - *Pregnancy morbidity* is defined as otherwise unexplained fetal death at ≥10 weeks' gestation of a morphologically normal fetus, *or* ≥1 premature births before 34 weeks' gestation because of eclampsia, preeclampsia, or placental insufficiency, *or* ≥3 embryonic (<10 weeks' gestation) pregnancy losses unexplained by maternal or paternal chromosomal abnormalities or by maternal anatomical or hormonal causes.
- Laboratory criteria—the presence of antiphospholipid antibodies, on ≥2 occasions ≥12 weeks apart and ≤5 years before clinical manifestations, as demonstrated by ≥1 of the following:
  - Immunoglobulin (Ig)G or IgM (or both) anticardiolipin antibodies in moderate or high titer (>40 GPL or >40 MPL, respectively, or >99th percentile for the testing laboratory).
  - Antibodies to β_2-glycoprotein I of IgG or IgM isotype at a titer >99th percentile for the testing laboratory when tested according to recommended procedures.
  - Lupus anticoagulant activity detected according to published guidelines.

Abbreviations: GPL, IgG antiphospholipid units per milliliter; MPL, IgM antiphospholipid units per milliliter.

Adapted from Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999 Jul;42(7):1309–11.

should include a complete blood cell count, erythrocyte sedimentation rate, partial thromboplastin time, and international normalized ratio. Selected patients may need further testing, such as evaluation of coagulation factors, phospholipid antibodies (typically an arterial clot), lupus anticoagulant, β_2-glycoprotein, factor V and prothrombin 20210 mutations (typically a venous clot), and hemoglobin electrophoresis. Note that if the level of protein C or protein S is decreased at the time of an event, subsequent testing may be necessary to confirm its presence after 6 weeks. Treatment varies depending on the cause.

Sickle cell anemia often results in stroke due to narrowing or occlusion of the large cerebral arteries. Cerebral ischemia peaks in patients aged 2 to 9 years and in adults older than 29. Hemorrhage is less common. Transcranial Doppler ultrasonography may help to determine whether patients with sickle cell anemia are at risk for cerebral ischemia by measuring blood flow velocities through intracranial vessels. Annual transcranial Doppler ultrasonography is generally recommended for patients with sickle cell anemia who are older than 2 years. For patients at high risk, exchange transfusion with a goal hemoglobin S of less than 30% is useful for preventing stroke.

Antiphospholipid antibody syndrome should be considered if a young patient has 1 or more unexplained thrombotic events, an unexplained prolongation of the partial thromboplastin time, or thrombocytopenia and 1 or more adverse outcomes related to pregnancy. Evaluation should include phospholipid antibody, β_2-glycoprotein antibody, or lupus anticoagulant testing. For patients with cryptogenic stroke and minimally elevated or transient antibody levels, an antiplatelet agent is recommended. For patients who meet the criteria for antiphospholipid antibody syndrome, warfarin is recommended. The Sapporo criteria for antiphospholipid syndrome are shown in Box 10.5.

Elevated levels of homocysteine are commonly noted in patients with ischemic stroke. However, numerous clinical trials have not shown any clinical benefit in treating mildly elevated homocysteine levels.

- The pretest probability of a coagulation disorder may increase among younger patients, patients with malignancies, patients who are pregnant or are taking a contraceptive, patients who have a history of miscarriages, patients with a personal or family history of a clotting disorder, or patients with cryptogenic stroke.

11 Ischemic Stroke: Uncommon and Special Situations

KELLY D. FLEMMING, MD

Introduction

Most ischemic stroke is caused by atherosclerosis (large- and small-vessel disease) and cardioembolic sources (eg, atrial fibrillation). However, it is important to recognize the clinical, laboratory, and radiologic manifestations of rarer causes of stroke since the treatment may vary from the treatment of more typical causes. This chapter reviews the less common causes of stroke in addition to stroke in special situations: stroke in children, stroke in pregnant women, spinal cord infarction, and venous thrombosis.

Uncommon Causes of Stroke

Genetic

A number of heritable conditions may include cerebral ischemia among their clinical manifestations. These are discussed below and summarized in Table 11.1.

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy Syndrome

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome is an autosomal dominant condition characterized clinically by migraine, stroke, and dementia. The defect is on chromosome 19 at 19q13.1 (a missense mutation in the *Notch3* gene). The *Notch3* gene codes a transmembrane protein thought to be involved in cell signaling during

Table 11.1 • Genetic Causes of Cerebral Ischemia

Condition	Genetic Features	Key Features
CADASIL syndrome	Autosomal dominant Mutation at 19q13.1	Migraine Transient ischemic attack or stroke Dementia Extensive leukoaraiosis involving temporal lobes
Marfan syndrome	Autosomal dominant Mutation in fibrillin 1 (*FBN1*) gene (usually) at 15q-21.1	Ischemic stroke Cerebral aneurysms possible
MELAS syndrome	Mutations in genes of mitochrondrial DNA	Encephalopathy Seizures Ischemic stroke Deafness Myopathy (ragged red fibers on biopsy) Short stature Elevated level of lactic acid
Fabry disease	X-linked Mutations in the α-galactosidase A gene at Xq22.1	Deficiency of α-galactosidase Cutaneous angiokeratomas Lens opacities Painful paresthesias Stroke

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes.

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CT, computed tomography; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes; MRI, magnetic resonance imaging; TIPS, Thrombolysis in Pediatric Stroke; tPA, tissue plasminogen activator

embryonic development. Pathologically, there is evidence of widespread myelin pallor of the white matter and multiple small infarcts in the white matter and basal ganglia. The vessels of the white matter and meninges are thickened with a smudgy granular aspect of the media and loss of muscular nuclei (Figure 11.1). This granular osmophilic material is visible by electron microscopy but is of uncertain significance.

Clinically, patients with CADASIL syndrome often have migraine headaches in their youth and 20s, stroke or strokelike episodes in their 40s to 60s, and often a progressive dementia later. Other clinical symptoms may include pseudobulbar affect, urinary incontinence, gait disturbance, and upper motor neuron signs.

The diagnosis can be made by pedigree analysis (family history), typical magnetic resonance imaging (MRI) findings, skin biopsy, or genetic testing. MRI of the brain generally shows confluent deep white matter changes often involving the anterior temporal lobes (Figure 11.2). Skin biopsy may show granular osmophilic material with electron microscopy.

No current treatment is known to delay progression of the disease. Antithrombotics are typically used to prevent general ischemic stroke.

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) syndrome, an autosomal recessive variant, has been described. CARASIL syndrome results from mutations in the *HTRA1* gene and differs from CADASIL syndrome in its inheritance pattern. Patients with CARASIL syndrome often have an associated alopecia and lumbar spondylosis.

Marfan Syndrome

Marfan syndrome is an autosomal dominant condition that may also predispose a patient to stroke and cerebrovascular disease. The defect is in the *FBN1* gene that encodes the connective protein fibrillin 1. Patients may have ischemic stroke related to mitral or aortic valve disease, aortic dissection, and a predisposition to cerebral aneurysm formation.

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum is an autosomal recessive disease of connective tissue characterized by progressive dystrophic mineralization of elastic fibers. Clinically, patients have skin lesions, and they may have loss of visual acuity, cardiovascular and cerebrovascular complications, ischemic stroke, a syndrome resembling Binswanger disease, and a predisposition to aneurysm formation.

Vascular Type of Ehlers-Danlos Syndrome

The vascular type of Ehlers-Danlos syndrome (formerly type IV) is an autosomal dominant disorder due to a mutation of the gene that encodes type III procollagen. Patients with this disorder are predisposed to rupture of arteries,

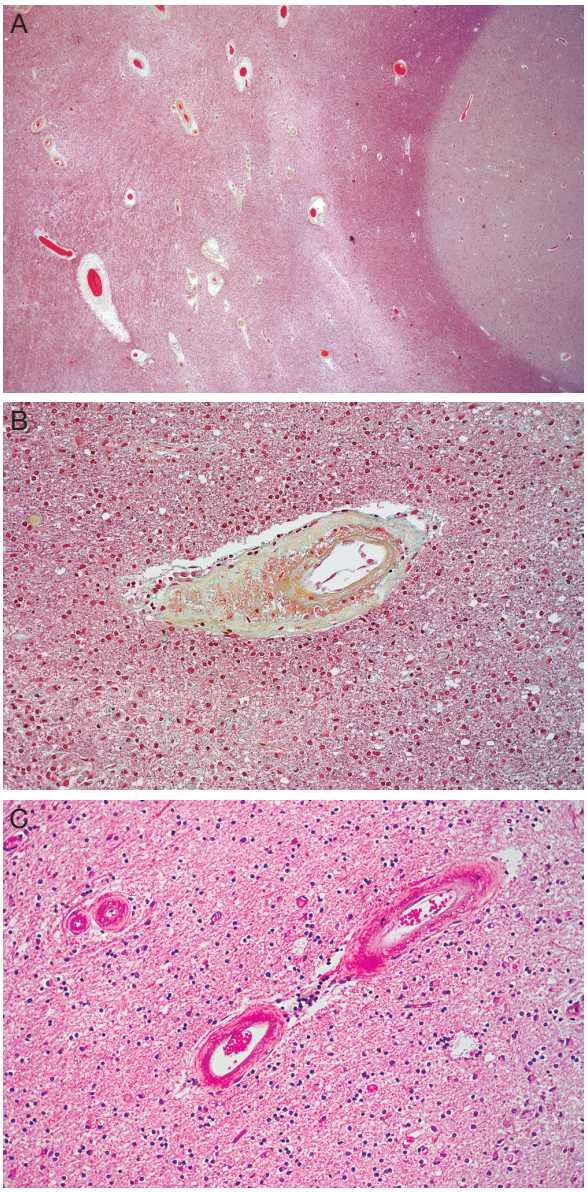

Figure 11.1 *Histopathology of Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) Syndrome.*
A, Subcortical microcavitation, pallor, neuronal loss, and gliosis, with relative preservation of the cerebral cortex (on right) and U fibers beneath the cortex (Movat stain). B, Small artery with deposition of granular material in the media, degeneration of the arterial wall, and destruction of the media (Movat stain). C, Subcortical small arteries with eosinophilic granular material in the media of the vessel wall (hematoxylin-eosin).
(Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.)

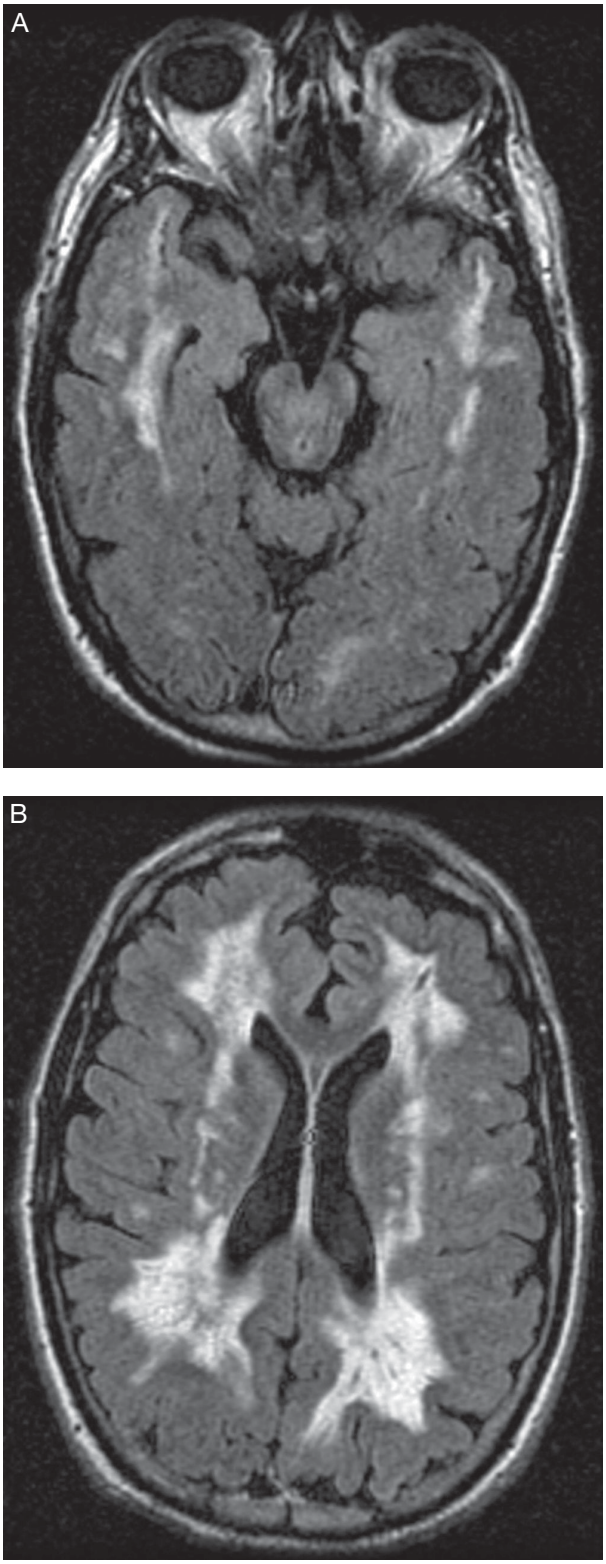

Figure 11.2 *CADASIL.*
Magnetic resonance imaging of the brain shows a T2 signal change in the anterior temporal lobes (A) and deep white matter (B) consistent with the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome.

the bowel, and the uterus. Cerebrovascular complications include a predisposition to intracranial aneurysm formation, arterial dissection, and possible carotid-cavernous fistula.

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Strokelike Episodes Syndrome

Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome is caused by a rare disorder of mitochondrial DNA (most cases result from a point mutation, from A to G, in the dihydrouridine loop of the transfer RNA gene at mt3243). Clinically, patients may present variably with a combination of progressive encephalopathy, seizures, ischemic stroke, deafness, and myopathy.

The diagnosis of MELAS syndrome is made through several investigations. MRI of the head often shows ischemic areas crossing arterial boundaries (Figure 11.3). In addition, patients may have basal ganglia calcification. Patients may have an elevated level of blood lactic acid and an increased lactate to pyruvate ratio. Similarly, in the cerebrospinal fluid, the lactate level may be elevated. Muscle biopsy may show ragged red fibers in skeletal muscle. Molecular genetic analysis and magnetic resonance spectroscopy of the brain can also be performed to secure the diagnosis.

Treatment of MELAS syndrome is supportive, and the disease is progressive. L-arginine and coenzyme Q10 are often used.

Fabry Disease

Fabry disease is an X-linked deficiency of α-galactosidase. Clinically, patients have cutaneous angiokeratomas (Figure 11.4), corneal and lenticular opacities, and often painful paresthesias. Patients may have stroke, but they may also be prone to coronary and renal artery disease. Patients with Fabry disease should receive α-galactosidase replacement therapy.

Inflammatory and Noninflammatory Arteriopathies

Rare inflammatory and noninflammatory causes of stroke are noted in Table 11.2.

- CADASIL syndrome is an autosomal dominant condition characterized clinically by migraine, stroke, and dementia.
- Clinically, patients with CADASIL syndrome often have migraine headaches in their youth and 20s, stroke or strokelike episodes in their 40s to 60s, and often a progressive dementia later.
- MRI of the brain of a patient who has CADASIL syndrome generally shows confluent deep white matter changes often involving the anterior temporal lobes.

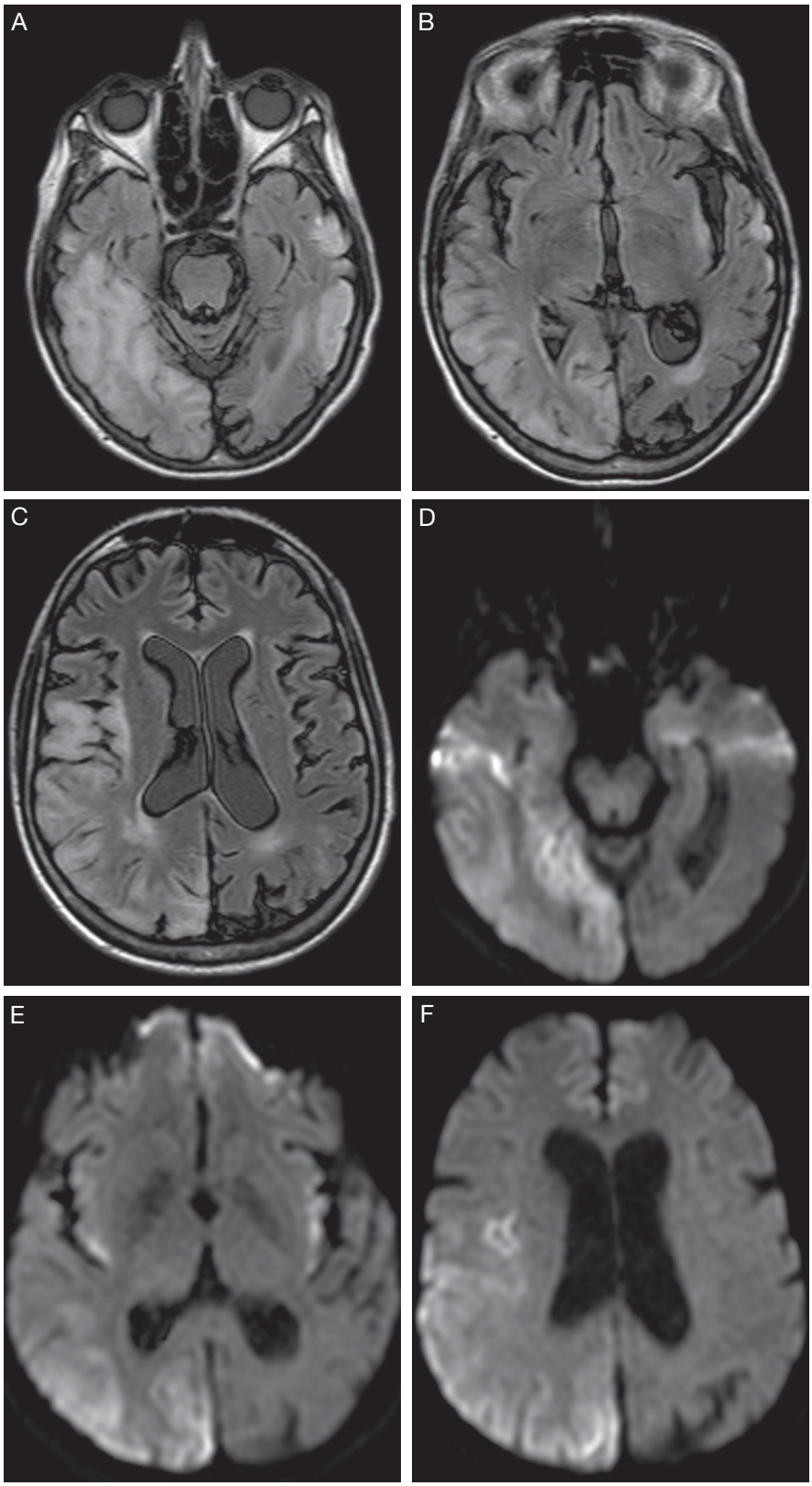

Figure 11.3 *MELAS Syndrome.*
Magnetic resonance imaging (MRI) shows evidence of an old inferior left temporal and occipital stroke on fluid-attenuated inversion recovery images (A-C) and, with diffusion-weighted imaging, a new lesion in the right temporal and occipital areas (D-F). This patient also had short stature, hearing loss, and a history of seizure. The MRI pattern crosses typical arterial boundaries and is consistent with mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome.

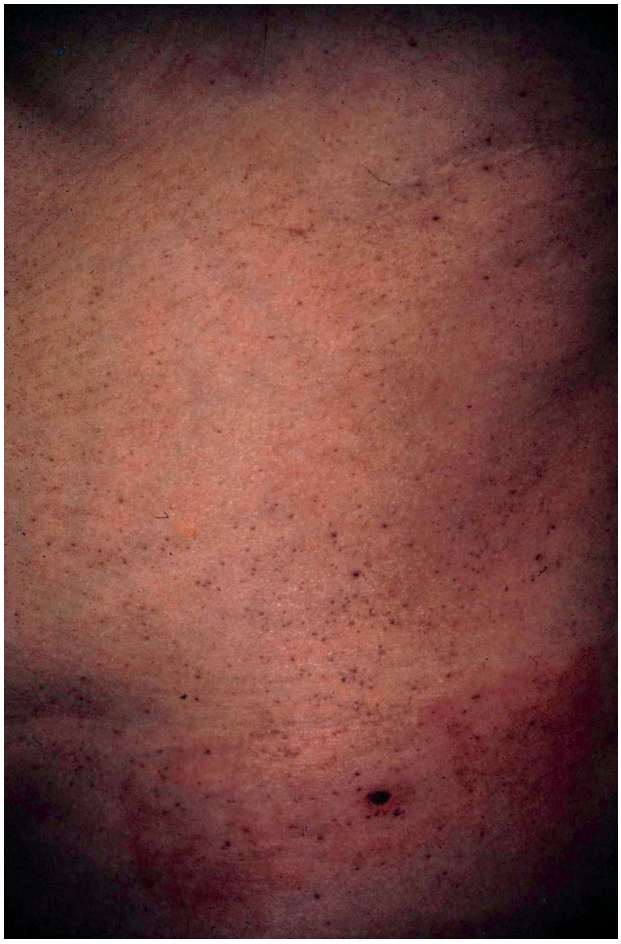

Figure 11.4 *Fabry Disease.*
Cutaneous angiokeratomas are common in Fabry disease.

- Patients with MELAS syndrome may present variably with a combination of progressive encephalopathy, seizures, ischemic stroke, deafness, and myopathy.
- Patients with Fabry disease should receive α-galactosidase replacement therapy.

Special Situations in Stroke

Stroke in Children

Stroke in childhood is very rare but devastating. The incidence is 2 to 5 per 100,000. In adults, 80% of strokes are ischemic; in children, 55% are ischemic and 45% are hemorrhagic.

Perinatal stroke is generally defined as any hemorrhagic or ischemic event occurring from 28 weeks of gestation through the first 7 days of life. Cerebral ischemia, hemorrhage, and venous thrombosis can occur. Focal deficits or seizures may be presenting signs. Risk factors include cardiac disorders, coagulation disorders, infection, trauma, drugs, maternal disorders, and perinatal asphyxia. Cranial ultrasonography, computed tomography (CT), or MRI may be used to diagnose stroke in neonates. MRI has superior sensitivity and specificity for detecting ischemia and venous thrombosis.

Treatment depends on the potential cause. In neonates with intracranial hemorrhage, coagulation disorders should be corrected and surgery or ventricular drainage performed as necessary. Anticoagulation is considered in select patients with severe thrombophilic disorders, multiple systemic emboli, or progressive propagation of venous thrombosis. However, until further information is available on safety, anticoagulation should be reserved for these patients. Robust safety data on thrombolytic use are not available for patients 18 years or younger.

Periventricular-intraventricular hemorrhage can occur in up to 20% to 40% of premature neonates weighing less than 1,500 g. Half occur within the first 24 hours and 90% within the first 72 hours. The hemorrhage occurs in the subependymal germinal matrix, often in the region of the caudate near the foramen of Monro (Figure 11.5). Hemorrhages are often graded according to severity (Table 11.3). Patients may be asymptomatic (grade 1) or have acute neurologic deterioration with coma, stupor, tense fontanelle, apnea, bradycardia, and hypotension. Changes in muscle tone, seizures, and pupillary changes may also occur. Diagnosis can be made with cerebrospinal fluid analysis, ultrasonography, or CT. Surgery is generally not indicated because of poor operative outcome. Patients with grade 1 or 2 hemorrhage have a good prognosis. Treatment is aimed at reducing hydrocephalus as a complication of the hemorrhage.

In children, 30% of strokes are cryptogenic. The most common causes of stroke in children are acquired or congenital heart disease and sickle cell anemia. Arteriopathies are also fairly common. The differential diagnosis of stroke in children is shown in Box 11.1.

The safety and efficacy of acute stroke therapy in children has not been established. Case reports of select patients have shown potential efficacy for intravenous thrombolytics; however, the safety has not been proved. Thrombolysis in Pediatric Stroke (TIPS) was a safety and dose-finding study of intravenous tissue plasminogen activator (tPA) therapy in children with acute ischemic stroke. However, lack of patient accrual resulted in the study being terminated. The American Heart Association recommendations state that thrombolytic therapy with tPA may be considered for select children with cerebral venous thrombosis. However, tPA generally is not recommended for children with acute ischemic arterial stroke except in a clinical trial. There is no consensus about the use of tPA in older adolescents who otherwise meet standard adult tPA eligibility criteria.

The use of anticoagulation and antiplatelet agents for stroke in pediatric patients is highly individualized and beyond the scope of this text. A complete review of

Table 11.2 • Rare Inflammatory and Noninflammatory Causes of Stroke

Condition	Clinical Features	Diagnosis	Treatment
Cogan syndrome	Interstitial keratitis or scleritis Hearing loss or vestibular symptoms Stroke Systemic symptoms	Clinical picture Eye examination Rule out other vasculitides	Immunosuppressants
Eales disease	Stroke Young adults Visual loss with retinal vasculitis (veins or arterioles), vitreous hemorrhage, microaneurysms of retinal vessels Late complications: neovascularization, retinal detachment, glaucoma	Clinical presentation Fluorescein angiography Rule out other systemic vasculitides	Immunosuppressants may be considered
Susac syndrome (retinocochleo-cerebral vasculopathy)	Acute to subacute encephalopathy, vision loss, and sensorineural hearing loss Cerebral symptoms: behavioral, affect, cognitive dysfunction, ataxia, corticospinal tract involvement Ophthalmologic findings: visual field losses; retinal arteriolar stenosis or occlusions Otologic findings: low- to mid-frequency sensorineural hearing loss	Clinical picture MRI: multiple, small, punctate areas of T2 signal increase; contrast enhancement in cerebral gray matter and in white matter Lesions often involve corpus callosum Pathology: microangiopathy affecting the arterioles of the brain, retina, and cochlea; some perivascular lymphocytic infiltration, but not definitively vasculitic Rule out other vasculitides	Immunosuppressants Plasma exchange
Sneddon syndrome	Livedo reticularis (reticulated skin pattern caused by impaired superficial venous drainage of the skin) Ischemic stroke Seizures Dementia	Clinical picture Livedo reticularis may be associated with other entities; rule out systemic vasculitides Sneddon syndrome may also coexist with antiphospholipid antibody syndrome Pathology: vasculopathy without vasculitis has been found on brain biopsies; skin biopsy may show noninflammatory vasculopathy of medium-sized arteries with intimal hyperplasia	Antithrombotics (antiplatelet agents or warfarin) have been used
Kohlmeier-Degos disease (malignant atrophic papulosis)	Skin manifestations: raised papules with white center Cerebral ischemia	Pathology: vasculopathy of the skin, cerebral circulation, and other organs; fibrous intimal proliferation accompanied by thrombosis	Not clear
Isolated CNS vasculitis (granulomatous vasculitis)	Ischemic stroke Seizures Headache	Systemic markers negative MRI: cerebral ischemia; with or without leptomeningeal enhancement CSF: mildly elevated white blood cell count and protein Cerebral angiography: beading of vessels Brain biopsy: granulomatous vasculitis	Glucocorticoids Cyclophosphamide

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

guidelines should be considered before treating such a patient.

- *Perinatal stroke* is generally defined as any hemorrhagic or ischemic event occurring from 28 weeks of gestation through the first 7 days of life.
- Periventricular-intraventricular hemorrhage can occur in up to 20%–40% of premature neonates weighing less than 1,500 g.
- The most common causes of stroke in children are acquired or congenital heart disease and sickle cell anemia.

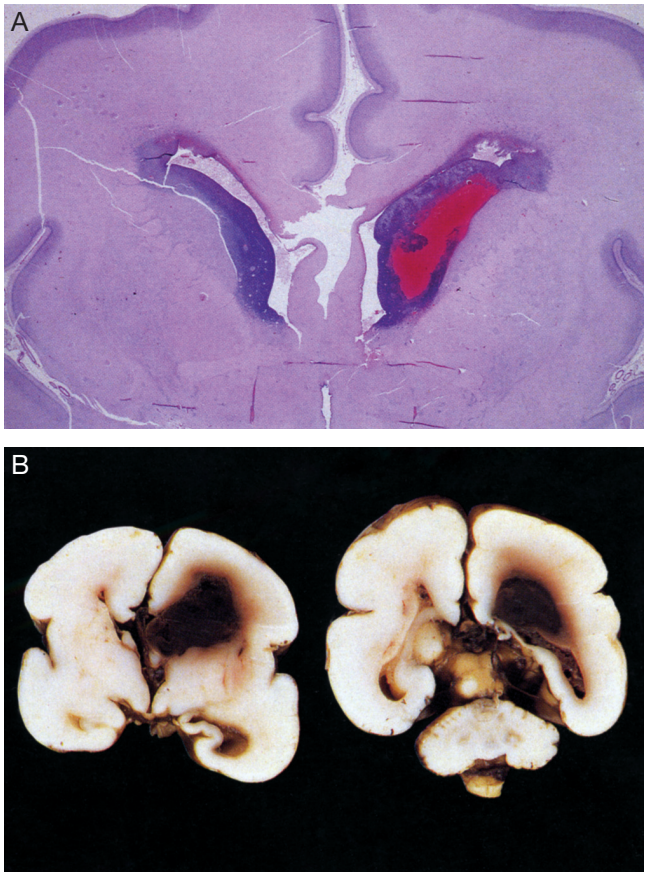

Figure 11.5 *Periventricular-Intraventricular Hemorrhage. A, Coronal section shows a typical periventricular-intraventricular hemorrhage (grade 1) involving the germinal matrix overlying the caudate head, rostral to the foramen of Monro. B, Postmortem specimen from a different neonate shows a larger hemorrhage (grade 4) extending into the brain parenchyma and lateral ventricle.*
(Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. Chapter 8, Perinatal CNS injuries and congenital malformations; p. 277–94. Used with permission of Mayo Foundation for Medical Education and Research.)

- TIPS is a safety and dose-finding study of intravenous tPA therapy in children with acute ischemic stroke. Its purpose is to determine the maximal safe dose for children aged 2–17 years within 4.5 hours of symptom onset.

Stroke in Pregnancy

Pregnancy is a special situation in which the body is preparing for an event that requires rapid coagulation at the time of birth. A number of changes occur during pregnancy and the puerperium. Typically, changes begin in the first trimester and continue into late pregnancy (Box 11.2). The

Table 11.3 • Grading of Periventricular-Intraventricular Hemorrhage of the Germinal Matrix

Grade	Description
1	Confined to caudate head and subependymal layer (usually asymptomatic)
2	Extension into lateral ventricle without ventriculomegaly
3	Extension into lateral ventricle with ventriculomegaly
4	Extension into parenchyma

Box 11.1 • Differential Diagnosis of Stroke in Children

Cardiac disorders
- Congenital heart disease
  - Transposition of the great vessels
  - Atrial or ventricular septal defect
  - Patent foramen ovale
  - Pulmonary stenosis
  - Tetralogy of Fallot
  - Truncus arteriosus with decreased flow
  - Patent ductus arteriosus
  - Endocardial cushion defect
  - Hypoplastic left ventricle
  - Ebstein anomaly
  - Pulmonary atresia
  - Coarctation of the aorta
- Valvular heart disease
  - Congenital
  - Rheumatic
  - Prosthetic valve
  - Mitral valve prolapse
  - Infective endocarditis or noninfective endocarditis
  - Aneurysm of the sinus of Valsalva
- Cardiac arrhythmias
  - Atrial fibrillation
  - Supraventricular tachycardia
  - Sick sinus syndrome
- Cardiomyopathy
  - Kearns-Sayre syndrome
  - Myocardial infarction
  - Left ventricular aneurysm
  - Intracardiac tumors
  - Muscular dystrophy
  - Myocarditis
  - Friedreich ataxia
- Cardiac surgery and catheterization
- Extracorporeal membrane oxygenation
- Kawasaki disease

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(Continued)

- Arteriopathies
  - Dissection
  - Moyamoya disease
  - Fibromuscular dysplasia
  - Vasculitis
  - Transient cerebral arteriopathy
  - Postvaricella angiopathy
  - Migrainous infarction
  - Ergotism
  - Traumatic
  - Radiation-induced
  - Tumor-encased arteries
  - Hypoplasia or agenesis of cervicocephalic vessels
- Hypercoagulable states
  - Primary hypercoagulable states
    - Antithrombin III, protein C, or protein S deficiency
    - Factor V Leiden or prothrombin 20210 mutation
    - Disorders of fibrinogen or plasminogen activator inhibitor
    - Antiphospholipid antibody syndrome
    - Elevated factor VII, VIII, or XII
  - Secondary (acquired) hypercoagulable states
    - Malignancy
    - Pregnancy
    - Oral contraceptive
    - Ovarian hyperstimulation syndrome
    - Hormonal treatments (erythropoietin, anabolic steroids)
    - Nephrotic syndrome
    - Polycythemia vera
  - Essential thrombocytopenia
  - Paroxysmal nocturnal hemoglobinuria
  - Hyperlipidemia, elevated lipoprotein (a)
  - Heparin-induced thrombocytopenia
  - Homocystinuria
  - Sickle cell disease
  - Thrombotic thrombocytopenic purpura
  - Chemotherapeutic agents
- Miscellaneous and genetic risk factors for stroke
  - Hereditary dyslipoproteinemia (familial hypoalphalipoproteinemia, familial hypercholesterolemia, type III or IV hyperlipoproteinemia, Tangier disease, progeria)
  - Heritable disorders of connective tissue (vascular type of Ehlers-Danlos syndrome, Marfan syndrome, pseudoxanthoma elasticum, homocystinuria, Menkes syndrome)
  - Organic acidemias (methylmalonic acidemia, propionic acidemia, isovaleric acidemia, glutaric aciduria type II)
  - Mitochondrial encephalomyopathy (MELAS syndrome, MERRF syndrome, Kearns-Sayre syndrome)
  - Fabry disease (α-galactosidase A deficiency)
  - Leigh disease (subacute necrotizing encephalomyelopathy)
  - Sulfite oxide deficiency
  - 11β-ketoreductase deficiency
  - 17α-hydroxylase deficiency
  - Purine nucleoside phosphorylase deficiency
  - Ornithine transcarbamylase deficiency
  - Neurofibromatosis type 1
  - HERNS syndrome

Abbreviations: HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonic epilepsy with ragged red fibers.

Adapted from Biller J. Cardiac disorders and stroke in children and young adults. In: Biller J, editor. Stroke in children and young adults. 2nd ed. Philadelphia (PA): Saunders/Elsevier; c2009. p. 135–59. Used with permission.

Box 11.2 • Changes in Specific Coagulation Factors in Pregnancy

- Increased
  - Fibrinogen (doubles)
  - Factors VII, VIII, X, and XII
  - Plasminogen (50%)
  - PAI-1 and PAI-2
  - Blood volume
  - D dimer
  - β-Thromboglobulin (platelet)
  - Fibrinopeptide A (first peptide cleaved from fibrinogen)
- Decreased
  - Factors XI and XIII
  - Platelets (possibly)
  - Fibrinolytic systems (highest in third trimester)
  - Tissue plasminogen activator
  - Free protein S
- No change
  - Factors II, V, and IX
  - Angiotensin III
  - Total protein S
  - Protein C

Abbreviation: PAI, plasminogen activator inhibitor.

Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.

Table 11.4 • Cerebrovascular Complications During Pregnancy and the Postpartum State

Complication	Incidence	Causes	Comments
Subarachnoid hemorrhage	20 per 100,000	Aneurysm AVM Trauma	More common during pregnancy than in postpartum period
Intraparenchymal hemorrhage	4 per 100,000	AVM Cavernous malformation Eclampsia Venous thrombosis	More common in postpartum period than during pregnancy
Venous thrombosis	10–20 per 100,000	May have predisposing factor (eg, factor V Leiden mutation, dehydration, infection, sickle cell anemia)	80% are in postpartum period
Pituitary apoplexy	Rare	Preexisting pituitary adenoma	. . .
Arterial stroke	3.5–5 per 100,000	May be unrelated to pregnancy Specific rare causes of pregnancy-related stroke: eclampsia, choriocarcinoma, amniotic fluid embolism, reversible cerebrovasoconstrictive syndrome, peripartum cardiomyopathy	More common in postpartum period than during pregnancy
Reversible vasoconstrictive syndrome	Rare	Concomitant use of sympathomimetics and selective serotonin reuptake inhibitors	More common in postpartum period than during pregnancy

Abbreviation: AVM, arteriovenous malformation.

red blood cell mass increases at about 10 weeks and continues to increase progressively until term. The plasma volume begins to increase at about 10 weeks' gestation, it continues to increase progressively until 30 to 34 weeks, and then it plateaus. The mean increase in plasma volume by 30 to 34 weeks is 50%. Because volume increases by 50% and the red blood cell mass increases by only 18% to 30%, the hematocrit decreases to its nadir at 30 to 34 weeks, resulting in anemia.

When the placenta separates, maternal blood flow (700 mL/min) is reduced by myometrial compression and thrombotic occlusion of the vessels. Coagulation is activated, and fibrinogen increases and coagulation inhibitors decrease. The coagulation and fibrinolytic systems are important in controlling fibrin deposition in the uteroplacental circulation while preventing fibrin deposition in the rest of the vascular system.

Cerebrovascular complications during pregnancy and the postpartum state include subarachnoid hemorrhage, intraparenchymal hemorrhage, venous thrombosis, pituitary apoplexy, ischemic stroke, and reversible vasoconstrictive syndrome (peripartum angiopathy) (Table 11.4).

Spinal Cord Infarction

Spinal cord infarction is rare. Mechanisms include hypoperfusion, embolism, or thrombosis. The thoracolumbar segment is most vulnerable to hypoperfusion. The differential diagnosis of spinal cord infarction is listed in Table 11.5.

Table 11.5 • Differential Diagnosis of Spinal Cord Infarction

Etiologic Factor	Specific Conditions
Vasculitis	Polyarteritis nodosa, Behçet syndrome, giant cell arteritis
Embolism	Atrial myxoma, mitral valve disease, endocarditis, paradoxical emboli, fibrocartilaginous emboli from herniated disks
Systemic hypoperfusion	Cardiopulmonary arrest, aortic rupture or dissection, coarctation of aorta
Iatrogenic cause	Thoracolumbar sympathectomy, scoliosis surgery, cardiac catheterization, aortography, renal artery embolization, umbilical artery catheterization, vertebral angiography, aortic surgery, surgical repair of coarctation, retroperitoneal lymph node dissection
Infectious disease	Syphilis, mucormycosis, meningitis
Miscellaneous cause	Sickle cell anemia, cocaine, decompression sickness, antiphospholipid antibody syndrome, Crohn disease, cervical subluxation, atherosclerosis of the aorta

Patients with spinal cord infarction typically present with an anterior spinal artery syndrome. Posterior spinal artery syndromes are less common. With the anterior spinal artery syndrome, the posterior columns are spared. Thus, clinical examination may demonstrate loss of pain and

Table 11.6 • Risk Factors for Cerebral Venous Sinus Thrombosis

Risk Factor	Specific Conditions
General disorder	Dehydration Lumbar puncture or overshunting (ie, excessive drainage of cerebrospinal fluid) Hypoxia
Infection	Meningitis Mastoiditis Ear infections Tonsillitis Sinusitis
Blood disorder	Essential thrombocytosis Heparin-induced thrombocytopenia Polycythemia vera Sickle cell anemia Lymphoma Iron deficiency anemia Autoimmune hemolytic anemia Paroxysmal nocturnal hemoglobinuria Thalassemia
Coagulation disorder	Prothrombin 20210 mutation Factor V Leiden mutation Protein C or protein S deficiency Antithrombin III deficiency Phospholipid antibody syndrome Homocystinuria
Drug or toxin	Certain chemotherapeutic agents Estrogens Corticosteroids Epoetin alfa
Systemic disease	Malignancy Systemic lupus erythematosus Thyrotoxicosis Behçet syndrome Inflammatory bowel disease (ulcerative colitis, Crohn disease) Nephrotic syndrome

temperature sensation below the level of the lesion with sparing of vibratory and joint position sensation, upper motor neuron loss below the level of the lesion, and lower motor neuron function loss at the segment of the injury.

MRI of the spine (or, alternatively, CT myelography) may be helpful to rule out other causes of myelopathy. MRI may also show increased T2 signal intensity in the spinal cord. Further evaluation for potential causes may depend on history and recent procedures. Evaluation could include a search for aortic disease, cardioembolic disease, coagulopathies, or vasculitides, depending on the pretest probability.

There have been no clinical trials to guide treatment. Prevention of stroke during major abdominal aortic surgeries is common with the use of intraoperative monitoring with somatosensory evoked potential during aortic surgery and avoidance of hypotension. For the acute infarction, methylprednisolone and lumbar cerebrospinal fluid drainage to

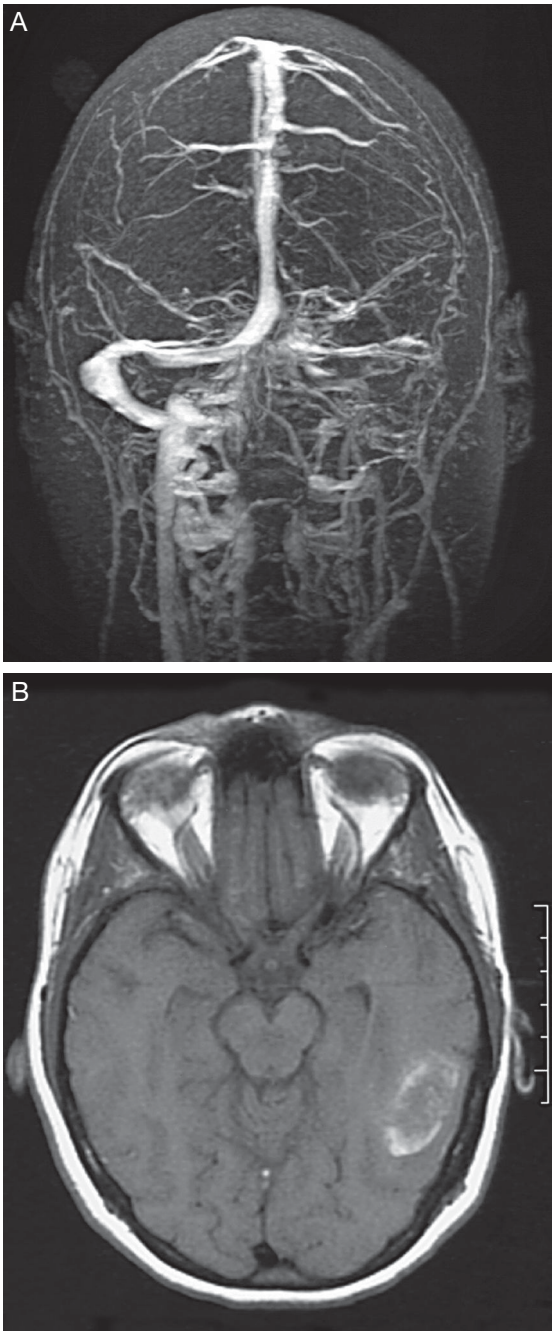

Figure 11.6 *Veno-occlusive Disease and Venous Infarction. The patient was a 47-year-old woman who was taking oral contraceptives. A, Magnetic resonance venogram demonstrates extensive thrombosis of the left transverse and sigmoid sinuses that extends to involve the left internal jugular vein. B, Nonenhanced T1-weighted magnetic resonance image shows hemorrhagic venous infarction in the left temporal lobe.*

(Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.)

reduce intrathecal pressure have been tried with variable success. Secondary prevention is based on treatment of the potential cause. Supportive treatment with rehabilitation and careful bowel and bladder management are important.

The prognosis is variable, depending on the degree of damage and the cause: 20% to 25% of patients have no improvement, 20% have good recovery with minimal disability, and the remainder have a poor prognosis. Chronic pain can be a disabling feature.

- Patients with spinal cord infarction typically present with an anterior spinal artery syndrome.

Venous Thrombosis

Venous thrombosis is less common than arterial stroke. The differential diagnosis includes malignancy, pregnancy or the postpartum state, oral contraception, factor V Leiden (common), hyperhomocysteinemia, prothrombin 20210 mutation, protein C or protein S deficiency, contiguous infectious extension, dural arteriovenous fistula, phospholipid antibody syndrome, essential thrombocytosis, or polycythemia vera. In children, dehydration, infection, and sickle cell anemia should also be considered. An exhaustive list of potential risk factors and conditions resulting in venous thrombosis is presented in Table 11.6.

Patients with venous thrombosis typically present with subacute, progressive headache, but they may rarely have thunderclap headache. Since they have elevated intracranial pressure, patients may also have papilledema, cranial nerve VI palsy, and transient visual obscurations (graying of vision bilaterally, often with sneezing or straining). Patients may also have focal neurologic deficits or seizures if cerebral venous congestion, infarction, or hemorrhage occurs.

The diagnosis can be made with magnetic resonance venography, CT venography, or conventional angiography (Figure 11.6).

Anticoagulation is generally recommended. If the patient has an increased intracranial pressure that cannot be controlled or is not responding to anticoagulation, or if the patient is somnolent, mechanical clot disruption or interventional administration of thrombolytics can be considered. The duration of anticoagulation treatment depends on the identified cause. If no specific entity is identified, anticoagulation generally is used for 3 to 6 months with follow-up imaging at that time.

- Patients with venous thrombosis typically present with subacute, progressive headache, but they may rarely have thunderclap headache.

12 Acute Ischemic Stroke Evaluation and Treatment

BART M. DEMAERSCHALK, MD

Introduction

According to World Health Organization statistics, stroke is the second leading cause of death worldwide, with an estimated 6.2 million deaths per year. In the United States, approximately 800,000 patients sustain an acute stroke annually. Acute stroke is a time-sensitive neurologic emergency. To take full advantage of the many new and existing acute stroke treatments, proper diagnosis and management must occur as soon as possible. The earlier the therapies are instituted, the higher the probability of the patient having a successful outcome and avoiding long-term disability. A suggested algorithm for the initial management of acute stroke and acute ischemic stroke is shown in Figure 12.1.

Acute Clinical Evaluation

Emergency Medical Services

Acute stroke is suspected when a patient presents with the sudden onset of focal central neurologic symptoms and signs. Emergency Medical Services (EMS) personnel are usually the first to evaluate the patient in the field. The standard evaluation and initial management include performing airway, breathing, and circulation assessments; inserting a peripheral intravenous (IV) catheter and administering fluids; checking the patient's blood glucose level with a glucose meter; evaluating the patient with a prehospital stroke assessment scale; administering supplemental oxygen; and transporting the patient. EMS personnel should transport the patient to the closest acute stroke–ready hospital. If EMS personnel cannot transport the patient by ground within 1 hour of arrival, air transport can be considered. EMS personnel should call ahead to the proposed receiving hospital to advise the emergency personnel of the patient's status, the prehospital stroke scale score, the time of stroke onset or the time the patient was last known to be at baseline state, and the estimated time of arrival at the destination.

Evaluation in the Hospital Emergency Department

Upon arrival at the emergency department, the patient is rapidly given a clinical assessment, and laboratory tests, electrocardiography, and neuroimaging are performed. The data help determine whether a patient is a candidate for IV thrombolysis (Box 12.1) or endovascular therapy. Increasingly, regional stroke systems of care include telemedicine (ie, telestroke) consultation to expedite the assessment, determine eligibility for thrombolytic therapy, begin thrombolysis if eligible, and transfer to a stroke center if indicated.

Clinical evaluation of the stroke patient includes taking a brief history to identify the last time the patient was known to be well, comorbidities, and medications that may contraindicate thrombolysis. A general examination and a neurologic examination should then be performed to confirm the suspected diagnosis and establish the degree of disability. The National Institutes of Health Stroke Scale (NIHSS) is a standardized method for providers to reliably

Abbreviations: BP, blood pressure; CT, computed tomography; EMS, Emergency Medical Services; FDA, US Food and Drug Administration; INR, international normalized ratio; IV, intravenous; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; PTT, partial thromboplastin time; tPA, tissue plasminogen activator

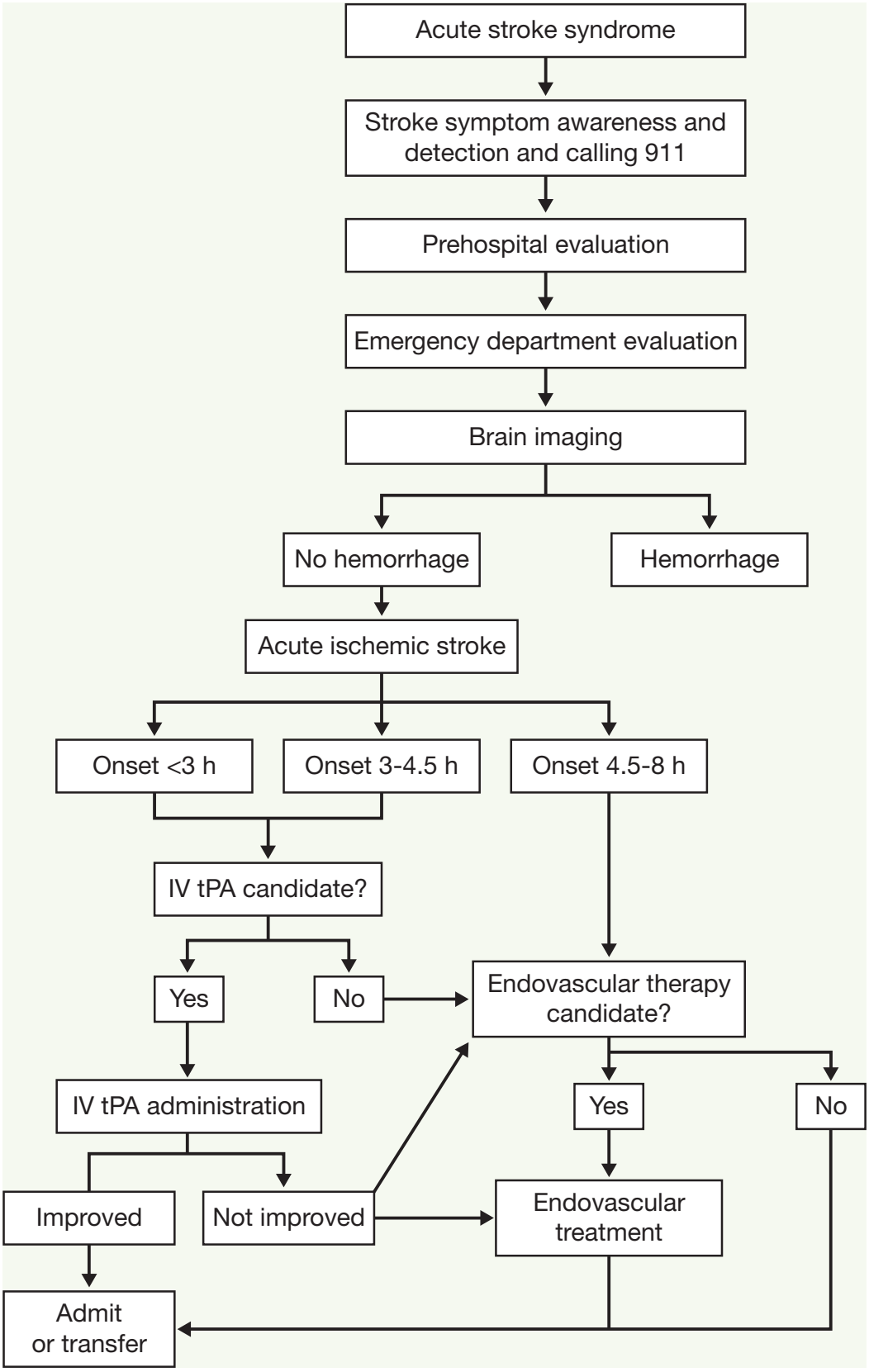

Figure 12.1 *Algorithm for Initial Management of Acute Stroke and Acute Ischemic Stroke. IV indicates intravenous; tPA, tissue plasminogen activator.*

Box 12.1 • Contraindications for the Use of Intravenous Tissue Plasminogen Activator

Standard contraindications
- Neurologic symptoms and signs are clearing rapidly and spontaneously
- Neurologic symptoms and signs are minor and isolated
- Suggestion of subarachnoid hemorrhage
- Head trauma or prior stroke in previous 3 mo
- Myocardial infarction in previous 3 mo
- Gastrointestinal tract or genitourinary tract bleeding in previous 21 d
- Major surgery in previous 14 d
- Arterial puncture at noncompressible site or lumbar puncture in previous 7 d
- Prior history of intracranial hemorrhage
- Blood pressure: systolic >185 mm Hg or diastolic >110 mm Hg
- Active bleeding or acute trauma
- Receiving warfarin, and INR >1.7
- Has received heparin in previous 48 h, and PTT is elevated
- Platelet count $<100 \times 10^3/\mu L$
- Blood glucose <50 mg/dL
- Seizure with postictal deficit
- Receiving dabigatran, apixaban, or rivaroxaban

Additional contraindications for use during hours 3–4.5
- Any standard contraindication
- Age ≥80 y
- Anticoagulant use (regardless of INR)
- NIHSS score >25
- History of prior stroke and diabetes mellitus

Abbreviations: INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; PTT, partial thromboplastin time.

quantify the abnormalities from a stroke patient's neurologic examination (Table 12.1). There is no absolute lower threshold for an NIHSS score below which recombinant tissue plasminogen activator (tPA) should be withheld. Instead, it is more important to evaluate the level of disability in the context of the patient's health state. Even a very low NIHSS score (eg, an NIHSS score of 2 for a homonymous hemianopia) may be disabling for a 45-year-old college professor and warrant consideration of thrombolysis.

Laboratory testing should include determination of capillary blood glucose, a complete blood cell count and differential blood count, blood chemistry tests, prothrombin time, international normalized ratio (INR), partial thromboplastin time (PTT), and β-human chorionic gonadotropin

Table 12.1 • National Institutes of Health Stroke Scale (Condensed Version)

Instructions	Definition	Score
Level of consciousness	Alert	0
	Drowsy	1
	Stuporous	2
	Coma	3
Level of consciousness questions	Answers both correctly	0
	Answers 1 correctly	1
	Answers neither correctly	2
Level of consciousness commands	Obeys both correctly	0
	Obeys 1 correctly	1
	Obeys neither correctly	2
Best gaze	Normal	0
	Partial gaze palsy	1
	Forced deviation	2
Visual	No visual loss	0
	Partial hemianopia	1
	Complete hemianopia	2
	Bilateral hemianopia	3
Facial palsy	Normal facial movement	0
	Minor paresis	1
	Partial paresis	2
	Complete palsy	3
Motor arm—left arm	No drift	0
	Drift	1
	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
Motor arm—right arm	No drift	0
	Drift	1
	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
Motor leg—left leg	No drift	0
	Drift	1
	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
Motor leg—right leg	No drift	0
	Drift	1
	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
Limb ataxia	Absent	0
	Present in 1 limb	1
	Present in 2 limbs	2
Sensory	Normal	0
	Partial loss	1
	Dense loss	2
Best language	No aphasia	0
	Mild to moderate aphasia	1
	Severe aphasia	2
	Mute	3
Dysarthria	Normal articulation	0
	Mild to moderate slurring	1
	Severe and nearly intelligible or worse	2
Extinction and inattention	No neglect	0
	Partial neglect	1
	Profound neglect	2

Adapted from NIH Stroke Scale [Internet]. Bethesda (MD): NIH. c2003 – [cited 2014 Apr 22]. Available from: http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf.

level for women of childbearing age who have childbearing potential. If a patient is determined to be a candidate for thrombolysis and there is no reason to expect an abnormal laboratory test result, IV tPA may be administered without waiting for delayed laboratory test results.

At a minimum, noncontrast computed tomography (CT) of the head (or magnetic resonance imaging [MRI] of the head) should be conducted within 25 minutes and interpreted within 45 minutes after the patient arrives in the emergency department.

Management in the Hospital Emergency Department

While the patient with acute stroke is undergoing critical tests, medical management proceeds (Box 12.2).

Excessively elevated blood pressure (BP) may increase the risk of intracerebral hemorrhagic complications from thrombolysis. Systolic BP greater than 185 mm Hg or diastolic BP greater than 110 mm Hg exceeds acceptable thresholds for thrombolysis and must be decreased before therapy with IV tPA can be initiated. When the BP is less than 185/110 mm Hg, administration of IV tPA may proceed in eligible patients with acute ischemic stroke.

If the patient's BP remains refractive to these recommended treatments, the patient should not receive IV tPA.

Box 12.2 • Medical Management of Acute Stroke

- Maintain serum glucose <140 mg/dL; avoid hyperglycemia
- Administer normal saline IV, 1.5 mL/kg hourly initially, with a goal of euvolemia; avoid dextrose-containing maintenance fluid
- Continue telemetry and cardiac monitoring
- Treat fever with antipyretics
- Give nothing by mouth until a swallowing assessment confirms that the patient can swallow safely
- Acute BP goal <220/110 mm Hg (without IV tPA) or <185/110 mm Hg (with IV tPA or if patient is a tPA candidate)
- If tPA was administered:

  Admit to intensive care unit

  Avoid invasive procedures (avoid use of indwelling urinary catheter, nasogastric tubes, and intra-articular catheters for ≥4 h)

  Do not administer antiplatelet or anticoagulant medications for ≥24 h

  Frequently check vital signs (goal BP <185/110 mm Hg) and neurologic status

Abbreviations: BP, blood pressure; IV, intravenous; tPA, tissue plasminogen activator.

However, efforts to decrease the BP below 220/120 mm Hg should continue. Permissive hypertension (ie, BP ≤220/120 mm Hg) is recommended for patients with ischemic stroke who are not eligible for IV tPA. Use of titratable agents such as labetalol and nicardipine is preferred.

- Clinical evaluation of the stroke patient includes taking a brief history to identify the last time the patient was known to be well, comorbidities, and medications that may contraindicate thrombolysis.

Acute Treatment Options

Intravenous Thrombolysis

Hours 0 to 3

If less than 3 hours has elapsed from when the patient was last known well until the stroke team assesses the patient, the priority is to confirm the patient's eligibility for IV tPA (Box 12.1). Besides elapsed time, the most common exclusion criteria are rapid, spontaneous improvement and mild deficit. These are, naturally, subjective determinations and are probably exaggerated as exclusion criteria. A rule of thumb is to proceed with IV tPA, despite early reports of clinical improvement, if a patient's stroke symptoms and signs are still present at the conclusion of the stroke team's preliminary assessment (which includes history, physical examination, evaluation with the NIHSS, laboratory tests, and neuroimaging).

The use of IV tPA during hours 0 to 3 is contraindicated for patients who are receiving vitamin K antagonists such as warfarin and whose INR is 1.7 or more. The use of IV tPA in patients prescribed direct thrombin inhibitors or direct factor Xa inhibitors (dabigatran, rivaroxaban, and apixaban) may be harmful and is not recommended unless the patient has not received a dose of these medicines for more than 48 hours or unless the results are normal from sensitive laboratory tests (eg, activated PTT, INR, platelet count, ecarin clotting time, thrombin clotting time, and special assays).

Hours 3 to 4.5

The US Food and Drug Administration (FDA) has not approved the use of IV tPA beyond hour 3, but tPA is approved for use during hours 3 to 4.5 in Canada and Europe. Despite the lack of FDA approval in the United States, IV tPA is widely used during hours 3 to 4.5, and the practice is recommended by an American Heart Association/American Stroke Association scientific statement. For the use of IV tPA 3 to 4.5 hours after the onset of stroke symptoms, 4 unique criteria are applicable in addition to all the usual eligibility criteria (Box 12.1).

Administration of IV tPA

The goal is to complete an evaluation and to begin thrombolysis within 60 minutes of the patient's arrival in an

emergency department. Two peripheral IV catheters should be placed, and the patient should be weighed. The dose of IV tPA is 0.9 mg/kg to a maximum of 90 mg. The first 10% of the total dose is administered as an IV bolus over 1 minute, and the remaining 90% should follow and be infused over 1 hour. It is advisable to monitor the patient frequently for complications of IV tPA, including hemilingual edema, angioedema, intracranial hemorrhage, and systemic hemorrhage. Hemorrhagic transformation is a consideration if a patient has a sudden, severe headache; worsening neurologic deficit; or reduced level of consciousness. The tPA infusion should be discontinued, blood should be drawn for laboratory tests (prothrombin time, INR, PTT, platelet count, fibrinogen level, and blood typing and cross matching), and CT of the head should be performed immediately. If hemorrhage is confirmed on CT, the neurosurgery department should be consulted or alerted. Administer 6 to 8 units of IV cryoprecipitate and 6 to 8 units of platelets and consider administering 40 to 80 mg/kg of recombinant activated factor VIIa while waiting for the response to platelets and cryoprecipitate.

Intra-arterial Therapy Following IV Thrombolysis

Endovascular therapy has been considered for select patients with persistent arterial occlusion after IV thrombolysis. Currently, the utility of postthrombolysis endovascular therapy is in question after evaluations of large populations. Further refining the selection of appropriate patients is necessary.

Endovascular (Intra-arterial) Therapy

For patients who have large arterial occlusions (eg, in the middle cerebral artery, intracranial internal carotid artery, or basilar artery) and whose stroke symptoms began no more than 8 hours earlier, intra-arterial thrombolysis (≤6 hours after symptom onset) or mechanical thrombectomy (with a Merci [Stryker], Penumbra [Penumbra, Inc], Solitaire [Covidien], or Trevo [Stryker] device) (≤8 hours after symptom onset), or both, may allow successful arterial recanalization. IV thrombolysis is considered first since it is the standard of care. However, if the patient is not a candidate for IV thrombolysis or if the window for such therapy has passed, endovascular treatment is considered. Patients under consideration for this type of therapy should be cared for at comprehensive stroke centers that have the expertise to perform such procedures.

Large intracranial arterial occlusions are generally suspected clinically first (moderate or severe stroke syndrome NIHSS score >10 or 20), and confirmed radiologically by CT angiography, magnetic resonance angiography, or conventional catheter angiography. Sometimes advanced neurovascular imaging may be used in selecting patients for endovascular treatments by measuring the infarct core and the ischemic penumbra (with CT or MRI perfusion techniques).

- For the use of IV tPA 3–4.5 hours after the onset of stroke symptoms, 4 unique criteria are applicable in addition to all the usual eligibility criteria (Box 12.1).
- The dose of IV tPA is 0.9 mg/kg to a maximum of 90 mg.
- Hemorrhagic transformation is a consideration if a patient has a sudden, severe headache; worsening neurologic deficit, or reduced level of consciousness.
- For patients who have large arterial occlusions (eg, in the middle cerebral artery, intracranial internal carotid artery, or basilar artery) and whose stroke symptoms began ≤8 hours earlier, intra-arterial thrombolysis (≤6 hours after symptom onset) or mechanical thrombectomy (with a Merci, Penumbra, Solitaire, or Trevo device) (≤8 hours after symptom onset), or both, may allow successful arterial recanalization. However, exact selection criteria are evolving.

Posttreatment Guidelines

After acute intervention is considered, patients are admitted to an appropriate location. After intervention (IV or intra-arterial treatment), patients are often admitted to an intensive care unit for close monitoring of vital signs and neurologic status. Patients whose status is at risk for deterioration due to malignant middle cerebral artery ischemic stroke (see also the discussion of hemicraniectomy in Chapter 2, "Principles and Management of Alterations in Intracranial Pressure"), and who have a reduced level of consciousness or other comorbidities requiring frequent monitoring should also be admitted to an intensive care unit. Other patients may be admitted to a designated stroke unit.

Admission orders should address, at a minimum, blood glucose level, temperature, volume status, swallowing assessment, placement of catheters, and deep vein thrombosis prevention.

13 Secondary Prevention of Ischemic Stroke[a]

BART M. DEMAERSCHALK, MD

Introduction

After an ischemic stroke is diagnosed, a diagnostic evaluation ensues to determine the mechanism of the stroke and contributing risk factors. (See Chapter 10, "Ischemic Stroke: Common Causes and Diagnosis.") The appropriate antithrombotic is selected according to the mechanism of the stroke, and the contributing risk factors are treated with pharmacologic agents and lifestyle changes. This chapter discusses the selection of antithrombotic medication, lifestyle changes, and medical treatment of contributing risk factors. Treatment of specific mechanisms of stroke is also covered in Chapter 10, "Ischemic Stroke: Common Causes and Diagnosis."

Box 13.1 • Indications for Anticoagulation or Antiplatelet Agents in Patients With Ischemic Stroke[a]

- Indications for antiplatelet agent
  - Large-vessel stenosis (extracranial or intracranial)
  - Small-vessel disease or lacunar stroke
  - Cryptogenic stroke
- Indications for anticoagulation
  - Atrial fibrillation
  - Mechanical heart valve
  - Left ventricular or left atrial thrombus
  - Cerebral venous thrombosis

[a] Areas of controversy for antithrombotic selection: arterial dissection, cardiomyopathy.

Antithrombotic Therapy

Antiplatelet Management

All patients with ischemic stroke or transient ischemic attack (TIA) should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless there is an indication for anticoagulation (Box 13.1). Appropriate options are acetylsalicylic acid (50–325 mg), acetylsalicylic acid (25 mg) in combination with extended-release dipyridamole (200 mg), or clopidogrel (75 mg). Selection may be individualized according to cost, tolerances, and clinical circumstances.

Short-term use (≤90 days) of acetylsalicylic acid in combination with clopidogrel has not been shown to increase the risk of bleeding; however, long-term use (>90 days) is not generally recommended for secondary stroke prevention unless there is another indication, such as a drug-eluting carotid artery stent. Several clinical trials have shown that long-term dual antiplatelet therapy for stroke (acetylsalicylic acid in combination with clopidogrel) is not more effective and carries a higher bleeding risk.

No clinical trial has addressed therapy when a patient has a stroke while taking a specific antiplatelet agent.

[a]Portions previously published in Coutts S, Kelloway L, co-chairs, on behalf of the Prevention of Stroke Best Practices Writing Group 2012. Chapter 2: Stroke prevention: Update August 2014. In: Lindsay MP, Gubitz G, Bayley M, Phillips S, editors, on behalf of the Canadian Stroke Best Practices and Standards Working Group. Canadian best practice recommendations for stroke care: Update 2014. 5th ed. Canada: Canadian Stroke Network; c2014. 69 p. Used with permission.

Abbreviations: OSA, obstructive sleep apnea; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA, transient ischemic attack

Box 13.2 • Reasons for Failure of Antiplatelet Therapy

- Nonadherence to drug therapy
- Concomitant use of NSAIDs or COX-2 inhibitors with acetylsalicylic acid
- Poor absorption
- Impaired metabolism of clopidogrel (concomitant use with proton pump inhibitors or other medications; patient may be a genetically poor metabolizer [*CYP2C19*])
- Poor response (resistance)

Abbreviations: *CYP2C19*, cytochrome P450 2C19 isozyme gene; COX-2, cyclooxygenase 2; NSAID, nonsteroidal anti-inflammatory drug.

When antiplatelet therapy fails, options include 1) determining possible reasons for failure (Box 13.2), 2) searching for a mechanism requiring an alternative to an antiplatelet agent, and 3) switching to an alternative antiplatelet agent. In addition to consideration of the antiplatelet agent, other vascular risk factors should be assessed and modified.

Anticoagulant Management for Atrial Fibrillation

Atrial fibrillation is a significant risk factor for stroke that should be assessed and treated aggressively to reduce the risk of recurrent ischemic stroke. Multiple randomized clinical trials have shown that anticoagulation is superior to antiplatelet agents or antiplatelet agent combinations in preventing recurrent cerebral ischemia in patients with atrial fibrillation. If no contraindications exist, patients with both TIA and atrial fibrillation should begin oral anticoagulation after computed tomography or magnetic resonance imaging of the brain has excluded intracranial hemorrhage or large infarct. Choices include warfarin, dabigatran, rivaroxaban, or apixaban. The timing of anticoagulation depends on whether intravenous tissue plasminogen activator was administered (must wait 24 hours after administration) and on the size of the infarction and, therefore, the risk of hemorrhagic conversion.

The new oral anticoagulants (dabigatran, rivaroxaban, and apixaban) have been shown to have advantages in efficacy or safety over warfarin for stroke prevention. For patients prescribed these anticoagulants, renal function should be routinely monitored and measured at least once annually.

- Multiple randomized clinical trials have shown that anticoagulation is superior to antiplatelet agents or antiplatelet agent combinations in preventing recurrent cerebral ischemia in patients with atrial fibrillation.

Lifestyle Changes

All patients with stroke or TIA should be assessed for vascular risk factors. In addition to receiving pharmacologic therapy, patients should be counseled on lifestyle changes and referred to appropriate specialists. Some patients may need a structured assessment and risk factor management program. Lifestyle and risk factor information and counseling should include following dietary strategies, limiting sodium intake, exercising, maintaining a normal weight, stopping use of tobacco, and drinking no more than moderate amounts of alcohol (Table 13.1).

Exercise is an important lifestyle change that deserves additional attention. Current guidelines suggest participating in moderate exercise 4 to 7 days weekly in addition to routine activities of daily living. The exercise may include (but is not limited to) walking (ideally brisk walking), jogging, cycling, swimming, or other dynamic exercise. A cumulative 150 minutes weekly of moderate to vigorous activity, in episodes of 10 minutes or more, may be advised for patients who can exercise.

In some situations, supervision by a health care professional (experienced in physical medicine and rehabilitation or cardiac rehabilitation) should be considered for patients with significant comorbidities (eg, orthopedic or cardiopulmonary) that place them at higher risk of medical complications.

Medical Management

Blood Pressure Management

Hypertension is the single most important modifiable risk factor for stroke. Blood pressure should be assessed, monitored, and managed for all patients with stroke to prevent recurrent stroke. Patients who have had a stroke or TIA should receive treatment to lower their blood pressure in the subacute to chronic phase to achieve a target of less than 140/90 mm Hg.

Randomized controlled trials have not defined the optimal time to initiate blood pressure–lowering therapy after stroke or TIA. Blood pressure–lowering treatment should be initiated or modified before patients are dismissed from the hospital.

The choice of agent is less important than achieving a lower blood pressure. Lowering the systolic blood pressure by as little as 10 mm Hg and the diastolic blood pressure by as little as 5 mm Hg can reduce the relative risk of recurrent stroke by about 25%.

Lipid Management

Patients with ischemic stroke or TIA should have their serum lipid levels assessed and managed. Therapeutic lifestyle changes in addition to use of a statin may

Table 13.1 • Lifestyle Change Recommendations

Recommendation	Specific Guideline
Maintain a healthy diet	Eat a diet high in fresh fruits, vegetables, low-fat dairy products, dietary and soluble fiber, whole grains, and protein from plant sources and low in saturated fat and cholesterol (<200 mg daily)
Limit daily sodium intake to <2,000 mg	Adequate intake level: for adults 50 y or younger, 1,500 mg; for persons 51–70 y old, 1,300 mg; for persons older than 70 y, 1,200 mg A daily upper consumption limit of 2,300 mg should not be exceeded by persons in any age group
Exercise	Moderate aerobic activity for ≥150 min weekly
Maintain a healthy weight	Maintain a BMI of 18.5–24.9 or a waist circumference of <80 cm for women and <94 cm for men
Consume no more than moderate amounts of alcohol	Limit daily consumption to ≤2 standard drinks for men and ≤1 drink for women who are not pregnant
Avoid use of estrogen-containing products	Patients who have had a stroke and are taking estrogen-containing oral contraceptives or hormone replacement therapy should understand the risks and benefits of these treatments Management alternatives should be considered for these patients
Stop use of tobacco	Complete tobacco cessation and avoidance of second-hand smoke is recommended Supportive quit programs may be useful A combination of pharmacologic therapy and behavioral therapy should be considered Pharmacologic agents that should be considered as first-line therapy for smoking cessation are nicotine replacement preparations, bupropion, and varenicline

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Adapted from Coutts S, Kelloway L, co-chairs, on behalf of the Prevention of Stroke Best Practices Writing Group 2012. Chapter 2: Stroke prevention: Update August 2014. In: Lindsay MP, Gubitz G, Bayley M, Phillips S, editors, on behalf of the Canadian Stroke Best Practices and Standards Working Group. Canadian best practice recommendations for stroke care: Update 2014. 5th ed. Canada: Canadian Stroke Network; c2014. 69 p. Used with permission.

be considered. High-intensity statin therapy should be considered for secondary prevention in patients who have had an ischemic stroke or TIA of atherosclerotic origin or who have a history of coronary artery disease. High-intensity statin therapy includes 40- to 80-mg doses of atorvastatin daily and 20- to 40-mg doses of rosuvastatin daily. Moderate-intensity statin therapy is recommended for patients older than 75 or for patients who have a high risk of statin-related complications.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial randomly assigned patients without coronary artery disease and noncardioembolic stroke to receive either 80 mg of atorvastatin or placebo. This was the first trial to show a reduction in the recurrent risk of ischemic stroke in addition to a reduction in myocardial infarction.

Diabetes Management

Patients with ischemic stroke or TIA who have diabetes mellitus should optimally manage their diabetes. Glycemic targets should be individualized. Most patients who have type 1 or type 2 diabetes mellitus and stroke or TIA should be treated to achieve a glycated hemoglobin A_{1c} level of 7.0% or less to decrease the risk of microvascular complications and, in patients with type 1 diabetes mellitus, macrovascular complications.

Obstructive Sleep Apnea Management

Obstructive sleep apnea (OSA) is recognized as an emerging risk factor for stroke. In addition, many patients have OSA after a stroke. Management of OSA should be initiated for patients with confirmed sleep apnea before or after stroke or TIA according to objective clinical assessment and investigations.

Continuous positive airway pressure is a common therapy for OSA, but certain lifestyle changes may also prove beneficial. These include weight loss; avoidance of sedatives, hypnotics, and alcohol; and positional therapy (avoidance of back sleeping). In some cases, dental appliances and, rarely, surgical operations are offered.

Asymptomatic Internal Carotid Artery Stenosis

Asymptomatic internal carotid artery stenosis increases the risk of ischemic stroke. Patients with a stenosis of more than 60% and no symptoms related to the internal carotid artery have an ipsilateral risk of ischemic stroke of approximately 2% to 3% annually. This risk can be reduced to 1% annually with intervention (carotid endarterectomy or angioplasty and stenting). Intervention carries a risk of approximately 1.5% to 3%. There is considerable controversy about intervention in this group of patients because the risk-benefit ratio is small. Antiplatelet therapy and

statins are indicated for these patients to reduce the risk of ischemic stroke.

- Patients who have had a stroke or TIA should receive treatment to lower their blood pressure in the subacute to chronic phase to achieve a target of less than 140/90 mm Hg.
- OSA is recognized as an emerging risk factor for stroke. In addition, many patients have OSA after a stroke.

14 Intraparenchymal Cerebral Hemorrhage[a]

MARIA I. AGUILAR, MD; BARRY D. BIRCH, MD

Introduction

Intraparenchymal cerebral hemorrhage (ICH) is the presence of blood in the brain parenchyma; it is a neurologic emergency and may carry significant morbidity and mortality. The broad differential of ICH is presented in Box 14.1. This chapter focuses mainly on spontaneous, nontraumatic ICH (ie, hemorrhage not related to arteriovenous malformation, cerebral aneurysm, or tumor).

Epidemiology and Risk Factors

Epidemiology

ICH accounts for 15% to 20% of all new strokes annually. Among the general population, the incidence is 15 per 100,000 people. The incidence is highest among Japanese (60 cases per 100,000 people), followed by African Americans (30 per 100,000 people).

ICH is twice as common as subarachnoid hemorrhage and just as deadly, with a 30-day mortality of 30% to 50%, which has not decreased since the early 2000s. The incidence and severity are likely to increase as the population ages.

Etiology

The most common cause of ICH is hypertension (about 50% of cases), followed by cerebral amyloid angiopathy (CAA) (about 20% of cases) (Figure 14.1). Anticoagulant use accounts for 15% to 17% of ICH cases. Other less common causes include other coagulopathies, hemorrhagic infarcts, reversible cerebral vasoconstriction syndrome, and arterial dissection.

Hypertensive ICH usually occurs in deep areas of the brain, such as the basal ganglia, pons, and cerebellum (Figure 14.2). The underlying mechanism is accelerated age-related degeneration of cerebral arterioles at their branch points.

In CAA, deposition of amyloid protein occurs in the media and adventitia of arteries and arterioles, usually in the cerebral cortex (Figure 14.3). CAA leads to lobar hemorrhages, and recurrent lobar ICH is common in CAA.

- ICH is twice as common as subarachnoid hemorrhage and just as deadly, with a 30-day mortality of 30%–50%.
- The most common cause of ICH is hypertension (about 50% of cases), followed by CAA (about 20% of cases).
- Hypertensive ICH usually occurs in deep areas of the brain, such as the basal ganglia, pons, and cerebellum.

Clinical Evaluation and Management

Clinical Presentation

Patients with ICH typically present with a sudden-onset, focal neurologic deficit. Headache, impaired level of consciousness, elevated blood pressure, nausea, and emesis are more common in ICH than in ischemic stroke.

[a]Portions previously published in Aguilar MI, Freeman WD. Spontaneous intracerebral hemorrhage. Semin Neurol. 2010 Nov;30(5):555–64. Epub 2011 Jan 4. Used with permission.

Abbreviations: ATACH, Antihypertensive Treatment of Acute Cerebral Hemorrhage; CAA, cerebral amyloid angiopathy; CT, computed tomography; FOUR, Full Outline of Unresponsiveness; ICH, intraparenchymal cerebral hemorrhage; INTERACT2, main-phase study of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; MRI, magnetic resonance imaging; PCC, prothrombin complex concentrate

Box 14.1 • Differential Diagnosis of Intraparenchymal Cerebral Hemorrhage

- Hypertensive—most commonly basal ganglia, internal capsule, pons, cerebellum
- Hypertensive vasculopathy, eclampsia
- Cerebral amyloid angiopathy—commonly lobar; older patients
- Arteriovenous malformation
- Cavernous malformation
- Aneurysm rupture—can result in both subarachnoid hemorrhage and intraparenchymal cerebral hemorrhage
- Moyamoya disease—typically basal ganglia
- Vasculitis
- Primary central nervous system tumor
- Metastatic tumor—renal cell carcinoma, melanoma, lung cancer, choriocarcinoma
- Bleeding diathesis—low platelet count, disseminated intravascular coagulation
- Hemorrhagic conversion of ischemic stroke
- Venous hypertension and infarction—typically cortical
- Traumatic contusion—usually frontal pole and tip of temporal lobe
- Medications—sympathomimetics, thrombolytic medication, warfarin

Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.

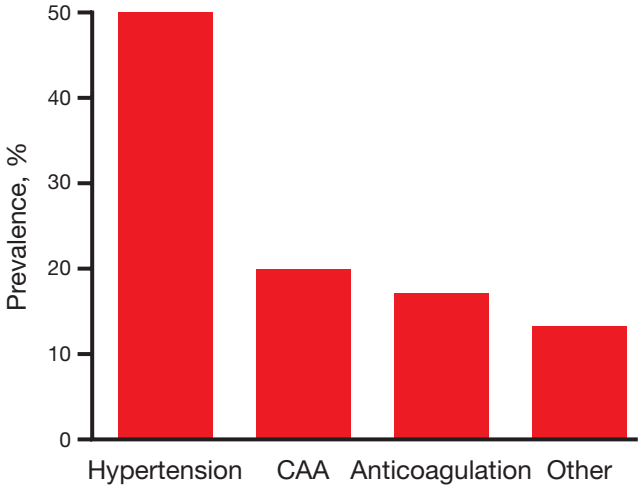

Figure 14.1 *Causes of Intraparenchymal Cerebral Hemorrhage.*
CAA indicates cerebral amyloid angiopathy.

Diagnostic Evaluation

Medical history should include time of symptom onset or time of symptom awareness. A hematoma may expand in the initial 6 hours in noncoagulopathic ICH and in the initial 24 hours in coagulopathy-related ICH. Perihematomal edema and increased intracranial pressure reach maximum levels around 72 hours after the ictus.

Associated activities at the onset might help identify the cause (eg, onset during coitus or physical activity suggests rupture of a vascular structure such as an aneurysm or an arteriovenous malformation). Additional medical history should include recent head trauma, vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, tobacco use, and alcohol use),

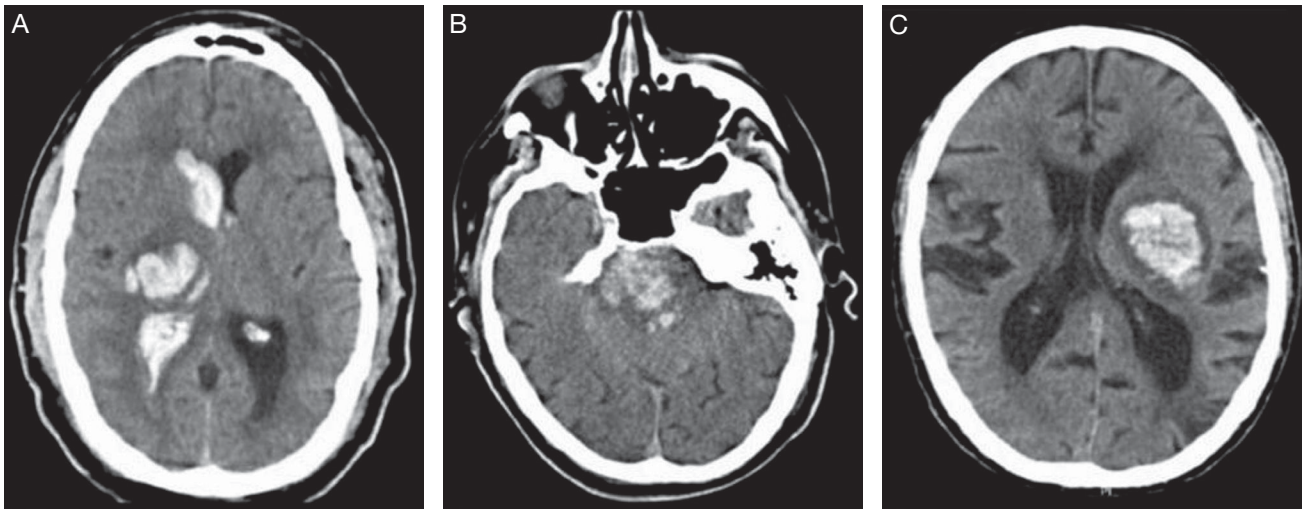

Figure 14.2 *Hypertensive Intraparenchymal Cerebral Hemorrhage on Noncontrast Computed Tomographic Imaging.*
A, Right thalamus with intraventricular extension. B, Pons. C, Left putamen and globus pallidus with extension superiorly.

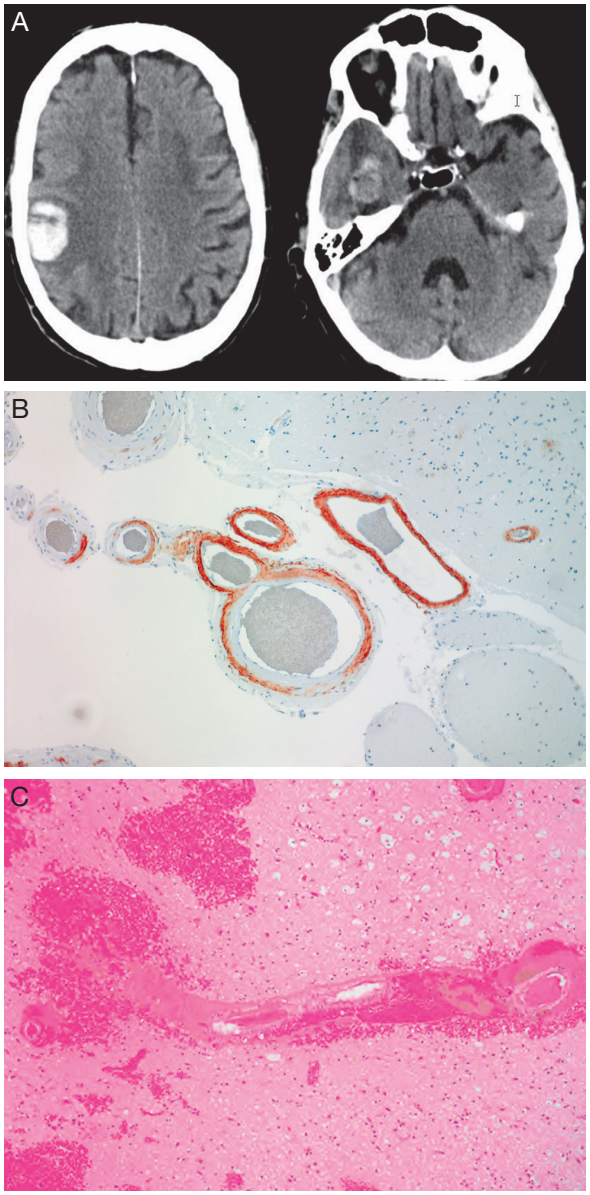

Figure 14.3 *Cerebral Amyloid Angiopathy (CAA).*
A, Computed tomography of intraparenchymal cerebral hemorrhage (ICH) secondary to CAA shows right posterior frontal hematoma (image on left) and right temporal lobar intraparenchymal hematoma (image on right). B, Cortical and leptomeningeal amyloid deposits are best demonstrated with β-amyloid immunohistochemistry. Note the extensive β-amyloid deposition in the media and adventitia of the leptomeningeal arteries and arterioles. C, Micrograph of ICH due to CAA shows patchy, confluent microhemorrhagic areas around an arteriole (hematoxylin-eosin).
(B and C, adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

medications (in particular, antithrombotic agents), history of both ischemic stroke and hemorrhagic stroke, and history of coagulopathies or systemic conditions that predispose to bleeding (eg, liver disease or hematologic malignancies).

Physical examination should include vital signs, a general medical examination, level of consciousness (Glasgow Coma Scale or Mayo Clinic Full Outline of Unresponsiveness [FOUR] score), and severity of neurologic deficit (National Institutes of Health Stroke Scale).

Routine laboratory studies should include a complete blood cell count, a platelet count, determination of electrolytes and renal function, a coagulation profile (prothrombin time, partial thromboplastin time, and international normalized ratio), a toxicology screen, and a pregnancy test when appropriate.

Noncontrast computed tomography (CT) of the head is considered the gold standard. Acute bleeding appears hyperdense compared with brain parenchyma and similar to bone or contrast agent on CT scans windowed to evaluate brain tissue. A fluid level within the hematoma or blood in different stages suggests a coagulopathy (eg, warfarin-related ICH) (Figure 14.4).

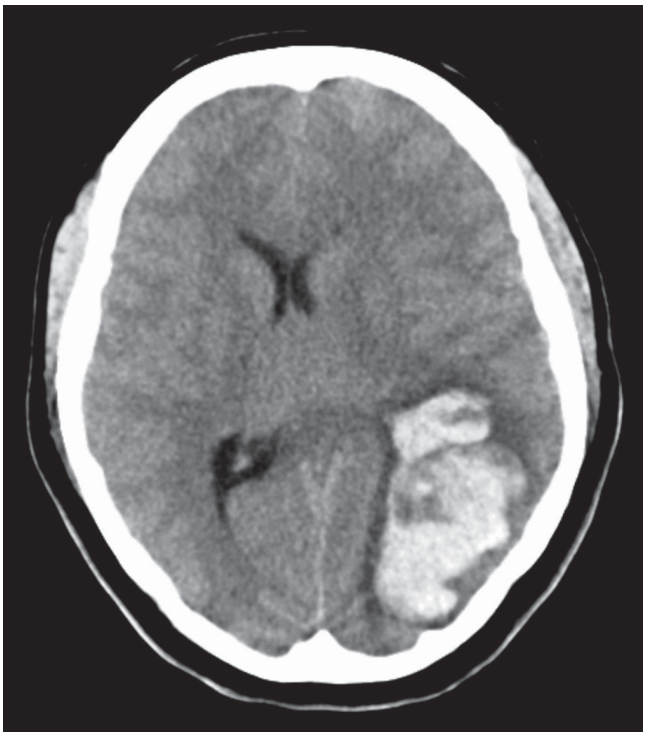

Figure 14.4 *Computed Tomography of Heterogeneous Left Occipital Intraparenchymal Cerebral Hemorrhage With Fluid Levels and Blood in Different Stages.*
The patient was receiving warfarin therapy. The international normalized ratio was 4.2.

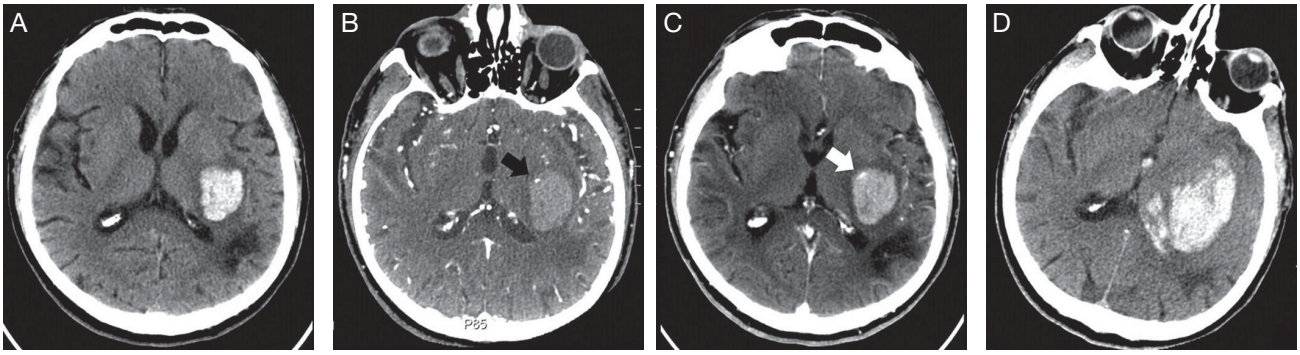

Figure 14.5 *Spot Sign, Extravasation, and Hematoma Expansion on Computed Tomography (CT).*
CT slice selection has been optimized for hematoma configuration, not for head position. A, Unenhanced CT demonstrates left posterior putaminal and internal capsule hematoma with mild surrounding edema. An old parietooccipital infarct is seen posterior to this. B, A small focus of enhancement is seen peripherally on CT angiography source images, consistent with the spot sign (black arrow). C, Postcontrast CT demonstrates enlargement of the spot sign, consistent with extravasation (white arrow). D, Unenhanced CT image 1 day after presentation reveals hematoma enlargement and intraventricular hemorrhage.
(Adapted from Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. Stroke. 2007 Apr;38[4]:1257–62. Epub 2007 Feb 22. Used with permission.)

If blood is seen on CT immediately after onset of symptoms, CT angiography and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion. A "spot" sign on postcontrast CT is due to a vascular leak at the point of enhancement and may predict hematoma enlargement (Figure 14.5).

Magnetic resonance imaging (MRI) is useful to rule out underlying structural abnormalities, such as tumors or arteriovenous malformations. The appearance of blood on MRI depends primarily on the age of the hematoma and the type of MRI sequence (Table 14.1). In addition, MRI may show alternative areas of microbleeds on gradient-echo or susceptibility-weighted images. Microbleeds or microhemorrhages are small areas (<10 mm) of ferritin and hemosiderin deposition appearing as signal dropout (profoundly hypointense) on T2 gradient-echo images and are considered the radiologic footprint of CAA when diffuse and predominantly in a cortical or subcortical location. When microbleeds are located in the basal ganglia, brainstem, or cerebellum of patients who have evidence of microvascular white matter disease or lacunar stroke (or both), they are likely part of the spectrum of small-vessel cerebrovascular disease (Figure 14.6). However, the differential diagnosis of these hypodense areas on gradient-echo

Table 14.1 • Magnetic Resonance Imaging Characteristics of Intraparenchymal Cerebral Hemorrhage

		T1 Signal[a]		T2 Signal[a]	
Stage	**Timing**	**Central[b]**	**Peripheral[c]**	**Central[b]**	**Peripheral[c]**
Hyperacute	<12 h	↔	↔	↑	↑
Acute	12–72 h	↔	↔	↓	↑
Early subacute	4–7 d	↔	↑	↓ or ↔	↓↓
Late subacute	1–4 wk	↑↑	↑↑	↑↑	↑↑
Chronic	Months	↑	↓	↑	↓
Late chronic	Months to years	↓↓	↓↓	↑	↓↓

[a] Arrows indicate the following: ↓, decreased, ↓↓, markedly decreased;↑, increased;↑↑, markedly increased; ↔, isodense.
[b] Central part of the hemorrhage.
[c] Peripheral part of the hemorrhage.

Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.

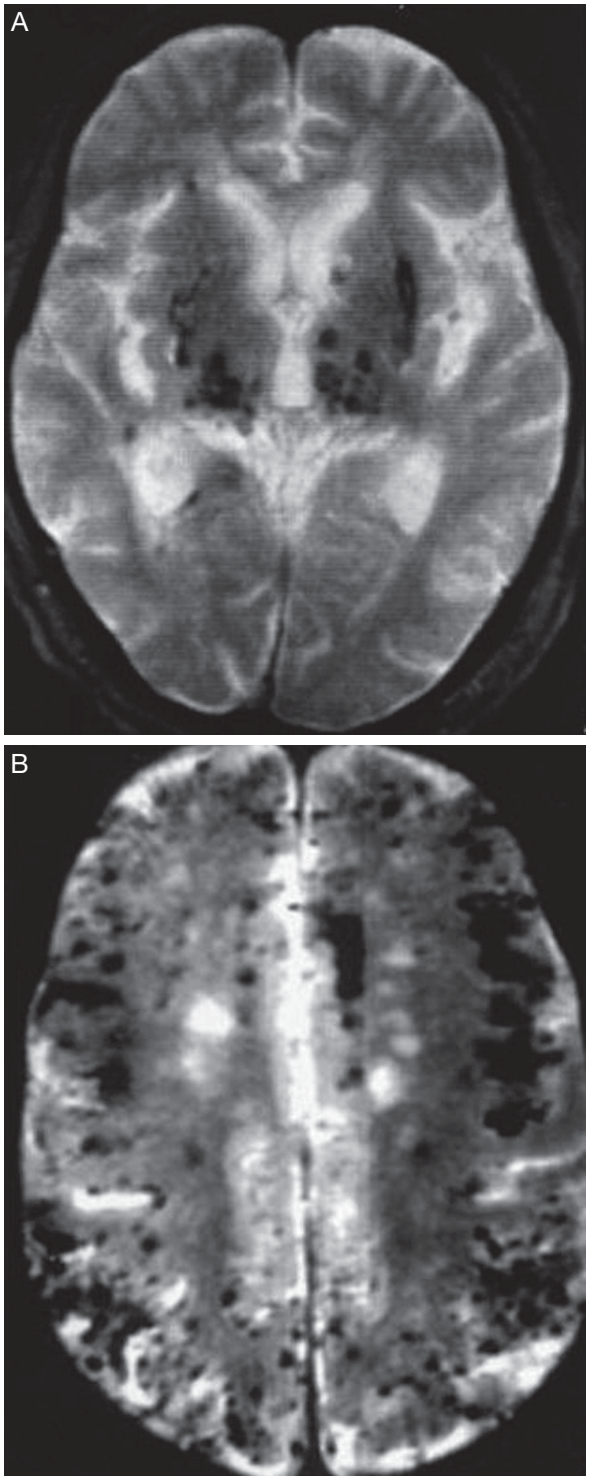

Figure 14.6 *Microbleeds.*
A, This patient had uncontrolled chronic hypertension and microbleeds that affected the basal ganglia and were apparent on T2-weighted gradient-echo magnetic resonance imaging. B, An 85-year-old patient had dementia, presumed cerebral amyloid angiopathy, diffuse cortical and subcortical microbleeds, and recurrent lobar intraparenchymal cerebral hemorrhage.*

or susceptibility-weighted images includes CAA, hypertensive microbleeds, multiple cavernous malformations, calcium, and mechanical heart valve emboli. Rarely, melanoma or myxomatous emboli have a similar appearance. The location and clinical context of the microbleeds is important in determining the potential cause. The clinical significance of these lesions continues to be elucidated.

Conventional angiography is indicated for patients who have an atypical clinical or radiologic presentation (eg, calcification within the hematoma), when another cause is not found, or when subarachnoid hemorrhage associated with ICH is present without associated head trauma.

Management

After the diagnosis of ICH has been established, supportive measures are instituted. Airway, breathing, and circulation are assessed, and the patient is intubated if needed. A target serum glucose level is 140 to 185 mg/dL. The precise blood pressure goal is a point of ongoing research (Antihypertensive Treatment of Acute Cerebral Hemorrhage [ATACH] II trial and the main-phase study of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial [INTERACT2]). In general, the recommendation is to lower the systolic blood pressure to less than 160 mm Hg and target a mean arterial pressure of 70 to 110 mm Hg.

Corticosteroids and prophylactic anticonvulsants have not been proved to be beneficial therapy for ICH. Therapy with antithrombotic agents should be discontinued and any coagulopathies corrected. Noncoagulopathic ICH is not an indication to treat with blood products or with recombinant factor VIIa. For warfarin-related ICH, treatment recommendations based on suboptimal evidence are to give vitamin K (10 mg as a slow intravenous infusion over 30 minutes), fresh frozen plasma (initial dose, 10–15 mL/kg), and 3- or 4-factor prothrombin complex concentrate (PCC) or, as off-label use, recombinant factor VIIa (40 mcg/kg intravenously, rounding up to the nearest 1.2-mg vial size). The dose of PCC is calculated according to the patient's weight and international normalized ratio at the time of ICH (Table 14.2).

For ICH related to new anticoagulants (dabigatran, apixaban, and rivaroxaban), the treatment recommendations, which are based on suboptimal evidence, are to treat with activated charcoal, intravenous hydration, 4-factor PCC, and hemodialysis.

For most patients with ICH, the usefulness of surgery is uncertain. Patients with cerebellar hemorrhage and a deteriorating neurologic status or who have brainstem compression or hydrocephalus (or both) from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible. For patients presenting with lobar hemorrhages larger than 30 cm^3 and within 1 cm of the surface, evacuation of the supratentorial hemorrhage by standard craniotomy may be considered.

Table 14.2 • Dosing of Prothrombin Complex Concentrate (PCC)

INR	PCC Dose, IU × Body Weight in Kilograms
>4.0	50
3.3–4.0	45
2.6–3.2	40
2.1–2.5	35
1.7–2.0	30
1.4–1.6	25

Abbreviations: INR, international normalized ratio; IU, international units.

The effectiveness of minimally invasive hemorrhage evacuation by stereotactic or endoscopic aspiration with or without thrombolysis is uncertain and is considered investigational.

A reasonable approach is to provide aggressive, full care early after ICH onset and to postpone new do-not-resuscitate orders until at least the second full day of hospitalization. After the bleeding has been stopped and the cessation documented, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility, 3 to 4 days after the ictus.

- A "spot" sign on postcontrast CT is due to a vascular leak at the point of enhancement and may predict hematoma enlargement.
- MRI is useful to rule out underlying structural abnormalities, such as tumors or arteriovenous malformations.
- Microbleeds or microhemorrhages are small areas (<10 mm) of ferritin and hemosiderin deposition appearing as signal dropout (profoundly hypointense) on T2 gradient-echo images.
- Corticosteroids and prophylactic anticonvulsants have not been proved to be beneficial therapy for ICH.

Table 14.3 • ICH Score

Variable	Component	Points
GCS score	3–4	2
	5–12	1
	13–15	0
ICH volume, cm^3	≥30	1
	<30	0
IVH present	Yes	1
	No	0
Infratentorial origin	Yes	1
	No	0
Age, y	≥80	1
	<80	0

Abbreviations: GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage.

- For most patients with ICH, the usefulness of surgery is uncertain.

Outcome

The overall mortality of patients with ICH is 30% to 40% at 30 days and 50% at 1 year. The ICH score is a simple, easy clinical grading scale to risk stratify patients at presentation (Table 14.3). The 30-day mortality based on the number of points in the ICH score is as follows: 0% (0 points); 13% (1 point); 26% (2 points); 72% (3 points); 97% (4 points); and 100% (5 or 6 points).

The best predictor of clinical outcome is hematoma volume at presentation. Hematoma volume is calculated as $(A \times B \times C)/2$, where A is the maximum ICH diameter, B is the maximum ICH diameter perpendicular to A, and C is the maximum vertical diameter (A, B, and C are in centimeters) (typically, the CT slice thickness is 0.4–0.5 cm).

- The ICH score is a simple, easy clinical grading scale for predicting 30-day mortality.

15 Unruptured Intracranial Aneurysms and Vascular Malformations[a]

ROBERT D. BROWN JR, MD, MPH

Introduction

Knowledge of the natural history of unruptured intracranial aneurysms and vascular malformations of the brain is important because this information may be weighed against the morbidity of intervention to decide on the most appropriate treatment for individual patients. This chapter reviews the epidemiology and natural history of common intracranial vascular abnormalities.

Unruptured Intracranial Aneurysms

Saccular Aneurysms

Epidemiology

Intracranial saccular or berry aneurysms are acquired lesions, accounting for about 80% of all nontraumatic subarachnoid hemorrhages (SAHs). Most saccular aneurysms are detected before rupture, during imaging performed for unrelated reasons. About 0.5% to 2% of the population has an unruptured intracranial saccular aneurysm (UIA), and multiple aneurysms are detected in 20% to 30% of these patients. This suggests that 3 to 6 million people in the United States have an intracranial aneurysm. The most feared complication is SAH, which occurs in about 30,000 people in the United States each year. About 85% of aneurysms occur anteriorly in the Circle of Willis, with common sites including the internal carotid artery terminus, posterior communicating artery origin, anterior communicating artery to anterior cerebral artery junction, and proximal middle cerebral artery. Posteriorly, the most common locations are the tip of the basilar artery and the superior cerebellar artery, anterior inferior cerebellar artery, and posterior inferior cerebellar artery junctions with the basilar artery (Figure 15.1).

Aneurysms are increasingly detected in older patients and are rarely detected in children, and aneurysms occur much more often in women than in men (3:1 ratio). In addition to age and female sex, risk factors include cigarette smoking, hypertension, selected inherited conditions, and a family history of *2 or more* first-degree relatives having a brain aneurysm (Box 15.1).

Aneurysm Screening

The overall occurrence of unruptured aneurysms in family members of patients with UIA is as follows: Among first-degree relatives (siblings, parents, and children) of patients with a history of SAH, 4% have a UIA; siblings are the most likely relatives to have an aneurysm detected. For patients with 2 or more relatives with brain aneurysm, the risk of UIA is about 9% for relatives older than 30 years. In families that have at least 2 members with brain aneurysm, the frequency of detection of UIA is nearly 20% among first-degree relatives who either smoke cigarettes or have hypertension and are older than 30 years. Screening is

[a] Portions previously published in Brown RD Jr, Flemming KD, Meyer FB, Cloft HJ, Pollock BE, Link ML. Natural history, evaluation, and management of intracranial vascular malformations. Mayo Clin Proc. 2005 Feb;80(2):269–81. Used with permission of Mayo Foundation for Medical Education and Research.

Abbreviations: AVM, arteriovenous malformation; CCM, cerebral cavernous malformation; CT, computed tomography; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SAH, subarachnoid hemorrhage; UIA, unruptured intracranial saccular aneurysm; VA, venous angioma

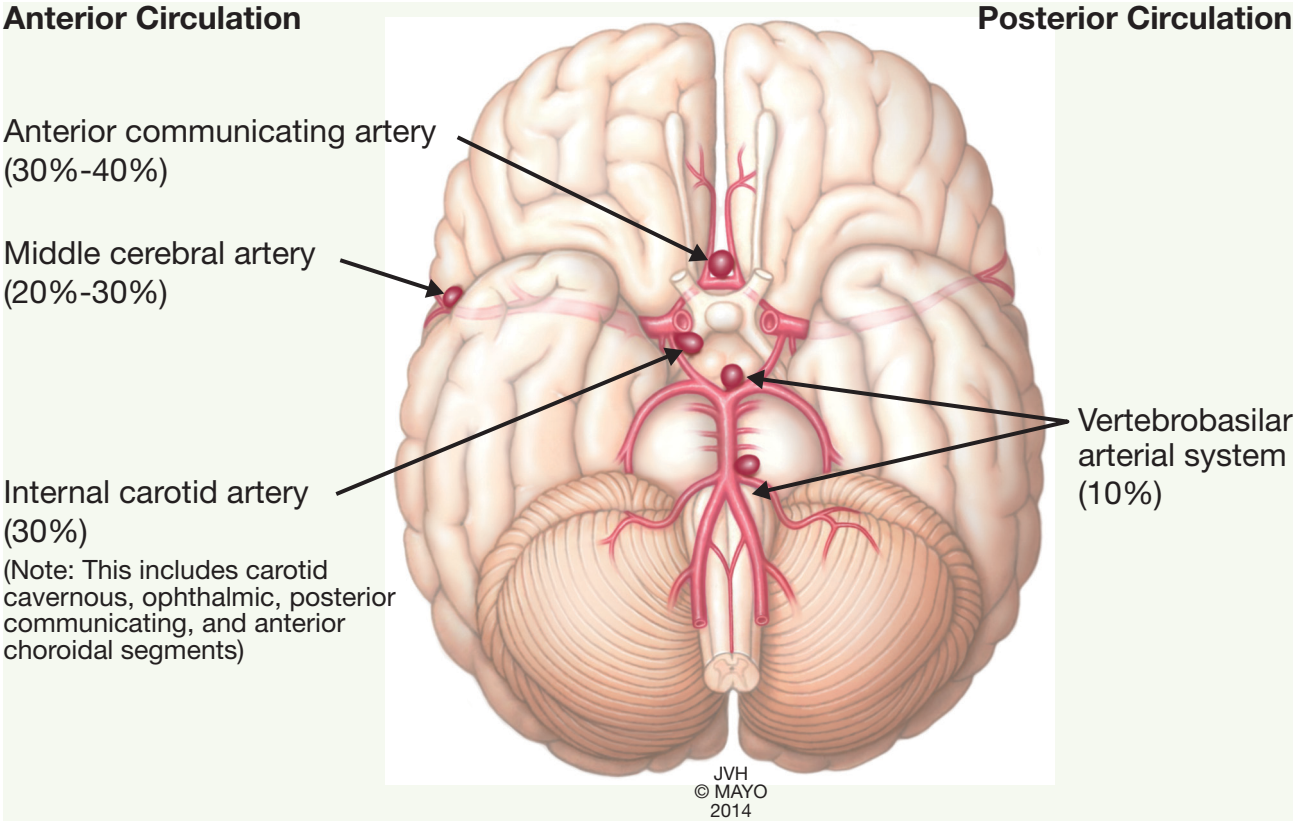

Figure 15.1 *Common Locations of Intracranial Aneurysms. Percentages are approximate frequencies.*
(Used with permission of Mayo Foundation for Medical Education and Research.)

typically recommended for the first-degree relatives of affected family members when there is a history of 2 or more family members with SAH or brain aneurysm. Screening is optional for families with 1 known family member affected with SAH or brain aneurysm. In families with autosomal dominant polycystic kidney disease, screening is recommended for patients who have polycystic kidney disease and a family history of aneurysm.

Clinical Presentation

Some patients present with SAH, but many saccular aneurysms are detected in patients without any symptoms. Besides SAH, UIA symptoms that may occur include an aneurysm mass effect, most commonly a cranial nerve palsy such as ipsilateral cranial nerve III compression due to aneurysms of the posterior communicating artery or compression of the trochlear nerve, abducens nerve, or first division of the trigeminal nerve. Headaches and seizures occur uncommonly. Transient ischemic attacks or cerebral infarction rarely occur from distal embolization of material from within the aneurysm.

On computed tomography (CT) of the head without contrast medium or on magnetic resonance imaging (MRI) of the brain, a UIA may appear as a well-circumscribed structure that is slightly hyperintense, and it may have calcification in the wall. UIAs are more readily detected and assessed noninvasively with CT angiography (CTA) or magnetic resonance angiography (MRA) (Figure 15.2). Both techniques are sensitive for saccular aneurysms with diameters of at least 4 mm. Cerebral arteriography may be necessary for clarifying the details of the aneurysm and defining the optimal treatment strategy if treatment is being considered.

Natural History

The risk of aneurysm rupture appears to depend on aneurysm size, with larger aneurysms predicting a higher risk of hemorrhage, and on aneurysm location, with posterior circulation and posterior communicating artery aneurysms potentially being associated with a higher risk of rupture compared with anterior circulation. Anterior communicating artery location has been variably associated with a higher risk of hemorrhage. The risk of hemorrhage is also increased with enlarging UIAs. The morphologic characteristics of aneurysms, such as the presence of a daughter sac, have been inconsistently predictive of rupture. Family history of aneurysm may also predict a higher risk of rupture. A large international epidemiologic cohort study (the International Study of Unruptured Intracranial Aneurysms) assessed the risk of aneurysm hemorrhage among patients with UIA. The 5-year cumulative rupture

Box 15.1 • Risk Factors and Genetic and Medical Conditions Associated With Cerebral Aneurysm Formation

- Risk factors for cerebral aneurysm formation
  - Age
  - Female sex
  - Hypertension
  - Cigarette smoking
- Predisposing genetic conditions for cerebral aneurysms
  - Autosomal dominant polycystic kidney disease (prevalence, 10%)
  - Vascular type of Ehlers-Danlos syndrome (formerly type IV)
  - Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
  - Neurofibromatosis type 1
  - Pseudoxanthoma elasticum
- Medical conditions associated with cerebral aneurysms
  - Fibromuscular dysplasia
  - Systemic lupus erythematosus
  - Sickle cell disease
  - Intracranial arteriovenous malformations
  - Moyamoya disease
  - Coarctation of the aorta

rates from that study are shown in Table 15.1. The PHASES score is also used to predict which aneurysms may rupture (see Greving JP, Wermer MJH, Brown RD Jr, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol. 2014 Jan;13(1):59–66).

Treatment Interventions

Management options for UIAs include conservative management with follow-up or an interventional procedure with surgical clipping and endovascular management, the most common of which is placing tiny platinum coils directly into the aneurysm. Optimal treatment is selected according to the predicted risk of rupture, treatment risks, patient age, and presence of comorbidities. No direct comparison studies of unruptured aneurysms have been performed, but a randomized clinical trial of ruptured aneurysms did suggest that the risk of complications was lower with aneurysm coiling. When UIAs are managed conservatively, annual follow-up imaging with CTA or MRA is typically recommended to assess for aneurysm growth.

Other Aneurysm Types

Infectious ("Mycotic") Aneurysms

Mycotic aneurysms are relatively uncommon; about 3% of all intracranial aneurysms are mycotic aneurysms. About

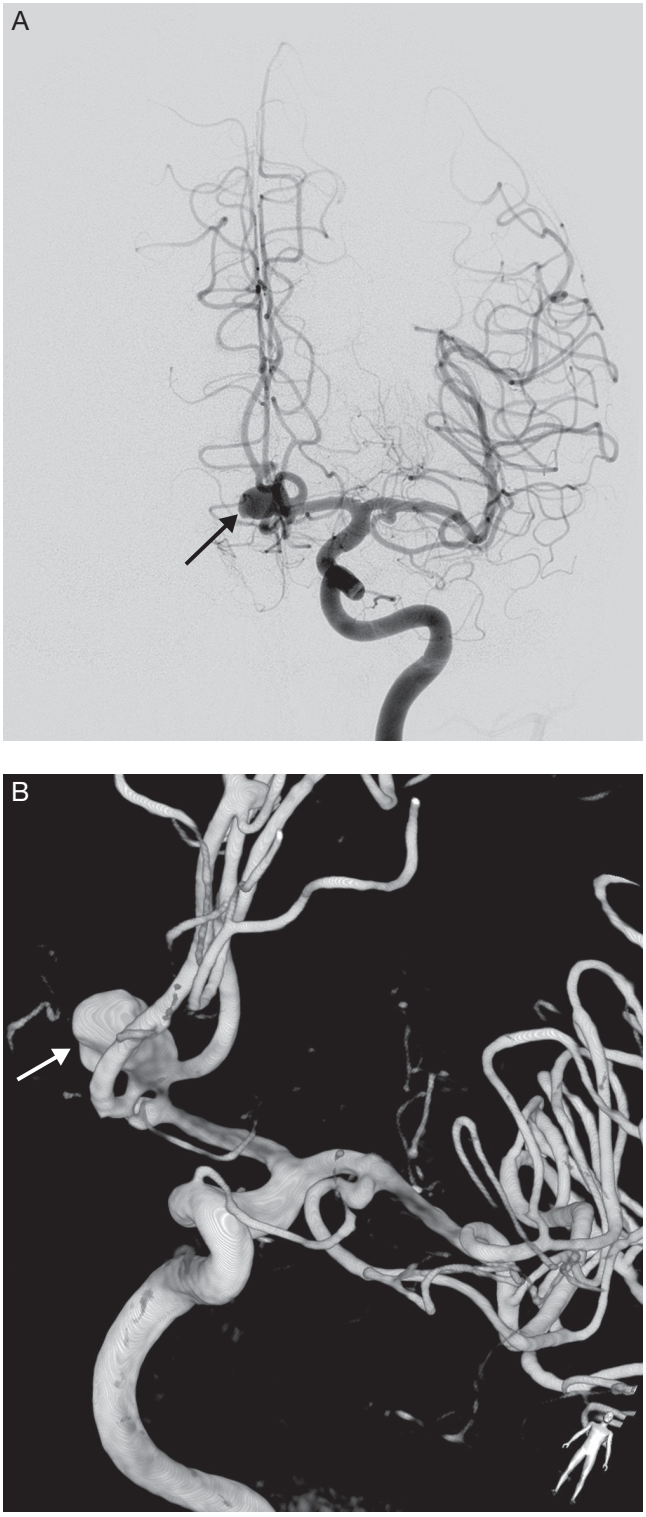

Figure 15.2 *Unruptured Anterior Communicating Artery Aneurysm.*
Conventional angiography (A) and conventional angiography with 3-dimensional reconstruction (B) reveal a 7 × 9-mm saccular aneurysm (arrows) of the anterior communicating artery segment.

Table 15.1 • Five-Year Cumulative Rupture Rates According to Size and Location of Unruptured Aneurysm

	Rupture Rate, %				
	<7 mm				
Location	Group 1	Group 2	7–12 mm	13–24 mm	≥25 mm
Cavernous carotid artery (n = 210)	0	0	0	3.0	6.4
AC, MC, or IC (n = 1,037)	0	1.5	2.6	14.5	40
Post-P comm (n = 445)	2.5	3.4	14.5	18.4	50

Abbreviations: AC, anterior communicating or anterior cerebral artery; IC, internal carotid artery (not cavernous carotid artery); MC, middle cerebral artery; Post-P comm, vertebrobasilar, posterior cerebral arterial system, or posterior communicating artery.

Adapted from Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, et al; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003 Jul 12;362(9378):103–10. Used with permission.

2% to 12% of patients with infectious endocarditis have an intracranial aneurysm, which results from septic emboli that either infect the intima and cause inflammation of the muscularis or lodge in the vasa vasorum and cause destruction of the adventitia and muscularis. Mycotic aneurysms are usually bacterial in nature. The most common organism is *Streptococcus*, followed by *Staphylococcus aureus* and *Enterococcus*. Fungal intracranial aneurysms caused by *Aspergillus* and other fungi rarely occur and are more commonly due to contiguous spread.

Patients with mycotic aneurysms often present incidentally, but mycotic aneurysms can also cause headache, or they can rupture, leading to intracranial hemorrhage. They commonly occur distally in the arterial tree, a key feature that differentiates them from saccular aneurysms (Figure 15.3). They can sometimes be detected on MRI, MRA, or CTA, but they may be too small and too distal to be seen with any imaging other than conventional angiography. Treatment includes antibiotic treatment and, in some cases, surgery.

Fusiform Aneurysms

Fusiform aneurysms are relatively uncommon lesions with an overall frequency of detection that is much less than 1%. Risk factors include smoking, hypertension, male sex, and older age. It is not uncommon for abdominal aortic aneurysms to co-occur. Fusiform aneurysms are most common in the posterior circulation. An imaging diagnosis is based on dilatation of an arterial segment, 1.5 times the normal size, without any definable neck (Figure 15.4). Fusiform aneurysms can sometimes be suggested on cross-sectional imaging of the head with unenhanced CT or on MRI of the brain; they can then be further characterized on MRA or CTA. They are most commonly detected in patients older than 60 years in an asymptomatic state. However, patients may present with SAH, with ischemia, or with mass effect. The risk of hemorrhage may be as high as 2% annually with the risk of the cerebral infarction as high as 5% to 6% annually. Treatment options are limited. Flow-diverting stents or surgical treatment may be considered.

Dissecting Aneurysms

Dissecting aneurysms are false aneurysms resulting from an intimal tear and intramural hemorrhage. Their location is most typically extracranial, and they can have a saccular or fusiform appearance. MRA, CTA, or cerebral angiography may be useful for distinguishing between dissecting aneurysms and more common acquired aneurysms. Suggestive features include evidence of a false lumen, an intimal flap, and retention of contrast agent in the lumen or a tapering of the artery at the proximal end. Dissecting aneurysms are most commonly due to trauma. Clinical presentations include transient ischemic attack or cerebral infarction and, rarely, aneurysm rupture. When the aneurysms extend intracranially, patients can present with ischemia or, with the intradural extension, SAH. Surgical or endovascular repair may be needed in some of these patients.

Neoplastic Aneurysms

Neoplastic aneurysms are rare, but they can occur with some types of primary and metastatic brain tumors. They typically occur distally in intracranial arteries. Tumor emboli that infiltrate and weaken the vessel wall may result in aneurysm formation.

- About 0.5%–2% of the population has a UIA.
- About 85% of aneurysms occur anteriorly in the Circle of Willis, with common sites including the internal carotid artery terminus, posterior communicating artery origin, anterior communicating artery to anterior cerebral artery junction, and proximal middle cerebral artery.
- Screening is typically recommended for the first-degree relatives of affected family members when there is a history of ≥2 family members with SAH or brain aneurysm.

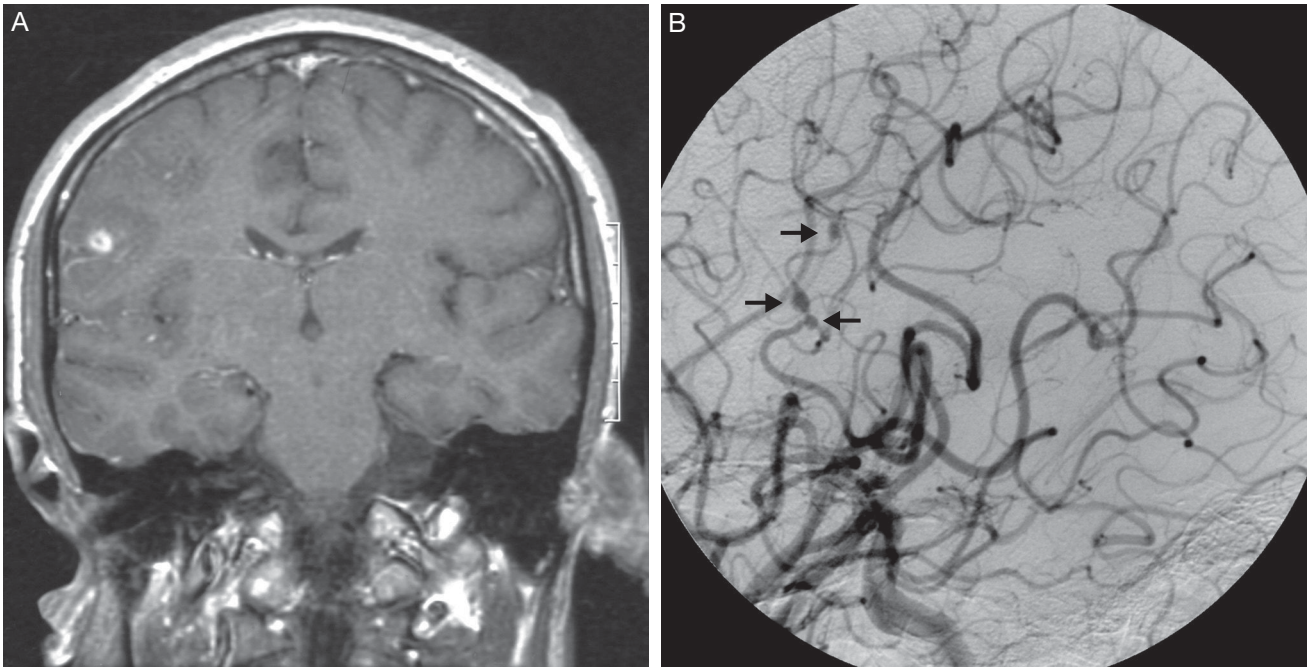

Figure 15.3 *Infectious ("Mycotic") Aneurysm.*
A, Coronal magnetic resonance image, T1-weighted with gadolinium, shows area of enhancement in right frontal lobe. B, Conventional angiogram demonstrates 3 small fusiform aneurysms (arrows) of the opercular branch of the right middle cerebral artery.
(Adapted from Flemming KD. Principles of critical care neurology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 401–34. Used with permission of Mayo Foundation for Medical Education and Research.)

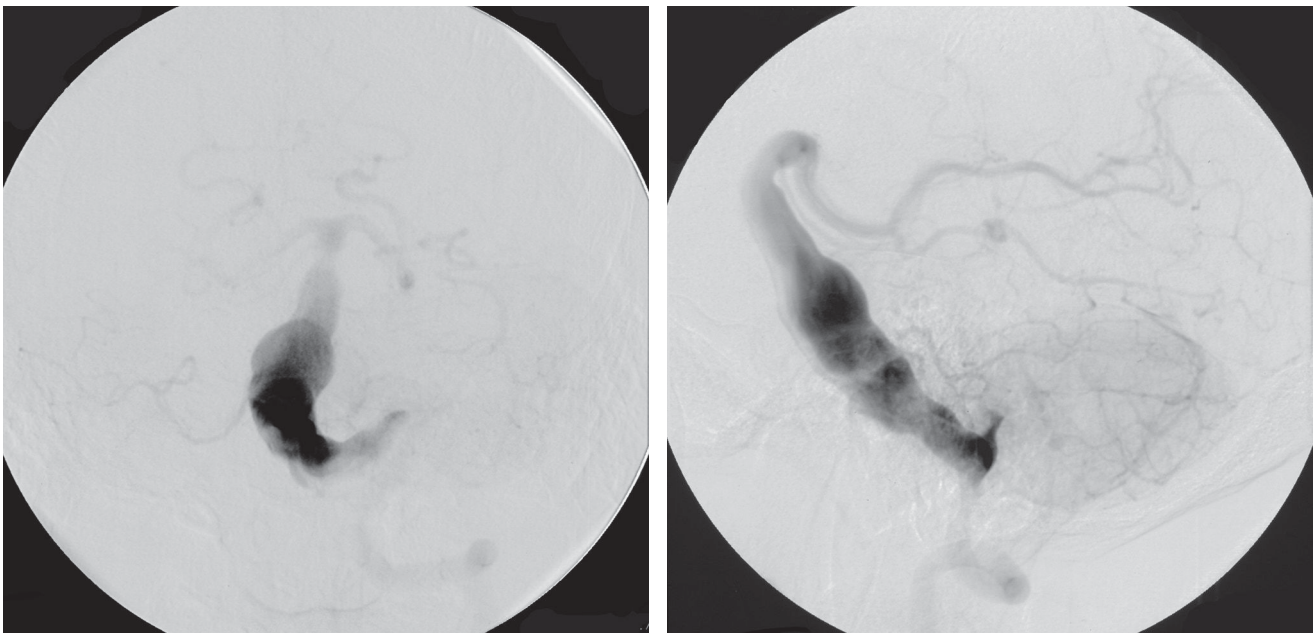

Figure 15.4 *Angiograms of a Fusiform Aneurysm of the Basilar Artery.*
Left, Anteroposterior view. Right, Lateral view.
(Adapted from Flemming KD, Wiebers DO, Brown RD Jr, Link MJ, Nakatomi H, Huston J 3rd, et al. Prospective risk of hemorrhage in patients with vertebrobasilar nonsaccular intracranial aneurysm. J Neurosurg. 2004 Jul;101(1):82–7. Used with permission.)

- The risk of aneurysm rupture appears to depend on aneurysm size, with larger aneurysms predicting a higher risk of hemorrhage, and on aneurysm location, with posterior circulation and posterior communicating artery aneurysms potentially being associated with a higher risk of rupture compared with anterior circulation.

Intracranial Vascular Malformations

Arteriovenous Malformations

Arteriovenous malformations (AVMs) are congenital, most commonly occurring in the supratentorial region. They consist of multiple arteries and veins connecting as a fistula without an intervening normal capillary bed. They are typically single. Histologically, they are clusters of normal or dilated arteries and abnormal veins with calcification; some show evidence of prior hemorrhage.

Patients with AVMs generally present between the age of 20 and 40 years, and AVMs occur equally in men and women. Frequency of detection increases with age, with about half presenting with hemorrhage and other symptoms, including seizures, headache, focal neurologic deficit, and pulsatile tinnitus.

Unenhanced CT has a relatively low sensitivity, but calcification and hypointensity may be noted. AVM is seen with contrast enhancement. MRI of the brain is

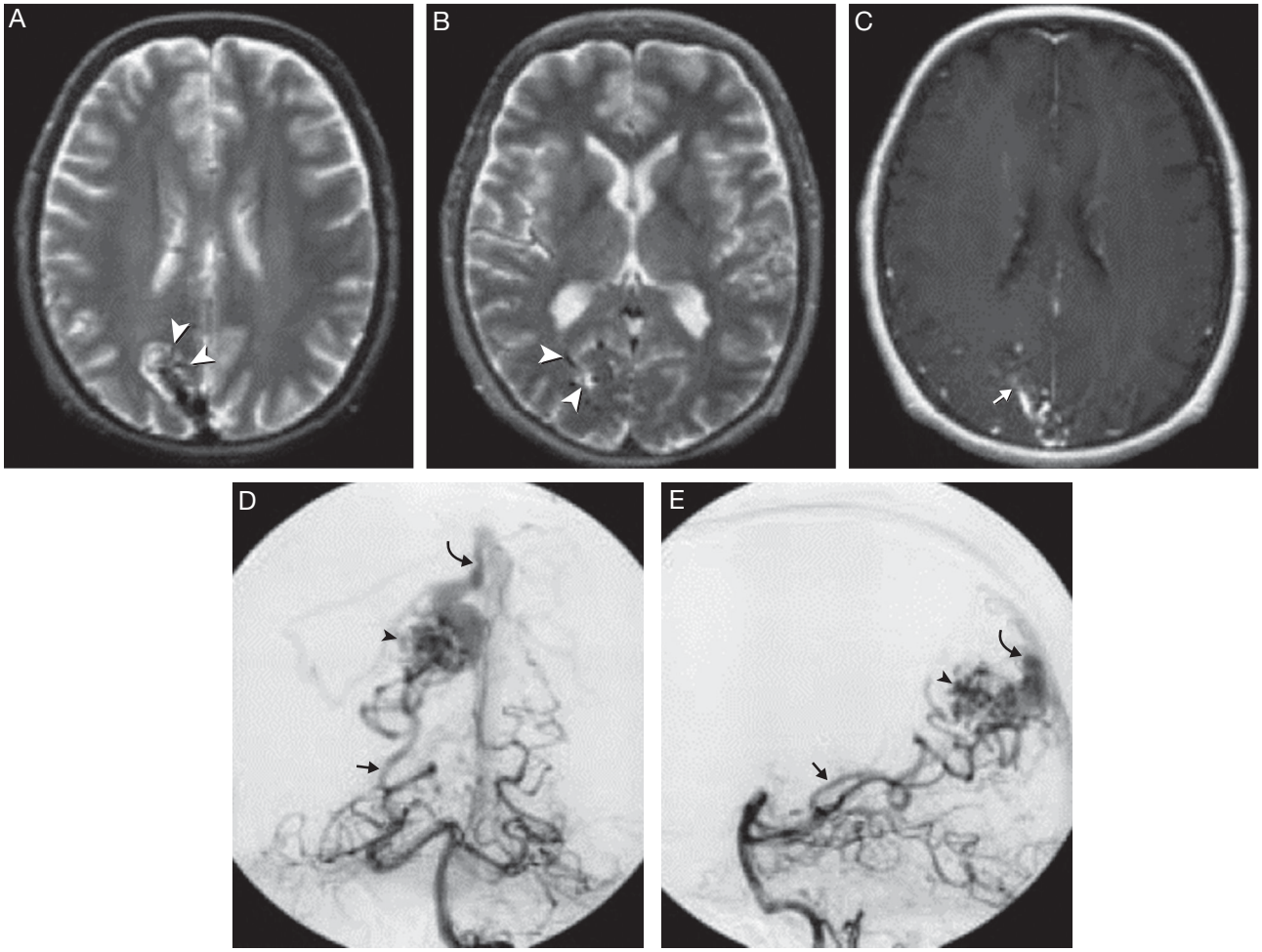

Figure 15.5 *Right Parietooccipital Arteriovenous Malformation (AVM).*
A and B, T2-weighted magnetic resonance image (MRI) shows flow voids consistent with AVM (arrowheads). C, T1-weighted MRI with contrast agent shows partial enhancement of the AVM (arrow). D and E, Arteriograms with vertebral injection. Anteroposterior view (D) and lateral view (E) show posterior cerebral artery feeders (small arrows) to the AVM (arrowheads), with a large draining vein into the superior sagittal sinus (curved arrows).
(Adapted from Brown RD Jr, Flemming KD, Meyer FB, Cloft HJ, Pollock BE, Link ML. Natural history, evaluation, and management of intracranial vascular malformations. Mayo Clin Proc. 2005 Feb;80[2]:269–81. Used with permission of Mayo Foundation for Medical Education and Research.)

more sensitive, with findings that include hemosiderin deposition and signal voids on T1- and T2-weighted imaging (Figure 15.5). MRA or CTA can add more detail. Cerebral arteriography provides the most detailed information, fully characterizing the feeding arteries and draining veins. The natural history of AVMs suggests a risk of hemorrhage of 2% to 3% annually with a risk of recurrent hemorrhage of 6% to 17% in the first year after the initial hemorrhage; thereafter, the risk decreases. Clinically, prior hemorrhage is a strong predictor of hemorrhage. Other predictors may include impaired venous drainage, single draining vein, presence of very distal aneurysms on the feeding arteries, presence of multiple aneurysms, and feeding via perforators. Deep location and small size may also be predictive.

Unruptured AVM lesions may be treated with observation, surgery, endovascular therapy, or radiosurgery. Radiosurgery is often used for small (<3 cm), deep lesions, and microsurgical treatment is often used for lesions with a predicted high risk of rupture, for lesions in patients with a predicted low surgical morbidity, and for ruptured AVMs.

Cavernous Malformations

Cavernous malformations are typically well-circumscribed, small, "popcornlike" lesions that can appear either in the brain or in the spinal cord. The overall frequency of detection is about 0.5%. The peak incidence is in the fourth and fifth decades, and they occur equally in men and women.

Cavernous malformations may be sporadic or inherited. In the familial form, multiple lesions are common. Three inherited forms of cerebral cavernous malformation (CCM) have been elucidated: CCM1, CCM2, and CCM3 (Table 15.2).

Grossly, these lesions are well circumscribed, lobulated, and raspberrylike. On microscopy, they are composed of dilated, thin-walled capillaries with 1 layer of endothelial lining and a variable layer of fibrous adventitia.

Cavernous malformations are most readily detected on MRI with a combination of high and low T1- and T2-weighted signals that show the surrounding hemosiderin (Figure 15.6). Cerebral angiography is often negative for cavernous malformations.

Table 15.2 • Genetics of Cerebral Cavernous Malformation (CCM)

	Type		
Feature	**CCM1**	**CCM2**	**CCM3**
Locus	7q11-q22	7p15–13	3q25.2-q27
Gene	*KRIT1*	*MGC4607* (malcavernin)	*PDCD10*
Clinical	Common in Hispanic population	. . .	Presentation is often in childhood

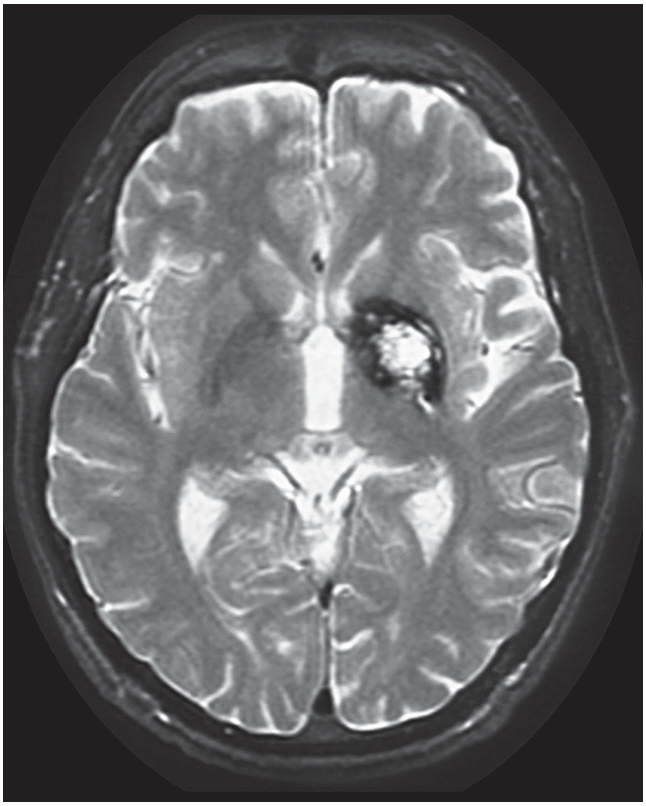

Figure 15.6 *Magnetic Resonance Image of Cavernous Malformation (CM).*
Axial T2-weighted image demonstrates characteristic appearance of CM in deep gray matter. The area with the characteristic, reticulated "mulberry" or "popcornlike" appearance is surrounded by a hypointense rim consistent with hemosiderin deposition.
(Adapted from Flemming KD. Cerebrovascular disease. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 435–84. Used with permission of Mayo Foundation for Medical Education and Research.)

Patients with cavernous malformation can present without symptoms, with seizures, or with a focal neurologic deficit that was abrupt in onset or slowly progressive. The natural history suggests that the overall frequency of hemorrhage depends on the nature of the initial diagnosis. If patients present incidentally or with seizures, the overall risk of a clinically apparent hemorrhage is less than 1% annually. Among patients who have had a symptomatic hemorrhage, the annual rate of recurrent hemorrhage after the first hemorrhage is higher (10%–15%) in the next year.

Conservative management with observation is often recommended for asymptomatic patients. If a patient has

had multiple episodes of clinically or radiographically apparent hemorrhage, or if the patient has poorly controlled epilepsy and the lesion is accessible, surgical excision may be performed. There is no clear evidence that radiosurgery is beneficial.

Venous Angiomas

Venous angioma (VA) is a congenital lesion with thin-walled venous channels and normal intervening neural tissue. VAs are typically incidental findings. MRI with a contrast agent is more sensitive than CT and shows a radial pattern, the classic caput medusae pattern (Figure 15.7). VAs are commonly detected at autopsy (in up to 2%–3% of all autopsies).

Most often VAs are detected on CT or MRI of the brain without any associated symptoms. Very rarely they may be associated with seizures or with sensory or motor deficits, or spontaneous thrombosis of a venous malformation may cause hemorrhage, infarct, seizure, or compression of a cranial nerve at the root entry zone.

In general, these lesions are thought to have an exceedingly benign natural history. Because of the extremely low risk of hemorrhage, removal of a venous malformation is not recommended.

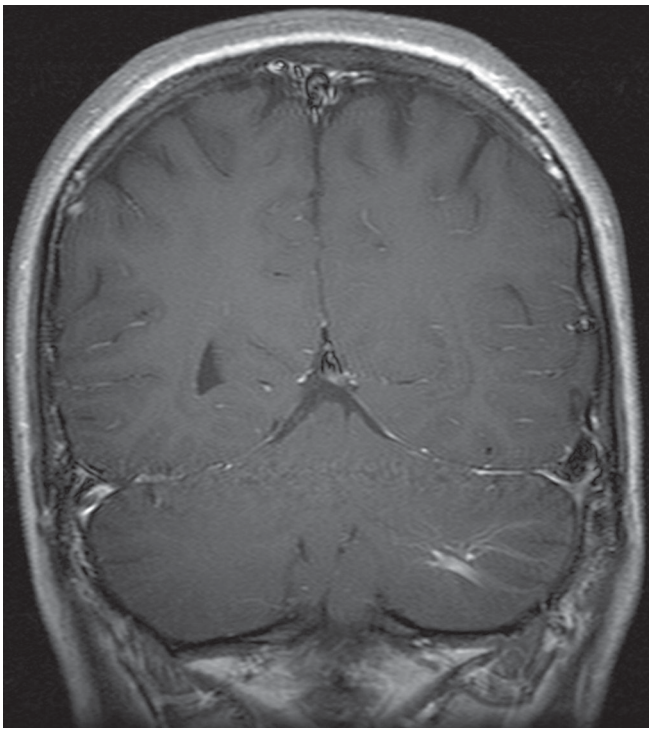

Figure 15.7 *Venous Angioma.*
Coronal T1-weighted contrast-enhanced magnetic resonance imaging demonstrates a left cerebellar venous angioma.

Dural Arteriovenous Fistulas

A dural arteriovenous fistula is a vascular malformation of the wall of 1 of the major venous sinuses. The fistula is typically acquired. Patients present between the ages of 40 and 60 years. Risk factors for development include a prior history of sinus thrombosis and head trauma. Patients may present with pulsatile tinnitus, hemorrhage, seizure, or focal neurologic deficit. Patients with cavernous sinus lesions may have double vision and exophthalmos.

MRI with MRA is more sensitive than CT in showing diagnostic dilated veins and feeding arteries. Cerebral arteriography with selective external carotid artery injection is the gold standard for their detection and characterization.

The overall risk of hemorrhage is about 2% annually and varies with the site and hemodynamics. A cortical site carries the highest risk.

Treatment options include surgical excision, radiosurgery, or embolization.

Capillary Telangiectasias

Capillary telangiectasias are somewhat enlarged ectatic capillaries. They are typically noted in the posterior fossa (pons) or spinal cord on MRI imaging with a contrast agent. They are unlikely to cause symptoms and, in general, do not require any treatment.

Vein of Galen Malformations

Vein of Galen malformation is a type of arteriovascular malformation that affects the median vein, which develops into the true vein of Galen. This malformation is present during gestation and often leads to heart failure in newborns or the development of hydrocephalus (due to interference with venous return). In some cases, the diagnosis is delayed from infancy when patients present with headache or other neurologic symptoms.

MRI of the brain suggests the diagnosis, and angiography confirms the diagnosis (Figure 15.8).

Osler-Weber-Rendu Disease (Hereditary Hemorrhagic Telangiectasia)

Olser-Weber-Rendu disease is an autosomal dominant vascular disorder. Typically patients present in childhood to early adulthood with epistaxis or episodes of gastrointestinal tract bleeding. Patients often have tiny telangiectasias on their lips or fingertips. Neurologic manifestations may include concomitant cerebral vascular malformations, cerebral ischemia, or abscesses due to associated pulmonary shunts. To prevent further cerebral ischemia, pulmonary shunts are coiled and obliterated. (See also Chapter 72, "Neurocutaneous Disorders.")

Sturge-Weber Syndrome

Sturge-Weber syndrome is a vascular disorder with a leptomeningeal capillary-venous malformation affecting the brain. Ipsilateral to the vascular malformation, patients often have a port-wine stain (ie, a facial capillary malformation). Patients

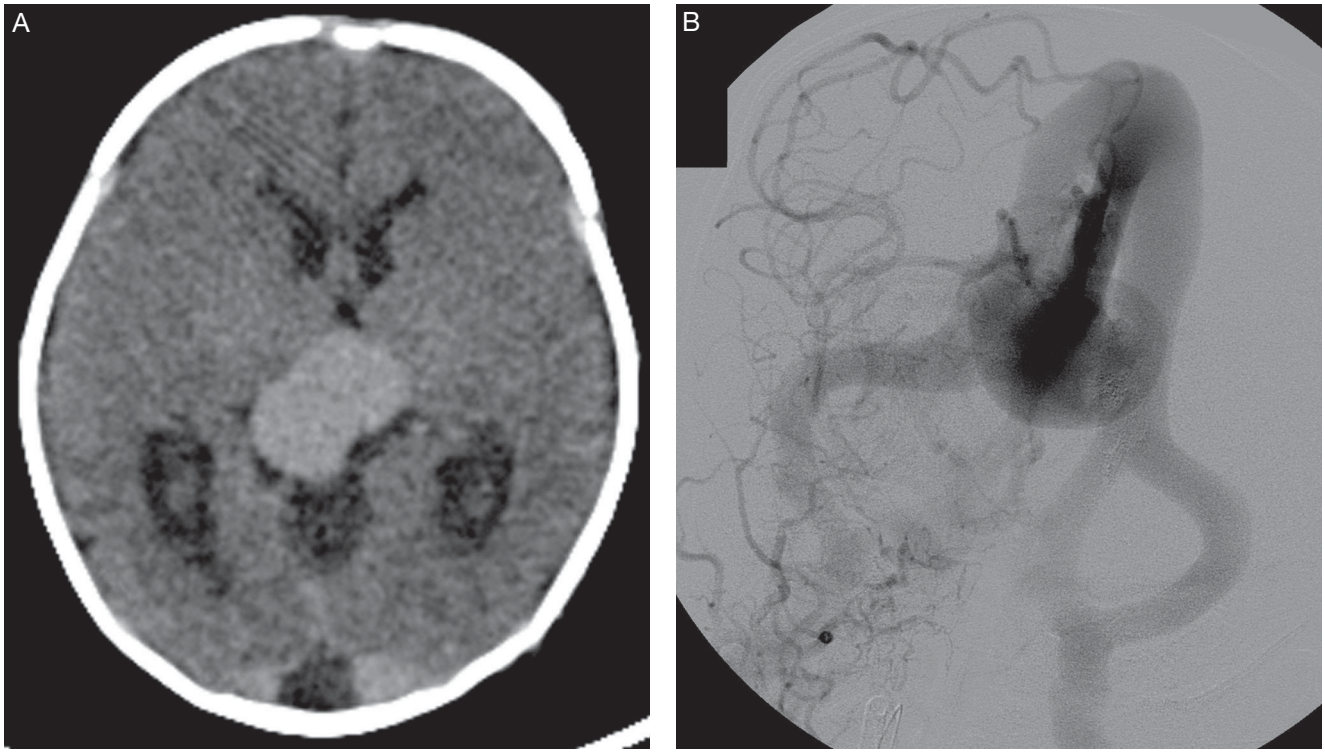

Figure 15.8 *Vein of Galen Malformation.*
The patient was a newborn who became lethargic and apneic after birth. A, Computed tomography demonstrates an enlarged vein of Galen and hydrocephalus. B, Conventional angiography confirms the massively enlarged vein of Galen.

may present with focal neurologic deficits, seizures, or mental retardation. Patients are also at risk for glaucoma. Recently, the cause of Sturge-Weber syndrome was confirmed to be due to a somatic mosaic mutation in the *GNAQ* gene.

- Patients with AVMs generally present between the age of 20 and 40 years.
- The natural history of AVMs suggests a risk of hemorrhage of 2%–3% annually with a risk of recurrent hemorrhage of 6%–17% in the first year after the initial hemorrhage; thereafter, the risk decreases.
- Cavernous malformations may be sporadic or inherited. The Krit-1 mutation commonly occurs in the Hispanic population and is the most common familiar form of cavernous malformation.
- Dural arteriovenous fistulas are typically acquired. Patients present between the ages of 40 and 60 years with pulsatile tinnitus, hemorrhage, seizure, or focal neurologic deficit.
- Vein of Galen malformation is a type of arteriovascular malformation that affects the median vein, which develops into the true vein of Galen. This malformation is present during gestation and often leads to heart failure in newborns or the development of hydrocephalus (due to interference with venous return).

16 Neurorehabilitation[a]

BILLIE A. SCHULTZ, MD

Introduction

Physical medicine and rehabilitation—physiatry—is the medical specialty focusing on the restoration of functional status of patients with musculoskeletal, nervous system, or congenital disorders. Working within the definition of *disability* as described by the World Health Organization, a physiatrist addresses the 3 domains of the International Classification of Functioning, Disability, and Health definition of disability: impairment, activity limitation, and restricted participation (Table 16.1). This approach accounts for the patient's health status in addition to personal and environmental factors that may lead to barriers to participation. For example, in a nonaccessible community, the participation of a person with spinal cord injury (SCI) may be quite restricted, whereas in an accessible community with adequate parking, curb cutouts, and ramps, the participation of the same person would be less restricted. Physiatrists work together with the patient, community, and an interdisciplinary team to address the 3 domains for patients regardless of the patient's diagnosis.

Despite the potentially devastating consequences of any neurologic injury, the life expectancy of many patients is increasing. Therefore, quality of life, including independence, safety, and function need to be addressed. Coordinated rehabilitation services, with evidence-based interventions, may affect all 3 domains. Further advances in neurorehabilitation, with implications for all diagnoses, are expected as patients' needs continue to grow.

Table 16.1 • ICF Domains of Functioning and Disability

Functioning	Disability
Body functions and structures	Impairments
Activities	Activity limitations
Participation	Participation restrictions

Abbreviation: ICF, International Classification of Functioning, Disability, and Health.

Rehabilitation Setting and Rehabilitation Team

Interdisciplinary Team

The rehabilitation team is multidisciplinary. Led by the physiatrist and the patient, team members may include the patient's primary care physician, specialty care physicians (eg, neurologist, neurosurgeon, or orthopedic surgeon), nurses, therapists (occupational, physical, recreational, music, or speech and language therapists), psychologists, and social workers. Often a prosthetist or an orthotist has a key role. The rehabilitation plan depends on the patient's prognosis: Is the underlying disease expected to resolve, stabilize, or progress? Equipment needs, physical or cognitive external supports, and dismissal location vary according to the neurologist's prognostic opinion.

[a] Portions previously published in Brown AW, Schultz BA. Recovery and rehabilitation after stroke. Semin Neurol. 2010 Nov;30(5):511–7. Epub 2011 Jan 4. Used with permission.

Abbreviations: ADL, activities of daily living; AFO, ankle-foot orthosis; ALS, amyotrophic lateral sclerosis; EXCITE, Extremity Constraint Induced Therapy Evaluation; LMN, lower motor neuron; SCI, spinal cord injury; TMS, transcranial magnetic stimulation

Levels of Rehabilitation

The patient's needs determine the level of ongoing care, which may include rehabilitation services during acute care hospitalization, specialized acute care inpatient rehabilitation, transitional care at a subacute care rehabilitation facility, or outpatient rehabilitation services, including day programs with a focus on community reentry.

Rehabilitation for Stroke

Specific Techniques in Stroke Rehabilitation

More people who have had a stroke are aging and living with residual symptoms, making stroke the leading cause of activity limitation related to neurologic conditions in adults. Brain plasticity after focal cortical infarctions has been well documented, and this plasticity can be molded by specific motor tasks. Thus, willful, repetitive, task-specific activity results in cortical structure changes, including an increase of dendritic arborization, synaptogenesis, and synaptic density. These changes translate into functional improvements in the patient's level of impairment. Initiation of rehabilitation within 72 hours after stroke is an established guideline to take advantage of brain plasticity. Current research is exploring very early rehabilitation, which begins within 24 hours of admission. Many therapeutic techniques are used to treat neurologic impairment after stroke, including proprioceptive neuromuscular facilitation and other technical approaches developed by Brunnstrom, Bobath, and Rood (Table 16.2).

Table 16.2 • Principles of Established and Emerging Therapeutic Techniques for Patients After Stroke

Therapy	Method
Proprioceptive neuromuscular facilitation	Use resistance provided by stronger muscles to facilitate the weaker components of the same motion pattern
Brunnstrom	Take advantage of both the stronger muscles and the primitive postural reactions to facilitate synergistic motor patterns in early recovery Isolated movements are incorporated at later stages of recovery
Bobath	Use reflexive movement patterns to inhibit increased tone
Rood	Use tactile stimulation to facilitate muscle movements
Constraint-induced movement	Require forced use of the affected limb by restraining the unaffected limb during treatment sessions

These strategies are still used frequently, but emerging therapeutic techniques are being explored, sometimes to augment the older techniques.

Historically, the focus of therapy was "learned disuse," in which the patient would avoid using the affected limb and be trained to use the unaffected limb for all activities. Time and knowledge have changed that philosophy, and current thought is that avoiding use of the affected limb may hinder participation in restorative therapies. Constraint-induced movement therapy involves restraining the unaffected limb and, thus, effectively forcing use of the affected limb in intensive motor shaping and repetitive task practice directed by a clinician. The Extremity Constraint Induced Therapy Evaluation (EXCITE) trial demonstrated statistically and clinically significant improvement in arm motor function lasting 1 year when compared with traditional therapy. The study required use of a restraint for 90% of the patient's waking hours and clinician-directed care for up to 6 hours daily for 14 consecutive days. In a clinical situation, the intensity of this therapy presents personnel and financial challenges.

Robotic technology is another emerging area of therapy. Devices have been developed for the upper extremities and for the lower extremities. Benefits of these devices are the possibility of multiple, consistent repetitions of specific motion patterns. Most research involving the robot-driven gait orthoses has been done in the area of SCI rather than stroke. A less expensive option for locomotion training is a harness-based, partial body weight–supported gait orthosis, which requires more physical assistance by the therapist.

Neuromuscular electrical stimulation, both percutaneous and implantable, activates the lower motor neuron (LMN), allowing contraction of the paretic muscle and thus facilitating movement during functional tasks and ambulation.

Virtual reality involves real-time simulation of an environment or activity through a user-computer interface that allows training in complex environments, adaptive changes in interactive parameters during sensorimotor performance, and multimodality sensorimotor feedback. This technology may have more important implications in telemedicine because the therapy can be guided from a distance.

Transcranial magnetic stimulation (TMS) is currently being investigated. Optimal timing of treatment, suppression compared with activation of the brain cortex, and the dose of TMS are unknown; however, further investigation will explore whether TMS would be an appropriate adjuvant treatment with conventional therapies.

Specific Rehabilitation Issues for Persons With Stroke

Swallowing is a complex biologic function involving many muscles that are controlled both voluntarily and

involuntarily. Not surprisingly, impaired swallowing or dysphagia occurs in one-third to three-fourths of patients after a stroke. Evaluation of swallowing can include bedside testing, videofluorography, and fiberoptic endoscopy. Most evaluations are done by speech pathologists; however, occupational therapists specially trained in dysphagia evaluation and treatment can assist. Ensuring appropriate hydration and nutrition is essential. Therefore, if swallowing is not expected to improve within the first 2 to 3 weeks after the stroke, percutaneous endoscopic gastrostomy feeding should be considered. A 2012 Cochrane Review concluded that percutaneous endoscopic gastrostomy is effective and safe, with a lower probability of intervention failure and higher feed delivery compared with nasogastric tube feeding. Other treatment includes compensatory techniques to ensure safe swallowing and therapy to improve swallowing. If vocal cord paralysis is suspected, an otolaryngologic evaluation may be indicated for consideration of vocal cord medialization.

A hallmark of stroke, and the residual symptom most noted by the patient, is weakness. Weakness can result in poor sitting, impairment in activities of daily living (ADL), and impaired locomotion. Although more than 85% of patients can ambulate after a stroke, a smaller percentage may be functional community ambulators. Adaptive equipment, such as a cane, walker, or brace can improve mobility.

An orthotic device commonly used after a stroke is an ankle-foot orthosis (AFO). This orthotic device includes the foot and ankle joint, but, depending on the ankle joint positioning, the knee may also be stabilized to improve the gait. Plantar flexion at the ankle creates a knee extension moment during gait, effectively stabilizing the knee; therefore, a balance between dorsiflexion for foot clearance and plantar flexion for knee stabilization needs to be met. AFOs can be restrictive and not allow ankle movement in any direction, including plantar, dorsiflexion, eversion, and inversion. A more restrictive brace can minimize the potential for injury, but it does alter gait mechanics, which should be taken into account. Other bracing or orthotic options for the lower extremities include and support more proximal joints. For patients with proximal upper extremity impairment, a balanced forearm orthosis can be considered, minimizing gravitational forces and allowing the patient easier use of the affected limb to complete ADLs. The treating therapist and orthotist can work together to determine the least restrictive device that adequately addresses the patient's needs.

Spasticity is a velocity-dependent increase in tonic stretch reflexes and has the potential to contribute to impairment and cause pain. All patients should be educated on the importance of stretching to manage spasticity. Orthotic devices are also used to treat spasticity (eg, AFOs are used to prevent plantar flexion), and orthotic devices are used to promote elbow, wrist, and finger extension. Static and dynamic splints provide a constant, low level of resistance. In addition to stretching and splinting, other commonly used methods for spasticity management include oral medication (Table 16.3), chemodenervation by either a lytic agent (alcohol or phenol) or a neuromuscular blocking agent (botulinum toxin), and delivery of medication directly to the intrathecal space.

- Initiation of rehabilitation within 72 hours after stroke is an established guideline to take advantage of brain plasticity.
- Constraint-induced movement therapy involves restraining the unaffected limb and, thus, effectively

Table 16.3 • Commonly Used Medications to Treat Spasticity

Medication	Mechanism of Action	Side Effects	Dosage
Baclofen	Agonist of presynaptic GABA B receptors, inhibiting calcium influx into presynaptic terminals and suppressing the release of excitation neurotransmitters	Sedation, weakness, GI symptoms, tremor, insomnia, confusion	Initially, 5 mg 3 times daily Increase by 15 mg daily every 3 d Maximum, 80 mg daily divided 3–4 times daily
Dantrolene	Reduces calcium release by sarcoplasmic reticulum, inhibiting skeletal muscle contraction	Hepatotoxicity (1% of patients), drowsiness or sedation, weakness, fatigue, diarrhea, nausea, vomiting	Initially, 25 mg daily Increase by 25–50 mg every 4–7 d Maximum, 400 mg divided 4 times daily
Diazepam	Enhances action of GABA A receptors, inhibiting muscle contraction	Sedation, memory impairment	Initially, 2 mg twice daily Increase as needed Maximum, 60 mg daily divided 2–4 times daily
Tizanidine	α-Adrenergic agonist, increasing presynaptic inhibition of motor neurons	Drowsiness, hypotension, dry mouth, bradycardia, dizziness	Initially, 2–4 mg daily Increase by 2–4 mg over 2–4 wk Maximum, 36 mg daily divided 3–4 times daily

Abbreviations: GABA, γ-aminobutyric acid; GI, gastrointestinal tract.

forcing use of the affected limb in intensive motor shaping and repetitive task practice directed by a clinician.

- In addition to stretching and splinting, other commonly used methods for spasticity management include oral medication (Table 16.3), chemodenervation by either a lytic agent (alcohol or phenol) or a neuromuscular blocking agent (botulinum toxin), and delivery of medication directly to the intrathecal space.

Rehabilitation for SCI

Spinal Cord Injury

SCI can be devastating to both the patient and the family. Historically, a patient with a diagnosis of SCI had a shorter life span; however, since the 1960s, with improved medical knowledge, medications, and tools available, life expectancy has increased and is approaching normal. SCI can be traumatic or nontraumatic and be related to cancer, infection, inflammatory process, or ischemia. Prognoses are better defined for patients with traumatic SCI. Depending on the level and completeness of injury, as defined by the International Standards for Neurological Classification of Spinal Cord Injury, information that can be shared with the patient and family includes expected outcomes in areas of locomotion, respiratory support, ADLs, bowel and bladder management, and pressure relief. Close follow-up with a physiatrist who has subspecialty training and certification in SCI is recommended because patients with SCI are at risk for complications specific to their injury.

Specific Rehabilitation Issues for Persons With SCI

Mobility limitations due to SCI can affect patients' life satisfaction. The spinal cord has the potential to generate motor control, allowing full weight-bearing locomotion without supraspinal influence. Therefore, patients and clinicians should address mobility training. Overground mobility training, body weight support ambulation training on a treadmill, and robotic-assisted locomotor training are forms of locomotor training currently used, although no training method is superior to another. The argument for robotic-assisted training is that it provides identical pattern repetitions and is less labor intensive, but some question its effectiveness. Robotically powered exoskeletons are currently under investigation as gait orthoses to determine whether they allow safe ambulation in a community setting for a person with paraplegia. Other equally important considerations besides locomotion are rehabilitation, including wheelchair mobility, transfers, bowel and bladder management, pressure relief, and increasing independence in ADL. Patient and family education that stresses the importance of all physical skills training is key.

Autonomic dysreflexia affects patients who have an injury at T6 or above. This syndrome results in an uninhibited sympathetic response to noxious stimuli. Symptoms typically include headache, blood pressure higher than baseline, diaphoresis, facial flushing, pupillary dilatation, and bradycardia. If untreated, autonomic dysreflexia can lead to prolonged hypertension, cerebral hemorrhage, or death. Treatment consists of loosening the patient's clothes, sitting the patient up, and trying to identify the source of noxious stimuli (often bladder related). If needed, fast-acting antihypertensive agents can be administered. Common choices include nitroglycerin or nifedipine.

Depending on the level of injury, various changes to the urinary system can be observed. If the injury occurs above the sacral segments, the result is an upper motor neuron bladder, in which urination cannot be initiated by voluntary relaxation of the external sphincter. Coordination between the detrusor and external bladder sphincter is lost, often resulting in detrusor-sphincter dyssynergy or a low-volume–high-pressure bladder with or without incontinence. Conversely, an injury at the sacral level results in an LMN or areflexic bladder. Typically, this patient has a high-volume–low-pressure bladder and incontinence.

Goals of bladder management are to achieve a socially acceptable emptying of the bladder and to reduce the risk of infection, calculi, and renal failure. The most common method of bladder emptying is intermittent catheterization, either by oneself or by a surrogate. The patient has a fluid schedule and a catheterization schedule with a goal of dryness between catheterizations and catheterized volumes of less than 500 mL. For tetraplegic patients or patients who cannot perform self-catheterization and who do not have a surrogate available, indwelling catheterization (either urethral or suprapubic) is an option. For patients with detrusor-sphincter dyssynergy, the goals of therapy also include prevention of reflux to the kidneys, which can result in kidney damage. The reflux risk is minimized by increasing the bladder volume with the use of anticholinergic agents, botulinum toxin injections, or bladder augmentation. Patients should be evaluated regularly by a urologist, preferably one with a special interest in neurologic urologic disease processes.

Similar to neurogenic bladder, bowel function is altered by SCI. If the injury occurs above the sacral levels, defecation cannot be initiated by voluntary relaxation of the external anal sphincter, although reflex-mediated colonic peristalsis can occur. LMN bowel, or injuries that occur at the sacral level, result in an areflexic bowel that has no reflex-mediated colonic peristalsis but only slow stool propulsion coordinated by the intrinsically innervated myenteric plexus. Because the sphincter is typically atonic, leakage of stool can result.

Bowel program goals are similar to those of bladder programs: Achieve a socially acceptable emptying of the bowel while maintaining evacuation of the bowels. Programs should be regularly scheduled to ensure complete emptying on a regular basis. Typically, fiber and medications are adjusted to modulate stool consistency. For patients with an intact colonic reflex (ie, upper motor neuron bowel), mini-enemas and suppositories can be used. Digital stimulation can also be used for patients with the sacral reflex arc intact. Digital evacuation (ie, manual evacuation of the stool) is more typically used for persons with an LMN bowel. If a bowel program is not successful and the patient has bowel accidents or soiling of wounds, colostomy is used.

As in stroke, spasticity management is an important part of SCI rehabilitation. Most concepts are similar. The spasticity is more likely to be generalized than in patients who have a focal cortical infarction, so systemic medications such as baclofen, tizanidine, diazepam, and dantrolene are more likely to be used. Also, intrathecal baclofen delivery has been very effective in this patient population.

- Since the 1960s, with improved medical knowledge, medications, and tools available, life expectancy has increased and is approaching normal.
- Autonomic dysreflexia affects patients who have an injury at T6 or above. This syndrome results in an uninhibited sympathetic response to noxious stimuli.

Rehabilitation for Other Neurologic Diseases

Multiple Sclerosis

Multiple sclerosis is usually a progressive disorder. Therefore, it does not follow the disease course of the above examples: acute event, recovery, plateau, and community reentry. The Medical Advisory Board of the National Multiple Sclerosis Society recommends referral for rehabilitation services, but referral is often delayed until fixed functional deficits are present. Early referral is preferred. It is unclear whether functional recovery is related to neural plasticity or to appropriate compensatory techniques. Symptom management is a focus of the rehabilitation endeavors and includes management of neurogenic bladder and bowel, spasticity, weakness, fatigue, visual impairment, depression, and cognitive dysfunction. An exercise program can improve the patient's symptoms of fatigue, but the program may need to be initiated in a supervised setting to encourage and guide the patient.

Amyotrophic Lateral Sclerosis

A neurodegenerative disease such as amyotrophic lateral sclerosis (ALS) leads to progressive function limitations, including dysphagia, communication limitations, weakness, muscular atrophy, spasticity, fatigue, mobility limitations, and respiratory compromise. Much of the rehabilitation focus is on equipment procurement to prepare for the future expected changes, which will lead to activity limitation and participation restriction. Both for high cervical SCI and for ALS, pulmonary function is of concern. Options for severely affected patients include ventilatory dependency or, for a carefully selected population, diaphragmatic pacing is being explored. Exercise and strengthening for patients with ALS, an ongoing area of controversy, continues to be explored. Animal studies show that moderate exercise may be beneficial but strenuous exercise may actually hasten the disease process. Owing to the limitations of published studies, including small sample size, and the limited number of studies on this subject, it is unclear whether these results apply to humans. Because of the limitations, a 2008 Cochrane Review could not state the degree to which strengthening is harmful or beneficial.

Parkinsonism

Parkinsonism often affects movements, specifically causing postural instability and bradykinesia. Cognitive deficit and mood disturbances can also be noted. Rehabilitation is based more on practical experience than on clinical data. A rehabilitation approach should be multifaceted and include education and gait and balance assessment, with the use of assistive devices as needed, and consideration of cognitive rehabilitation.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

II.1. Based on a contemporary tissue-based definition, the most sensitive technique to differentiate transient ischemic attack and ischemic stroke is which of the following?
a. Noncontrast head computed tomography
b. Contrast-enhanced head computed tomography
c. Diffusion-weighted brain magnetic resonance imaging
d. T1-weighted brain magnetic resonance imaging
e. Digital subtraction angiography

II.2. A 38-year-old man reports a 15-minute episode of weakness of the right side of the face and right arm that resolves spontaneously. He has a persistent left retro-orbital and hemicranial headache. Examination shows miosis and partial ptosis involving the left eye. Which of the following is the most likely mechanism of cerebral ischemia?
a. Cardioembolism
b. Extracranial carotid dissection
c. Penetrating artery disease
d. Hypercoagulable state
e. Intracranial atherosclerotic occlusive disease

II.3. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is associated with a missense mutation in which gene?
a. *NOTCH3*
b. *COL3A1*
c. *GLA*
d. Mitochondrial DNA
e. *COL4A*

II.4. A 64-year-old woman has abrupt development of speech difficulty and right-sided weakness. She was last seen in a normal condition at 1:15 PM and arrives in the emergency department at 2:30 PM. On examination she has expressive aphasia; right face, arm, and leg weakness; and partial right-sided sensory loss (National Institutes of Health Stroke Scale score = 9). Noncontrast computed tomography of the head was normal. What is the most appropriate initial therapeutic consideration?
a. Reperfusion therapy is contraindicated because of early ischemic changes on computed tomography of the head
b. Aspirin 325 mg × 1
c. Intravenous unfractionated heparin with a goal activated partial thromboplastin time of 50 to 70 seconds
d. Intravenous recombinant tissue plasminogen activator (0.9 mg/kg)
e. Mechanical thrombectomy

II.5. Which of the following was an exclusion criterion in the European Cooperative Acute Stroke Study III (ECASS III), a randomized clinical trial that demonstrated the safety and efficacy of the use of intravenous recombinant tissue plasminogen activator between 3 and 4.5 hours of the onset of acute ischemic stroke?
a. Age older than 90 years
b. History of stroke and diabetes
c. History of oral antiplatelet use
d. National Institutes of Health Stroke Scale score >10
e. History of childhood epilepsy

II.6. A 75-year-old man presents to the emergency department with slurred speech and left-sided weakness. On noncontrast computed tomography of the head, a 2.5 × 1.7-cm hyperdensity is found in the right lentiform nucleus. There is no history of anticoagulant use or head trauma. Which of the following is the most likely cause?
a. Hypertension
b. Cerebral amyloid angiopathy
c. Cerebral metastasis
d. Ruptured middle cerebral artery aneurysm
e. Factor VIII deficiency

II.7. What is the strongest predictor of outcome after spontaneous intraparenchymal hemorrhage?
a. Age
b. Severity of clinical deficit
c. Hematoma volume
d. Systolic blood pressure
e. Anticoagulant use

II.8. A 38-year-old woman presents to the emergency department with a 4-day history of gradually progressive headache and double vision. She smokes 1.5 packs of cigarettes daily. The neurologic examination is remarkable for near-complete ptosis and exotropia of the left eye. The left pupil is 5 to 6 mm and poorly reactive to light. Ocular motility testing shows impaired adduction, elevation, and depression of the left eye. Noncontrast computed tomography of the head shows no evidence of subarachnoid hemorrhage. What is the most appropriate next step in the management of this patient?
a. Four-vessel cerebral angiography
b. Computed tomography perfusion study
c. Computed tomography angiography of the cerebral vessels
d. Treatment with sumatriptan 50 mg × 1
e. Conservative follow-up in the neurology clinic

Answers

II.1. Answer c.

Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007 May;38(5):1655–711. Epub 2007 Apr 12. Errata in: Stroke. 2007 Jun;38(6):e38. Stroke. 2007 Sep;38(9):e96.

II.2. Answer b.

Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007 May;38(5):1655–711. Epub 2007 Apr 12. Errata in: Stroke. 2007 Jun;38(6):e38. Stroke. 2007 Sep;38(9):e96.

II.3. Answer a.

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II.4. Answer d.

Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke. 2009 Aug;40(8):2945–8. Epub 2009 May 28. Erratum in: Stroke. 2010 Sep;41(9):e562.

II.5. Answer b.

Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke. 2009 Aug;40(8):2945–8. Epub 2009 May 28. Erratum in: Stroke. 2010 Sep;41(9):e562.

II.6. Answer a.

Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001 May 10;344(19):1450–60.

II.7. Answer c.

Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001 May 10;344(19):1450–60.

II.8. Answer c.

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Section
III

Demyelinating Diseases

B. Mark Keegan, MD, *editor*

17 Pathology and Spectrum of Central Nervous System Inflammatory Demyelinating Diseases[a]

CLAUDIA F. LUCCHINETTI, MD

Introduction

Multiple sclerosis (MS) is the most common cause of nontraumatic disability in young adults. It is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Traditionally, MS has been considered an autoimmune disorder consisting of myelin autoreactive T cells that drive an inflammatory process, leading to secondary macrophage recruitment and subsequent myelin destruction. However, accumulating data based on increasing numbers of probes, which can be effectively applied to MS tissue, have indicated that the events involved in the immunopathogenesis of MS may be more complicated.

The advent of more sophisticated histologic and molecular tools to study MS pathology has contributed to evolving concepts regarding disease initiation and progression. MS lesions display pathologic heterogeneity. Apart from myelin and oligodendrocyte damage, axons are also injured in MS and are considered an important pathologic correlate of disability. In addition to the focal white matter MS lesion, the pathology of MS also involves the so-called normal-appearing white matter (NAWM) as well as cortical demyelination that develops early and accumulates with disease progression. MS pathology occurs on a background of inflammation. Although MS is the most common inflammatory demyelinating disease, a spectrum of inflammatory disorders may result in focal CNS demyelination and should be considered in the differential diagnosis of an acute leukoencephalopathy.

Pathologic Findings in MS

The MS Lesion

Chronic MS is the prototype of the demyelinating diseases and involves predominantly white matter at multiple CNS sites at different points in time. The basic pathologic feature unique to MS is the presence of multifocal demyelinated plaques scattered throughout the CNS, with a predilection for the periventricular white matter, optic nerves, brainstem, cerebellum, and spinal cord. These focal areas of myelin destruction occur on a background of an inflammatory reaction consisting predominantly of macrophages and T lymphocytes.

MS lesions can be characterized as active or inactive. Macrophage activation and phagocytosis of myelin proteins in the lesions are reliable indicators of ongoing demyelinating activity. Active lesions are heavily infiltrated by macrophages containing myelin debris and are often closely associated with the disintegrating myelin sheath (Figure 17.1). Intimately intermingled are hypertrophic (reactive) astrocytes with prominent, somewhat polymorphic nuclei and conspicuous eosinophilic cytoplasms.

[a] Portions previously published in Pittock SJ, Lucchinetti CF. The pathology of MS: new insights and potential clinical applications. Neurologist. 2007 Mar;13(2):45–56 and Hu W, Lucchinetti CF. The pathological spectrum of CNS inflammatory demyelinating diseases. Sem Immunopathol. 2009 Nov;31(4):439–53. Used with permission.

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; MRI, magnetic resonance imaging; MS, multiple sclerosis; NAWM, normal-appearing white matter

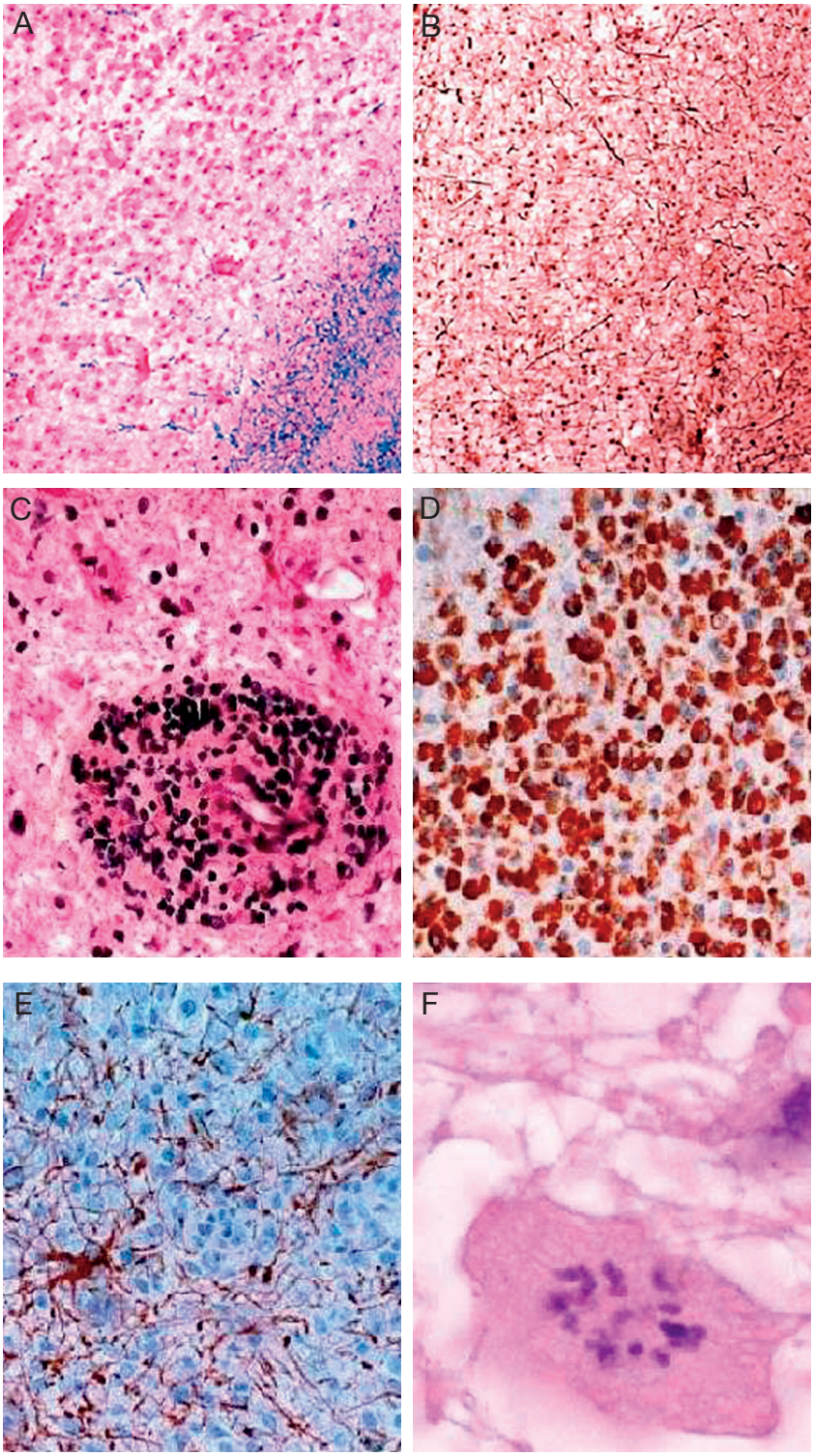

Figure 17.1 *Active Multiple Sclerosis Lesion.*
A, Highly cellular lesion with sharp border. Numerous macrophages are present (Luxol fast blue and periodic acid–Schiff myelin stain). B, Axons are reduced in number or lost and form so-called axonal balloons (Bielschowsky silver impregnation). C, Dense perivascular infiltrate is composed mainly of T cells (hematoxylin-eosin). D, Lesion is diffusely infiltrated by a large number of macrophages removing the myelin debris (Ki-M1P immunostain). E, Astrocytes are hypertrophic, with increased multiple processes (glial fibrillary acidic protein). F, A hypertrophic astrocyte, a so-called Creutzfeldt-Peters cell, shows granular mitosis.
(Adapted from Lucchinetti CF, Parisi J, Bruck W. The pathology of multiple sclerosis. Neurol Clin. 2005 Feb;23[1]:77–105. Used with permission.)

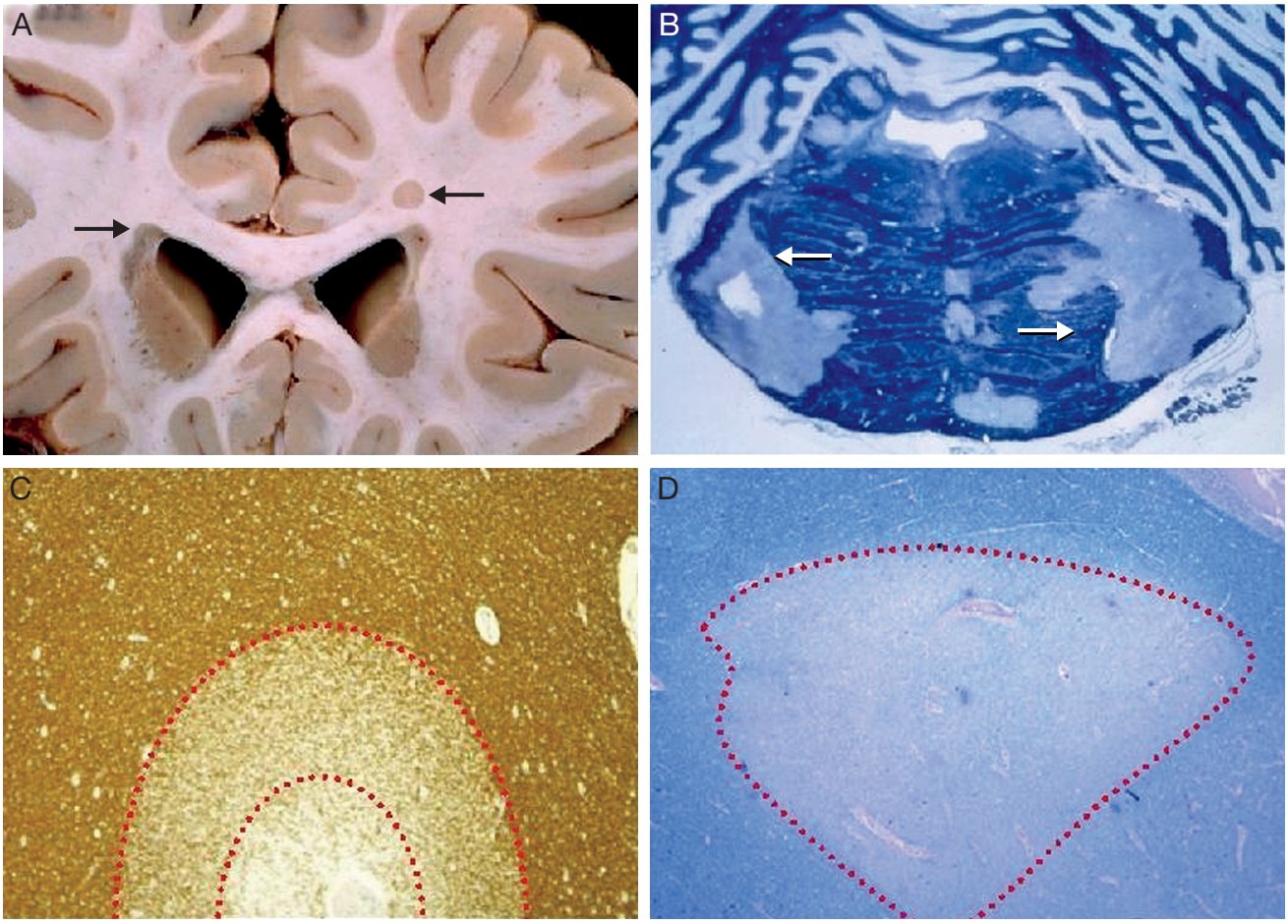

Figure 17.2 *Chronic Multiple Sclerosis Lesions.*
A, Gross specimen shows periventricular plaques (arrows) typical of multiple sclerosis. B, This section through the pons was stained for myelin (Luxol fast blue and periodic acid–Schiff myelin stain). Note the numerous demyelinated lesions (arrows). C and D, Remyelinated so-called shadow plaques are characterized by reduced staining intensity of myelin. Remyelination is either restricted to the lesion edge (dotted lines in C; stained for myelin basic protein) or present throughout the lesion (dotted line in D; Luxol fast blue and periodic acid–Schiff myelin stain).
(Adapted from Lucchinetti CF, Parisi J, Bruck W. The pathology of multiple sclerosis. Neurol Clin. 2005 Feb;23[1]:77–105. Used with permission.)

So-called granular mitosis is an unusual finding in reactive astrocytes (also referred to as Creutzfeldt-Peters cells) in demyelination and other reactive processes. The presence of these atypical astrocytes may suggest the possibility of a glioma; however, reactive astrocytes in active MS lesions are rather evenly distributed and avoid the tendency to clump together, as is common in gliomas.

The chronic inactive MS plaque is a sharply circumscribed hypocellular plaque with no evidence of active myelin breakdown (Figures 17.2 and 17.3). Fibrillary gliosis is prominent, and axonal density is often markedly reduced. Oligodendrocytes are markedly diminished or absent from chronic inactive lesions. However, variable degrees of inflammation may still be present, particularly in the perivascular region. Smoldering or slowly expanding demyelinated plaques have an inactive center surrounded by a rim of activated macrophages and microglia, few of which contain myelin degradation products.

Although MS is traditionally viewed as a disease causing primary demyelination with relative axonal sparing, it is important to emphasize that even the historical neuropathologic descriptions of Charcot (1880) and Marburg (1906) recognized the degeneration of axons in MS lesions, although they emphasized the primary demyelinating nature of the disease. Axonal density is reduced in most MS plaques and occurs in 2 phases. Acute axonal pathology may occur during active demyelination and may already be apparent at the earliest stages of disease evolution, as described in several MS neuropathology studies.

Histologically, active plaques predominate in acute and relapsing MS, when relapses and inflammatory activity on magnetic resonance imaging (MRI) are prominent, and

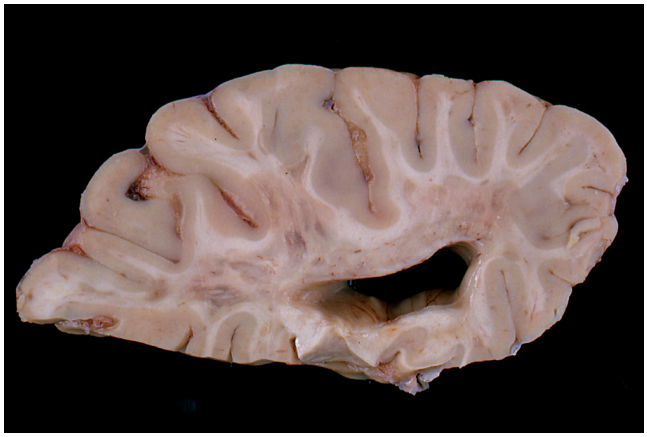

Figure 17.3 *Chronic Multiple Sclerosis.*
Gross specimen shows extensive confluent plaques in periventricular and juxtacortical white matter.
(Adapted from Kantarci OH. Inflammatory and demyelinating disorders of the central nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 559–88. Used with permission of Mayo Foundation for Medical Education and Research.)

may represent the pathologic substrate of clinical attacks. Chronic MS plaques predominate in patients with primary progressive or secondary progressive MS and are the lesion type typically found in archival autopsy tissues from individuals with long-standing chronic progressive MS without ongoing relapses or MRI activity.

Remyelination is also present in both chronic and early stages of MS, although in some chronic MS lesions, remyelination is often incomplete and generally restricted to the edge of the demyelinated plaque. Examination of plaques from other chronic cases may reveal extensive remyelination with evidence of "shadow plaques" (Figure 17.2D). These shadow plaques are sharply demarcated areas of myelin pallor and gliosis. The presence of cells in the very early stages of oligodendrocyte development has been identified in completely demyelinated plaques devoid of mature oligodendrocytes. During early stages of the disease, the extent of remyelination appears to depend on the availability of oligodendrocytes or their progenitor cells in the lesions.

Although MS research has largely focused on identifying a single cause and therapy for all MS patients, this approach fails to address the clinical, genetic, and radiographic heterogeneity that underlies the variable response of MS patients to any given treatment. Demyelinating antibodies, cytokines and other soluble mediators, cytotoxic T cells, reactive oxygen and nitrogen species, excitotoxic mechanisms, and primary oligodendrocyte injury have all been suggested as possible pathogenic contributors to myelin damage in MS. Studies on early active MS lesions have reported profound heterogeneity in immunopatterns of demyelination based on loss of specific myelin proteins, extent and topography of plaques, variable destruction of oligodendrocytes, and evidence for complement activation. Immunopathologic patterns among early active MS lesions have demonstrated high interindividual heterogeneity with intraindividual homogeneity. This suggests that the dominant immune effector mechanism of tissue injury in MS may differ among patient subgroups. Pathologic heterogeneity may also reflect different host genetic factors influencing the character of immune-mediated inflammation, as well as the susceptibility of the tissue to glial, axonal, and neuronal injury.

NAWM Damage in MS

Besides the focal demyelinated plaques, a diffuse global injury of the NAWM is found in the brains of MS patients. This is supported by several neuroimaging studies suggesting that diffuse pathology is present within the NAWM of MS patients. The pathology of the NAWM in MS is characterized by diffuse, mainly $CD8^+$ T-cell infiltrates; gliosis; microglial activation; diffuse axonal injury; and nerve fiber degeneration. It is uncertain whether these represent reactive changes rather than an inherent abnormality within the white matter of a subset of MS patients.

Cortical Pathology in MS

MS has traditionally been considered a disease primarily affecting the CNS white matter, mainly because identifying cortical lesions with the use of conventional histologic stains for myelin is difficult and detecting lesions with conventional neuroimaging techniques has limitations. However, with the advance of immunohistochemical analyses for myelin proteins and newer advanced imaging approaches, it has become apparent that cortical demyelination in MS is extensive and may occur spatially removed from white matter pathology.

Three main types of cortical demyelinated lesions have been described. *Leukocortical lesions* extend from white matter into adjacent cortex; *intracortical lesions* are small and centered on vessels; and *subpial lesions* extend from the pia mater into deeper cortex. Subpial demyelinated cortical plaques are most common in chronic MS and may span extended distances. Subpial lesions have a predilection for cortical sulci, as well as cingulate, temporal, insular, and cerebellar cortex. Cortical demyelination can be extensive, with up to 70% to 90% of the cortex demyelinated. It is most prominent in secondary progressive MS and primary progressive MS, suggesting that it may be an important pathologic correlate of irreversible disability and of cognitive dysfunction. Typically, conventional MRI techniques are not sensitive enough to detect intracortical or subpial lesions. However, more recent imaging protocols

Table 17.1 • Spectrum of IIDD: Comparison of Clinical Features

Clinical Characteristics	Acute MS Variants					
	Prototypic MS[a]	**Marburg[b]**	**Baló[c]**	**ADEM[d]**	**Devic NMO[e]**	**Tumefactive MS[f]**
Age at onset	30 (15–40) y	20–50 y	20–50 y	Mainly childhood, but 10% >16 y	40 (5–65) y	30 (15–40) y
Demographics	Most common in Northern Europe	Limited data	Common in Asia (China, Philippines)	Limited data	Common in Asia and Africa	Same as prototypic MS
Sex (F:M)	2:1	Limited data	Limited data	Equal	7:1 (relapsing form)	1:1
Clinical course	80% RRMS with or without SPMS 20% PPMS	Monophasic; may be rapidly progressive	Acute onset; monophasic; may be rapidly progressive	Acute onset; monophasic; 70% with prior viral or bacterial infection or vaccination	Acute onset; 20% monophasic; 80% relapsing	May remain isolated single event or become RRMS
Short-term prognosis	Highly variable: 20% benign MS, 50% progressive MS	Fulminant meningism; altered consciousness; with or without seizures and increased intracranial pressure	Fulminant meningism; altered consciousness; with or without seizures and increased intracranial pressure	Moderate to severe meningism, fever, altered consciousness, and headache; 70% with prodrome and immune trigger	Typically severe; reduced visual acuity, unilateral and bilateral blindness, hemiplegia and paraplegia, and death (respiratory compromise)	Highly variable
Long-term prognosis	With progressive MS: disability by 10 y and need for walking aid by 15 y after onset; 4-fold mortality rate; average life expectancy overall	Often fatal in ≤1 y	Often fatal in ≤1 y	Most with complete resolution; <50% with residual deficits; 10%-20% with no change	Variable, but usually poor if not treated; >50% blind or with walking aid after 5 y; 5-y survival <80%	Highly variable
Biomarker	None	None	None	None	NMO IgG	None
CSF						
Pleocytosis	Usually WBCs ≤50/mcL	Same as prototypic MS	Same as prototypic MS	Increased in 30%-80%; WBCs >50/mcL	Usually WBCs 50–100/mcL	Same as prototypic MS
Protein level	Normal in 75%, rarely >1 g/L	Same as prototypic MS	Same as prototypic vMS	Increased in 30%-60%	Frequently increased to 1.5 g/L	Same as prototypic MS
Intrathecal Ig with OCBs	Increased in ≥60%-80%; positive for OCBs	Same as prototypic MS	Same as prototypic MS	Increased in 5%-60%	<35% positive for OCBs	Same as prototypic MS

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; Ig, immunoglobulin; IIDD, idiopathic inflammatory demyelinating disease; MS, multiple sclerosis; NMO, neuromyelitis optica; OCB, oligoclonal band; PPMS, primary progressive MS; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; WBC, white blood cell.

[a] Weinshenker (1995) and Lucchinetti et al (2001, 2003).

[b] Genain et al (1999) and Storch et al (1998).

[c] Karaarslan et al (2001), Galluci et al (2001), and Stadelmann et al (2004).

[d] Wingerchuk (2003).

[e] deSeze et al (2002), Fardet et al (2003), Lucchinetti et al (2002), and Wingerchuk et al (1999).

[f] Kepes (1993) and Masdeu et al (1996, 2000).

Adapted from Morales Y, Parisi JE, Lucchinetti CF. The pathology of multiple sclerosis: evidence for heterogeneity. Adv Neurol. 2006;98:27–45. Used with permission.

Table 17.2 • Spectrum of IIDD: Comparison of Pathologic and Radiologic Features

Clinical Characteristics	Acute MS Variants					
	Prototypic MS[a]	**Marburg[b]**	**Baló[c]**	**ADEM[d]**	**Devic NMO[e]**	**Tumefactive MS[f]**
Inflammation	Many macrophages and microglia; T cells (perivenular and parenchymal); with or without complement and Ig deposition (ie, in early active demyelinating pattern II)	Same as prototypic MS, plus notable neutrophils; may find activated complement and Ig deposition (pattern II)	Same as prototypic MS, except for concentric rings of on-off inflammation; MAG loss (pattern III)	Limited to perivenular mononuclear cells; with or without microglia at lesion edge	Many perivascular macrophages and microglia, B cells, eosinophils; ring and rosette pattern of complement and Ig deposition	Same as prototypic MS; confused with gliomas because of Creutzfeldt-Peters astrocytes, but distinguished by macrophage infiltrate and border
Topography	Mainly WM, but occasionally cortex and DGM; common at angles of lateral ventricles and floor of fourth ventricle	Mainly cerebral WM tracts; may encompass entire cerebral hemispheres	Mainly cerebral WM tracts; may encompass entire cerebral hemispheres	Disseminated or multifocal perivenular lesions; ≥90% in cerebral subcortical WM (periventricular in 30%-60%), ≥90% in DGM, ≥65% in spinal cord	Both WM and GM; optic nerves or spinal cord (or both)	Juxtacortical; may extend into cortex
MRI findings	Usually small, unifocal or multifocal, circumscribed (with or without enhancing) lesions	Severe edema and necrosis; with or without encompassing entire cerebral hemispheres; mass effect	Severe edema and necrosis; with or without encompassing entire cerebral hemispheres; with or without mass effect	Minimal enhancement; perivenular or diffuse edema with or without multifocal lesions; no necrosis or atrophy (Figure 17.5)	Edema, necrosis, and cavitation; spinal cord lesions frequently extend beyond 3 vertebrae; bilateral optic neuritis is common	Tumorlike, enhancing open ring protruding into subcortical WM and opening to cortex (Figure 17.4G); mass effect or edema

Abbreviations: ADEM, acute disseminated encephalomyelitis; DGM, deep gray matter; GM, gray matter; Ig, immunoglobulin; IIDD, idiopathic inflammatory demyelinating disease; MAG, myelin-associated glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuromyelitis optica; WM, white matter.

[a] Weinshenker (1995) and Lucchinetti et al (2001, 2003).

[b] Genain et al (1999) and Storch et al (1998).

[c] Karaarslan et al (2001), Galluci et al (2001), and Stadelmann et al (2004).

[d] Wingerchuk (2003).

[e] deSeze et al (2002), Fardet et al (2003), Lucchinetti et al (2002), and Wingerchuk et al (1999).

[f] Kepes (1993) and Masdeu et al (1996, 2000).

Adapted from Morales Y, Parisi JE, Lucchinetti CF. The pathology of multiple sclerosis: evidence for heterogeneity. Adv Neurol. 2006;98:27–45. Used with permission.

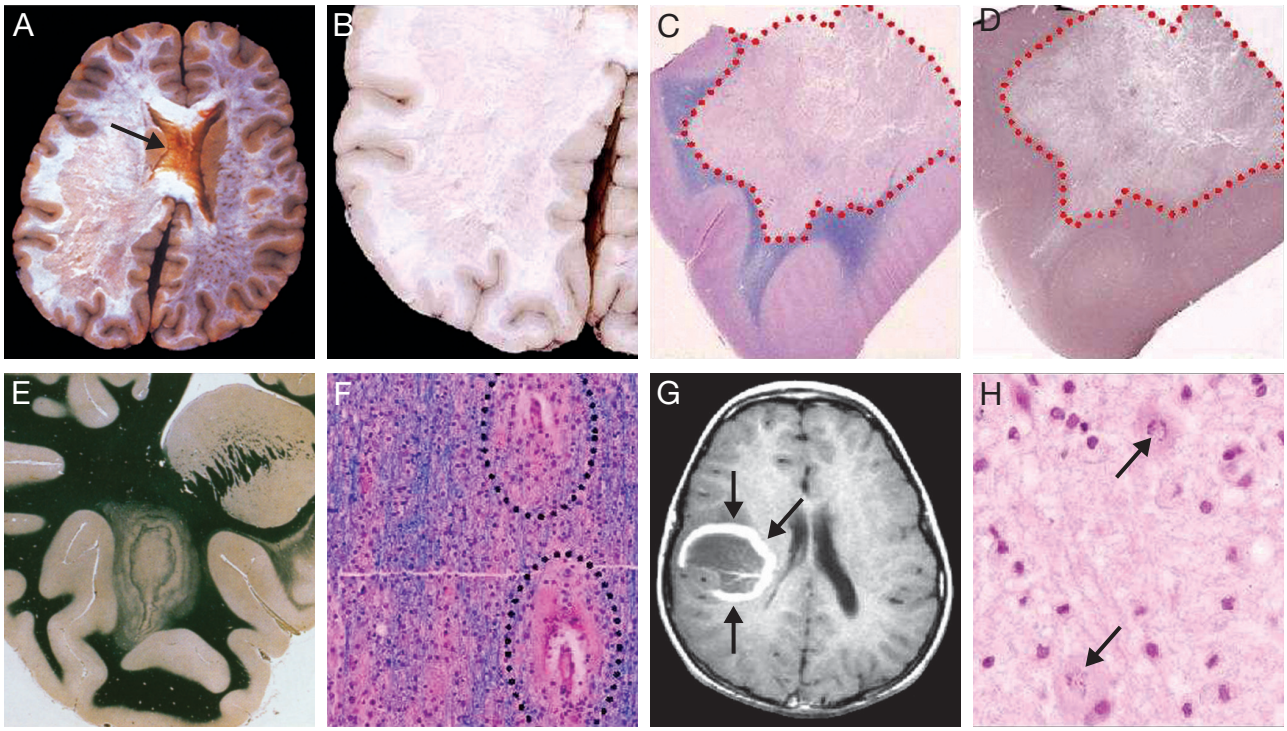

Figure 17.4 *Pathologic Spectrum of Idiopathic Inflammatory Demyelinating Diseases.*
A and B, Gross specimens of Marburg-type multiple sclerosis. Large confluent lesions lead to mass effect and herniation (arrow in A). C and D, Microscopic sections of the lesion in A and B show extensive demyelination (dotted line) (Luxol fast blue and periodic acid–Schiff myelin stain) and axonal loss (Bielschowsky silver impregnation). E, Baló concentric sclerosis shows the characteristic alternating bands of demyelination and preserved myelin. F, Lesions of acute disseminated encephalomyelitis are characterized by perivascular inflammation and only minimal, mainly perivenular demyelination (dotted circles). G, Tumefactive lesion (arrows) with severe edema and mass effect. H, Hypertrophic astrocytes (arrows) (Creutzfeldt-Peters cell) in an acute demyelinating lesion.
(A-D and F-H, Adapted from Lucchinetti CF, Parisi J, Bruck W. The pathology of multiple sclerosis. Neurol Clin. 2005 Feb;23[1]:77–105. Used with permission. E, Adapted from Okazaki H. Fundamentals of neuropathology: morphologic basis of neurologic disorders. 2nd ed. New York [NY]: Igaku-Shoin; c1989. p. 155. Used with permission.)

that use double inversion recovery show that intracortical and subpial lesions are more frequent in secondary progressive MS and also are present in early disease (ie, in both clinically isolated syndromes and early relapsing-remitting MS). Although chronic cortical MS lesions are largely devoid of inflammation, early cortical MS plaques show demyelination, and neurodegenerative changes occur on a background of inflammation. In addition, a striking topographic association exists between meningeal inflammation and cortical demyelination among MS patients, suggesting that meningeal inflammation may be important in initiating and propagating the MS disease process.

- The basic pathologic feature unique to MS is the presence of multifocal demyelinated plaques scattered throughout the CNS, with a predilection for the periventricular white matter, optic nerves, brainstem, cerebellum, and spinal cord.
- Although MS is traditionally viewed as a disease causing primary demyelination with relative axonal sparing, it is important to emphasize that even the historical neuropathologic descriptions of Charcot (1880) and Marburg (1906) recognized the degeneration of axons in MS lesions, although they emphasized the primary demyelinating nature of the disease.
- Remyelination is present in both chronic and early stages of MS.
- With the advance of immunohistochemical analyses for myelin proteins and newer advanced imaging approaches, it has become apparent that cortical demyelination in MS is extensive and may occur spatially removed from white matter pathology.

The Spectrum of Inflammatory Demyelinating Diseases

The classic clinicopathologic pattern of chronic MS represents only 1 member of a family of closely related inflammatory demyelinating leukoencephalitides that also

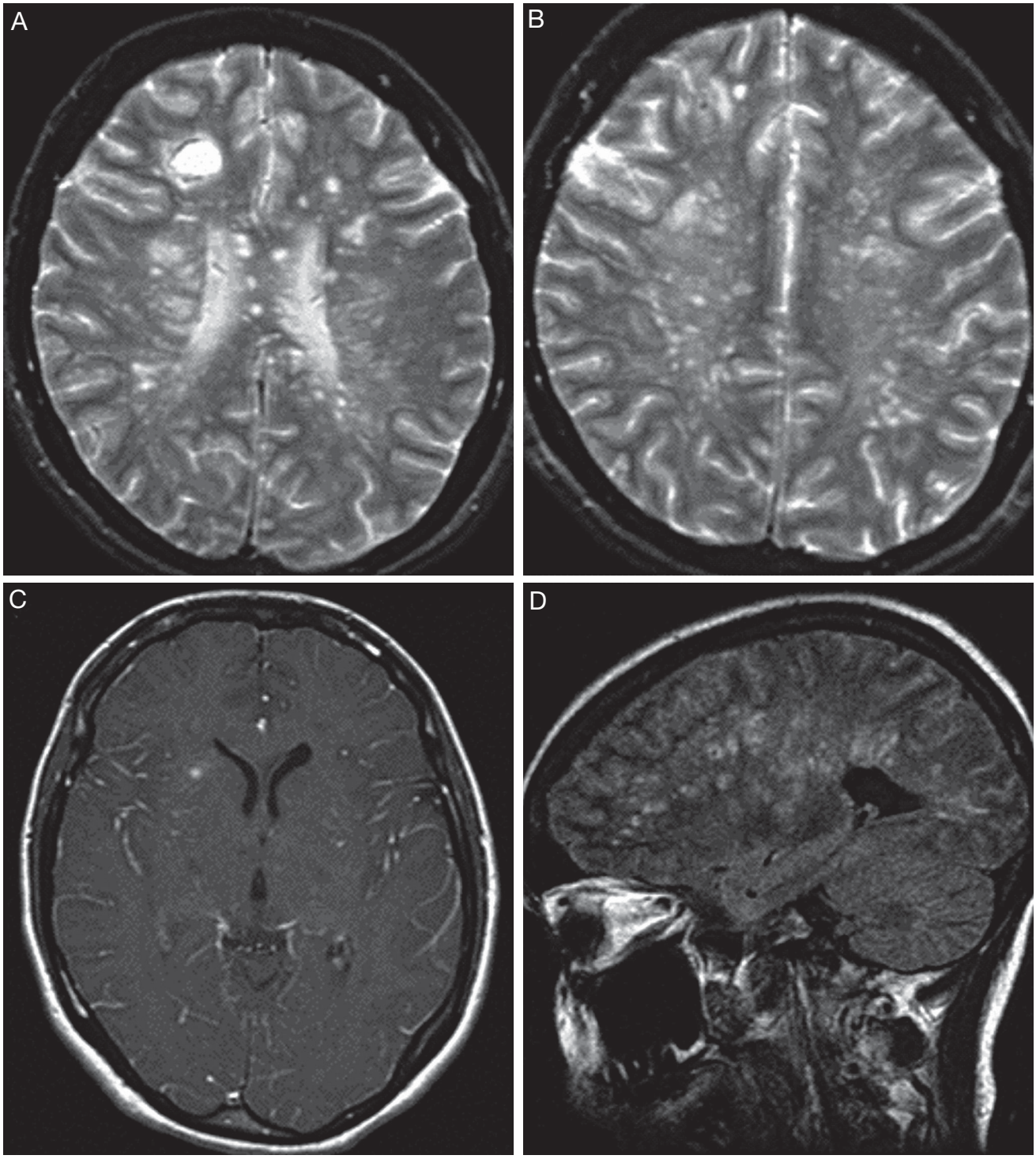

Figure 17.5 *Magnetic Resonance Imaging Findings in Biopsy-Proven Acute Disseminated Encephalomyelitis.*
For contrast with typical multiple sclerosis lesions, see Figure 17.2. A and B, Diffuse, punctate T2-weighted hyperintense lesions. C, Limited enhancement in T1-weighted image. D, Sagittal fluid-attenuated inversion recovery–weighted image shows diffuse hyperintense lesions.
(Adapted from Kantarci OH. Inflammatory and demyelinating disorders of the central nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 559–88. Used with permission of Mayo Foundation for Medical Education and Research.)

include acute MS (Marburg variant); Baló concentric sclerosis; acute disseminated encephalomyelitis (ADEM); neuromyelitis optica (Devic disease); and tumefactive MS.

Tables 17.1 and 17.2 summarize and compare the clinical, pathologic, and radiologic features of these disorders. Figures 17.4 and 17.5 review the pathologic findings. The literature on the classification of these syndromes is often confusing. Some studies emphasize specific clinical or pathologic features to distinguish between these syndromes. However, instances of transitional cases defy specific terminology. For example, the typical concentric lesions of Baló concentric sclerosis can be found adjacent to more typical MS plaques. In addition, some patients have lesions with histologic features of both ADEM and MS. Although the clinical and pathologic characteristics of these diseases are diverse, the presence of transitional forms suggests a spectrum of inflammatory diseases that may share a pathogenic relationship.

- Although the clinical and pathologic characteristics of idiopathic inflammatory demyelinating diseases are diverse, the presence of transitional forms suggests a spectrum of inflammatory diseases that may share a pathogenic relationship.

18 The Diagnosis of Multiple Sclerosis

ISTVAN PIRKO, MD†

Introduction

Multiple sclerosis (MS) is the most common idiopathic inflammatory demyelinating disease of the central nervous system, with a prevalence of 1 in 500 to 1 in 2,000 people, depending on geography and a number of other factors. Idiopathic inflammatory demyelinating diseases include other diseases, such as acute disseminated encephalomyelitis and neuromyelitis optica, and a number of less commonly seen varieties, such as Balo concentric sclerosis, tumefactive MS, or the Marburg variant, which is a fulminant, monophasic demyelinating disease. One way to characterize these diseases is whether a disease is acute or chronic and how severe it may become (Figure 18.1). On the basis of these characteristics, MS falls in the middle: it is typically a chronic disease, although acute MS varieties may be encountered rarely. MS may be disabling, but approximately 20% of patients have benign MS, with minimal or no motor disability, even after decades of MS activity.

This chapter reviews the clinical presentation and diagnostic criteria for MS. Many disorders may clinically or radiographically mimic MS. These are described in Chapter 20, "Mimickers of Multiple Sclerosis."

Epidemiology and Clinical Presentation

Risk Factors

MS has numerous known risk factors, including genetic characteristics (such as HLA status and others), race, and geographic location during the individual's first 16 years of life, which seems to mostly determine vitamin D levels as well as the type of infections one may encounter. Epstein-Barr virus infections, especially at an early age, may have some importance. Interestingly, while neuromyelitis optica shows a clear overlap with other autoimmune diseases (such as autoimmune thyroid disease, systemic lupus erythematosus, and rheumatoid arthritis), the same does not hold true for MS in most studies conducted to date, with the possible exception of inflammatory bowel diseases and a specific form of uveitis called pars planitis. In terms of the genetics of MS, up to 4% of asymptomatic relatives of sporadic MS patients have magnetic resonance imaging (MRI) evidence of MS lesions. This rate increases to 10% in families with multiple affected members, and the rate of detection of silent MRI lesions in non-MS discordant monozygotic twins is about 20%. The overall lifetime prevalence of MS in a monozygotic twin sibling of an MS patient is about 25% to 30%.

Clinical Presentation and Conversion to MS

The most common form of MS is relapsing-remitting MS (RRMS), which represents about 80% of all cases in a geographic area at a given time point. About 15% of patients have progressive forms of MS, with 5% or less having less commonly seen varieties, such as progressive-relapsing MS or cerebral MS, which represents a progressive variety with substantial and predominant cognitive dysfunction.

RRMS initially presents with an acute monophasic episode (or clinically isolated syndrome [CIS]) which, in MS patients, tends to be optic neuritis, transverse myelitis, or an isolated brainstem syndrome. These isolated single attacks may not evolve into MS and therefore may represent a true CIS. In some patients, MRI findings are strongly

Abbreviations: CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, primary progressive MS; RIS, radiographically isolated syndrome; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

† Died November 30, 2014.

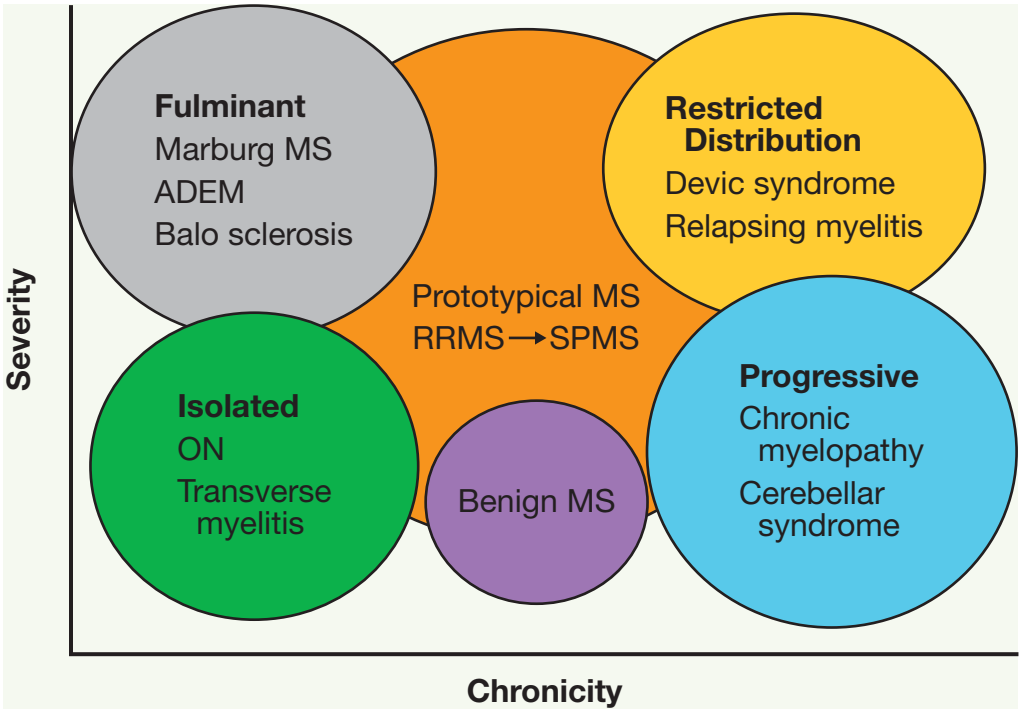

Figure 18.1 *The Spectrum of Idiopathic Inflammatory Demyelinating Diseases.*
The severe and chronic restricted distribution syndromes (right upper quadrant) encompass mainly neuromyelitis optica (NMO) and NMO spectrum disorder, which are no longer considered to overlap with prototypical multiple sclerosis (MS), given the different pathogenesis, histopathology, genetic background, imaging findings, and response to therapy. ADEM indicates acute disseminated encephalomyelitis; ON, optic neuritis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

suggestive of MS, even before any specific neurologic symptoms appear. These patients are typically identified as having radiologically isolated syndrome (RIS). RIS is a misnomer because these patients have no symptoms, whereas the word *syndrome* means a patient has a symptom complex. Many of these patients undergo MRI as a component of a work-up for headache or head trauma.

Several studies have addressed the risk of conversion from CIS to MS (Table 18.1) and concluded that the strongest predictor for conversion is the MRI result at the time of work-up of these isolated episodes. If the MRI shows more than just the symptomatic lesion (ie, more than 1 lesion), then the conversion risk over 20 years is higher than 80%, whereas in patients lacking lesions on MRI, the conversion risk is 21% at 20 years (Figure 18.2). The majority of patients who convert tend to do so early on, and the 5-year conversion risk is approximately 60% in MRI-positive patients. The risk of conversion to MS is lower in pediatric patients: 13% in 10 years and 26% in 40 years. The presence of oligoclonal bands in the cerebrospinal fluid, in addition to 3 or more lesions suggestive of MS, predicts conversion in 63% of patients within about 2 years after an isolated attack of optic neuritis, while the absence of either invariably predicts no conversion to MS. Although not routinely tested in clinical practice, the presence of HLA-DR2 (DR15) genotype has a positive predictive value of 44% and a negative predictive value of 71% in determining conversion to definite MS.

Phenotypically, optic neuritis is more benign from the standpoint of conversion to MS than transverse myelitis or brainstem-cerebellar syndromes. According to data from the placebo arms of the trial of interferon beta-1a in CIS (Cochrane Database Syst Rev. 2008 Apr 16;[2]:CD005278), reaching the same target takes about 17 months for patients

Table 18.1 • Conversion to MS After CIS

	Time After CIS Episode, y				
MRI Appearance[a]	**1**	**5**	**10**	**14**	**20**
Abnormal	30%	65%	83%	88%	82%
Normal	0%	3%	11%	19%	21%

Abbreviations: CIS, clinically isolated syndrome; MRI, magnetic resonance imaging; MS, multiple sclerosis.
[a] An abnormal MRI represents patients with more than just the symptomatic lesion; normal MRI represents patients with negative MRI or with MRI that shows only the symptomatic lesion.

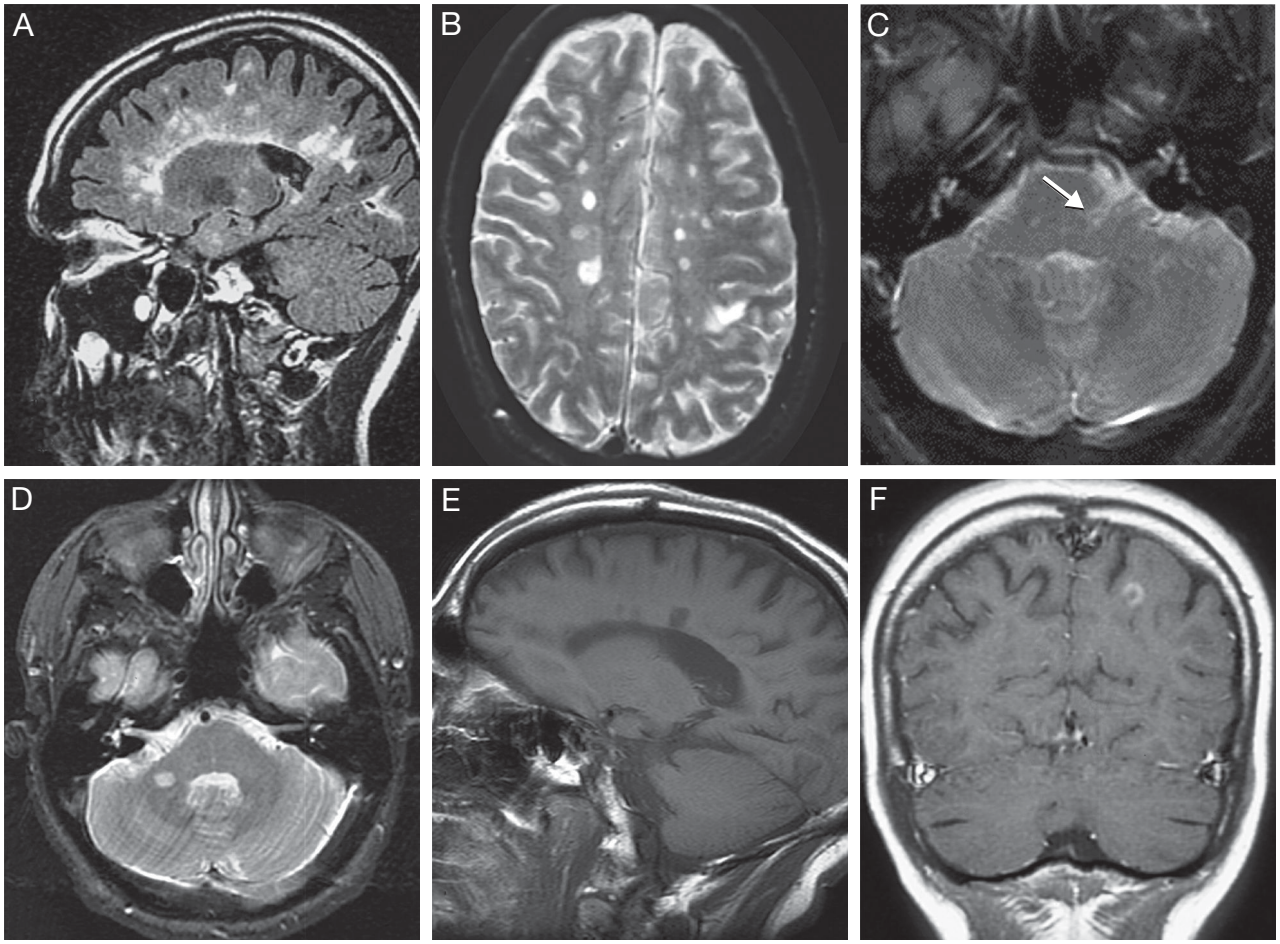

Figure 18.2 *Magnetic Resonance Imaging Findings in Multiple Sclerosis (MS).*
A, Sagittal fluid-attenuated inversion recovery image, and B, T2-weighted image showing multiple rounded areas of increased T2 signal in deep and periventricular white matter, some perpendicular to lateral ventricles (A). C, T2-weighted image from a patient with MS who presented with facial sensory symptoms. The image shows increased signal along the left trigeminal nerve (arrow). D, T2-weighted image of a plaque in the middle cerebellar peduncle, typical of MS. E, T1-weighted sagittal image with an old periventricular Dawson finger lesion appearing hypotense ("black hole") and perpendicular to the lateral ventricle. F, Gadolinium-enhanced T1-weighted image showing the typical enhancement pattern (open-ring enhancement) of a juxtacortical lesion.
(Adapted from Kantarci OH. Inflammatory and Demyelinating Disorders of the Central Nervous System. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 559–88. Used with permission of Mayo Foundation for Medical Education and Research.)

with isolated optic neuritis to develop a new relapse, about 15 months with isolated brainstem syndrome, and about 8 months with a transverse myelitis.

Radiologically Isolated Syndrome

RIS studies are not as extensive at this point as CIS studies; RIS was recognized more recently than CIS. The conversion rate from RIS to MS (development of first symptoms attributable to MS) is about 20% at 2 years and about 30% at 3 years from the initial MRI. Oligoclonal bands in cerebrospinal fluid and the presence of spinal cord lesions result in increased risk of conversion. Patients with RIS seemingly converted to MS at a slower rate than CIS patients in the placebo arms of CIS trials and no faster than the CIS patients in the treatment arms of the same trials. Therefore, until a specific treatment trial proves effective in RIS, there is no clear reason to initiate disease-modifying therapy; however, this question would be best answered by appropriately designed clinical trials.

- The most common form of MS is relapsing-remitting MS, which represents about 80% of all cases in a geographic area at a given time point.

- Several studies have addressed conversion risk from a clinically isolated syndrome to MS and concluded that the strongest predictor for conversion is the MRI result at the time of work-up of these isolated episodes. If the MRI shows more than just the symptomatic lesion (ie, more than 1 lesion), then the conversion risk over 20 years is higher than 80%, whereas in patients lacking lesions on MRI, the conversion risk is 21% at 20 years.
- The conversion rate from RIS to MS (development of first symptoms attributable to MS) is about 20% at 2 years and about 30% at 3 years from the initial MRI.

Diagnosis of RRMS

Most physicians easily recall "dissemination in space and time" as the key to diagnosing MS. Dissemination in space refers to different locations within the central nervous system giving rise to different symptoms, while dissemination in time refers to the fact that MS exacerbations do not occur simultaneously but typically occur several months to a few years apart. While even with the more recent evolution of diagnostic criteria, "dissemination in space and time" still holds true; however, several other neurologic diseases meet the same criteria. Therefore, only after ruling out MS mimics can one conclude that the correct diagnosis is truly MS. Although the classic definition suggests that at least 2 distinct relapses with different neurologic symptoms must occur prior to diagnosing MS, that observation is no longer considered valid. The previously used Poser criteria disregarded subclinical disease activity and required at least 2 distinct clinical events to diagnose MS. However, since the introduction of the McDonald criteria in 2001, "asymptomatic attacks" giving rise to new lesion formation but no new symptoms also qualify as precursors to diagnose MS. MS therefore can be diagnosed with just 1 clinical symptom attributed to demyelination and with MRI evidence for dissemination in space and time. More commonly, patients have subclinical disease activity resulting in new lesion formation at the MRI level than new clinical relapses. Therefore, the new diagnostic criteria have enabled the diagnosis of MS earlier and in more patients compared with earlier criteria. Dissemination in space is defined by at least 1 lesion in 2 of 4 typical locations (periventricular, juxtacortical, infratentorial, and spinal cord). The 2001 and 2005 McDonald criteria required 2 MRI time points to meet dissemination-in-time criteria. However, since the 2010 modification, representing the most recent criteria, a single MRI may be sufficient to meet both dissemination-in-space and dissemination-in-time criteria, as long as the MRI demonstrates MS-like lesions in different stages of lesion formation, ie, some with contrast dye enhancement, with others only visible on T2-weighted sequences and not on postcontrast T1-weighted sequences. Contrast dye uptake is seen in newly forming lesions, typically resolves in 2 to 3 weeks, and almost never persists beyond 2 months, even in larger lesions. (When enhancement persists, one should consider other diseases, such as brain tumors and sarcoidosis.) Enabling the use of just 1 MRI to meet dissemination-in-time criteria clearly results in earlier diagnosis and higher sensitivity; however, as often is the case, the price one pays for increased sensitivity is decreased specificity. For example, the presence of a small venous angioma may be mistaken for an enhancing MS lesion, especially when only 1 scan is available. That may give rise to an erroneous diagnosis of MS, decreasing the specificity of the new criteria (Boxes 18.1 and 18.2).

The original McDonald criteria led to a twofold to fourfold increase in the diagnosis of definite MS in the first 12 months after a CIS. Patients previously classified as having a CIS may actually fulfill dissemination-in-time-and-space criteria by MRI at the time of presentation, and they may be defined as having MS. In light of this, some of the pre-McDonald epidemiologic data require caution when interpreted in the context of the current diagnostic criteria.

In addition to introducing MRI to the diagnosis of MS, the McDonald criteria actually deemphasized electrophysiologic evidence of a subclinical attack to define different categories such as possible or probable MS, except in the diagnosis of primary progressive MS (PPMS) (see criteria for progressive MS in the ensuing paragraphs).

In addition to a valid and complete interpretation of the paraclinical markers to diagnose MS, it is important to differentiate true symptomatic relapses from pseudoattacks. Pseudorelapses are generally recurrences of previous symptoms, usually in the setting of infections or other reasons for increased body temperature, fatigue, and stress, without accompanying objective new lesion development. They last generally less than 24 hours, although exceptions exist. For example, if an infection keeps a patient

Box 18.1 • Dissemination-in-Space Criteria (2010 Modified McDonald MS Criteria)[a]

DIS can be demonstrated by ≥1 T2-weighted lesion in a least 2 of the following 4 areas of the CNS:

- Periventricular
- Juxtacortical
- Infratentorial
- Spinal cord

Abbreviations: CNS, central nervous system; DIS, dissemination in space; MS, multiple sclerosis.

[a] Gadolinium enhancement of lesions is not required for DIS. Also, when a patient has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to the lesion count.

Box 18.2 • The 2010 Dissemination-in-Time Criteria[a]

DIT can be demonstrated by either of the following:

1. New T2-weighted and/or gadolinium-enhancing lesion(s) on follow-up MRI with reference to a baseline scan, irrespective of timing of the baseline MRI
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Abbreviations: DIT, dissemination in time; MRI, magnetic resonance imaging.

[a] The interval between the baseline scan and the follow-up scan is no longer defined, and a single scan can fulfill DIT criteria if enhancing and nonenhancing lesions are present simultaneously.

febrile for longer than 24 hours, the pseudoattack can also last longer than that. In addition, pseudorelapses are self-limited and require only reassurance or treatment of the "offending agent," such as infection, ingrown toenail, or anxiety. Misdiagnosing these as true relapses may lead to unnecessary corticosteroid use and unjustified changes to disease-modifying treatments.

Clinical Evolution of RRMS

RRMS is characterized by multifocal inflammatory demyelination and accompanying axonal injury of variable degree. Up to one-third of patients remain indefinitely in the RRMS phase; however, most patients typically enter the progressive stage after 10 or more years of disease activity. No treatment is known to influence the progressive stage or to prevent the stereotypical slow progression except by preventing additional relapse-induced disability in the early progressive stage of some patients.

Patients who do not enter the progressive stage and have not developed relapse-related disability are often classified as having benign MS. Definitions of benign MS vary, but in general, these patients do not have noticeable disability (Expanded Disability Status Scale [EDSS] score of 3 or less) to an outside observer despite 15 or more years of disease activity. In the Olmsted County, Minnesota, cohort, approximately 1 in 5 patients is in this category. This classification may be biased toward motor disability only, and patients with an otherwise benign-appearing phenotype may actually have substantial cognitive involvement. While typically that is not the case, notable cognitive problems do develop in a small subset of MS patients.

The clinical predictors of a nonbenign MS course are male sex; polysymptomatic onset; older age (>40 years); motor, cerebellar, or sphincter symptoms at initial presentation; relatively frequent attacks in the first 5 years; a short interval between the first 2 attacks; and a relatively short time to reach an EDSS score of 4 (relatively severe disability but fully ambulatory without aid, self-sufficient, up and about 12 hours a day; able to walk 500 m without aid or rest). After reaching the EDSS score of 4, the course is usually independent of baseline predictive factors, and most of those patients enter the secondary progressive stage.

- MS can be diagnosed with just 1 clinical symptom attributed to demyelination and with MRI evidence for dissemination in space and time.
- The 2001 and 2005 McDonald criteria required 2 MRI time points to meet dissemination-in-time criteria. However, since the 2010 modification, representing the most recent criteria, a single MRI may be sufficient to meet both dissemination-in-space and dissemination-in-time criteria, as long as the MRI demonstrates MS-like lesions in different stages of lesion formation.
- The clinical predictors of a nonbenign MS course are male sex; polysymptomatic onset; older age (>40 years); motor, cerebellar, or sphincter symptoms at initial presentation; relatively frequent attacks in the first 5 years; a short interval between the first 2 attacks; and a relatively short time to reach an EDSS score of 4.

Progressive Forms of MS

A progressive disease course in MS is defined as insidious and irreversible worsening of neurologic function. Most progression, whether seen in the context of PPMS or secondary progressive MS (SPMS), represents progressive upper motor neuron signs and symptoms, bowel and bladder symptoms, and worsening spasticity and fatigue. Progression is attributed to progressive axonal injury as opposed to a direct consequence of demyelination. The term *progressive disease* should not be confused with *disability progression*, a term commonly used in MS clinical trials. Disability progression in MS can result from insufficient recovery from relapses, a progressive disease course, or both. An intervention, such as use of corticosteroids or plasma-exchange treatment, enhances recovery after a relapse, and disease-modifying agents can decrease the number of relapses. Although these interventions may have a measurable impact on disability progression, they may not prevent a true progressive disease course.

The diagnosis of progressive MS requires objective documentation of a progressive disease course of at least 1 year's duration (Box 18.3). PPMS is defined as progression without previous symptomatic attacks. Many PPMS patients have MRI lesions suggestive of previous asymptomatic attacks. SPMS is defined as progression following RRMS. A subset of these patients have only 1 attack; these

Box 18.3 • The 2010 Criteria for PPMS[a]

PPMS may be diagnosed in patients with the following:

1. Disease duration of 1 y (progressively or retrospectively defined)
2. Plus 2 of the following 3 criteria:
   - A. Evidence for DIS in at least 1 characteristic area of the brain (periventricular, juxtacortical, infratentorial)
   - B. Evidence for DIS in the spinal cord based on 2 or more T2-weighted hyperintense lesions
   - C. Positive CSF (OCB positivity, IgG index elevation, or both)

Abbreviations: CSF, cerebrospinal fluid; DIS, dissemination in space; OCB, oligoclonal bands; PPMS, primary progressive multiple sclerosis.

[a] Gadolinium enhancement of lesions is not required. Also, if a patient has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded.

are sometimes referred to as having single-attack progressive MS. Another rare but clearly existing subcategory is progressive relapsing MS, defined by relapses superimposed on progressive MS. Newer observations suggest that the age at onset of progression is almost identical between the subcategories of patients with PPMS and SPMS, and therefore, the onset of progression in MS seems to be mainly dependent on age rather than disease duration. Interestingly, similar to how the relapsing phase subsides, with fewer and fewer relapses, the rate of progression also slows and reaches a plateau with advancing age. Unfortunately, this plateau tends to occur at a severely disabled stage when assistive devices such as walkers and wheelchairs are required.

Relapsing MS only rarely leads to substantial long-term disability. In a newer study, only 2% of RRMS patients reached a sustained disability level with an EDSS score of 6 (needing unilateral support to walk). The onset of progressive phase appears to be the most important predictor of disability levels with an EDSS score of 6 or higher.

- The diagnosis of progressive MS requires objective documentation of a progressive disease course of at least 1 year's duration.
- The onset of the progressive phase appears to be the most important predictor of disability levels with an EDSS score of 6 or higher.

19 Treatment of Multiple Sclerosis[a]

ORHUN H. KANTARCI, MD

Introduction

Treatment of multiple sclerosis (MS) includes 3 categories: prevention of relapses and disease progression; treatment of individual relapses; and treatment of symptoms and complications. This chapter focuses mainly on prevention of relapses and progression by altering the natural course of MS. The medications used are known as disease-modifying drugs (DMDs). The treatment of individual relapses and symptomatic treatment is also briefly covered.

- Treatment of multiple sclerosis (MS) includes 3 categories: prevention of relapses and disease progression; treatment of individual relapses; and treatment of symptoms and complications.

Box 19.1 • Considerations for DMDs in Patients With Multiple Sclerosis

1. Clinical trial population effects may not translate to individual patient effect
2. DMDs may affect lesion burden on MRI but not symptomatic relapses
3. DMDs may not impact the progressive disease course (axonal loss)
4. Cost-effectiveness should be considered
5. A tiered approach to treatment should be considered, weighing the risks and benefits of individual medications

Abbreviations: DMD, disease-modifying drug; MRI, magnetic resonance imaging.

Guiding Principles for DMD Use to Prevent Relapses and Disease Progression in MS

Several factors should be considered when deciding on the use of DMDs for patients with MS. These are listed in Box 19.1.

All DMD studies have population-level effects quoted. For example, a 60% reduction in relapse rate reflects the average group data and does not necessarily indicate that in a given individual relapses are reduced by 60%. Individual response may vary from no response to complete response.

All DMDs are much more effective in the prevention of subclinical relapses, as evidenced by new magnetic resonance imaging (MRI) activity, than prevention of clinical relapses. A considerably higher number of silent lesions develops for every symptomatic lesion in MS.

While all DMDs decrease the number of clinical and subclinical relapses and the associated stepwise disability accumulation from incomplete resolution of such disease activity, none of the DMDs have a meaningful impact on a progressive disease course once it is established. All available DMDs target modification or inhibition of inflammation-related demyelination while a progressive disease course is typified by neurodegeneration associated

[a] Portions previously published in Pirko I, Noseworthy JH. Demyelinating disorders of the central nervous system. In: Goetz CG, editor. Textbook of clinical neurology. 3rd ed. Philadelphia (PA): Saunders/Elsevier; c2007. Used with permission.

Abbreviations: ARR, absolute risk reduction; CIS, clinically isolated syndrome; DMD, disease-modifying drugs; FDA, Food and Drug Administration; JCV, JC virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; NNT, number needed to treat; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting multiple sclerosis; RRR, relative risk reduction

with insidious axonal loss in the absence of notable inflammatory activity. Still, in a small subgroup of highly inflammatory forms of secondary progressive MS or primary progressive MS (as evidenced by ongoing relapses or MRI activity superimposed on a progressive disease course), DMD initiation or continuation is justified.

Currently available DMDs are expensive, and cost-effectiveness has to be considered every time a decision is made to initiate such treatment. For example, a group effect of 30% reduction in relapse rate and 50% reduction in new MRI lesion formation typical in response to a DMD justify initiation of treatment without doubt in a patient with 2 relapses within the first year of MS onset, with continued development of new enhancing lesions on serial MRIs. However, a patient whose first presenting event was 15 years ago with a recurrence today and MRI activity that is only minimally changed within this time may suitably be followed with imaging for a while but is unlikely to benefit from the DMD under consideration.

There is an inverse relationship between efficacy and serious complications in DMDs. Because of this risk-benefit balance, a tiered approach to DMD use is necessary, with careful consideration given to moving from 1 tier to another. Currently no evidence-based study exists to guide a specific tiered approach, but experience and common sense should guide it. This approach has to be bidirectional. For example, a patient may be changed to a higher-efficacy, higher-risk tier DMD for a period of time (minimum of 6 months to a year) when the disease activity is increased but can also be brought back to maintenance treatment with one of the lower-tier medications.

Currently (subject to change) 7 US Food and Drug Administration (FDA)–approved DMDs are available in the United States (4 self-injectable, 2 intravenous infusions, 1 oral). The ensuing discussion proceeds in a stage-specific manner for MS starting with a clinically isolated syndrome (CIS) and proceeding to relapsing-remitting MS (RRMS) and to progressive MS.

- The choice of a disease modifying drug is dependent on a number of considerations (Box 19.1).

DMD Use for Specific Syndromes

Clinically Isolated Syndrome

When a patient presents with his or her first clinical event or CIS, it is difficult to know if the patient has a high risk of developing further relapses quickly or will actually have quiet disease for a long time. If DMD therapy is initiated immediately, then when the patient wants to stop treatment after years of inactive disease, it is impossible to judge whether DMD use had a treatment effect. If an observation period starting with tight MRI monitoring (eg, every 6 months) is advocated, then the need for medication is better assessed; however, both the physician and the patient must contend with the uncertainty about the expected disease course. Since long-term disability does not develop in 20% of patients with MS, even when DMDs are not prescribed, one could justify either approach, but an open discussion with the patient about some of the early prognostic indicators may help. For example, early spinal cord involvement, poor recovery from individual relapses, and high active lesion load with back-to-back relapses push for an early treatment decision.

Several studies have shown some benefit of initiating DMDs in CIS. The early trials were done in "high-risk CIS cases," many of which today would be classified as having MS on the basis of 2010 diagnostic criteria. For example, in a patient with CIS, interferon beta-1a, 30 mcg administered weekly by intramuscular injection after an initial course of corticosteroid treatment, resulted in a relative risk reduction (RRR) of 38%, an absolute risk reduction (ARR) of 14.6%, and a number needed to treat (NNT) of 7 patients over 2 years to prevent 1 new clinical relapse. The population effect is limited because 50% of interferon-treated patients in the original trial had clinical or MRI evidence of recurrent disease within 18 months of starting treatment. The odds of NNT seem to be significantly improved if treatment is initiated for patients with brainstem-cerebellar or spinal cord syndrome rather than for those with optic neuritis at presentation. Follow-up in this study (71% at 1 year, 34% at 2 years, 16% at 3 years) was insufficient to determine the long-term benefit from early intervention with interferons.

The more recent study of daily glatiramer acetate vs placebo in 482 patients, based on approximate values from the provided survival curves, revealed an RRR of 40%, ARR of 10% at 1 year, and NNT of about 10 over 1 year.

None of these studies offer guidance when CIS presents with a brain MRI that is not suggestive of MS (ie, only 1 optic nerve, brainstem, or cord lesion) or recommend when initiation of treatment is indicated for CIS patients with fewer than 2 asymptomatic MRI lesions.

Relapsing-Remitting MS

In RRMS, a tiered approach to treatment is commonly used. This tiered approach varies from center to center and is based on the experience of the physician and is individualized to the practice (Box 19.2). Currently all approaches to CIS treatment fall in the tier 1 category of RRMS treatment.

Primary and Secondary Progressive MS

The progressive disease course in MS needs to be separated from disability progression. While all medication used for RRMS can potentially slow disability progression

Box 19.2 • Tiers of DMDs for Multiple Sclerosis

Tier 1
- Interferon beta-1b
- Interferon beta-1a
- High-dose interferon beta-1a
- Glatiramer acetate

Tier 2
- Natalizumab
- Fingolimod

Tier 3
- Mitoxantrone
- Cyclophosphamide

Abbreviation: DMD, disease-modifying drug.

through prevention of relapse-related disability accumulation, the majority of disability progression that is due to progressive disease is not impacted with DMDs. However, certain situations dictate continuation or initiation of treatment in patients with clinical or subclinical (MRI) relapses superimposed on a slowly progressive disease course and in patients in whom the recurrent, only partially healing relapses have the appearance of a progressive disease course but actually represent a rather stepwise disability progression. Any of the agents listed in Box 19.2 for RRMS can be used in these circumstances if appropriate. Unfortunately, none of the currently available DMDs offer any substantial benefit for classic primary progressive MS cases that present with insidious progression of myelopathic symptoms.

- Early spinal cord involvement, poor recovery from individual relapses, and high active lesion load with back-to-back relapses push for an early treatment decision in CIS.
- In RRMS, tiered approach to treatment is commonly used.
- While all medication used for RRMS can potentially slow disability progression through prevention of relapse-related disability accumulation, the majority of disability progression that is due to progressive disease is not impacted with these medications.

Disease-Modifying Drugs

Tier 1 Medications

Tier 1 medications include the interferon beta agents and glatiramer acetate. Adverse effects and monitoring of these medications are summarized in Table 19.1.

Interferon beta-1a and -1b have a generally poorly understood mechanism of action. Initial use of these interferons was guided by the following effects: reduced overall T-cell proliferation and production of tumor necrosis factor α3, decreased antigen presentation, a shift in T-cell response to a type 2 helper T-cell response, an increase in interleukin 10 and interleukin 4 secretion, and reduced immune cell trafficking through the blood-brain barrier by inhibiting adhesion molecules, chemokines, and proteases involved in the trafficking of lymphocytes.

Interferon beta is generally safe to use in MS with a good long-term track record. Adverse effects are noted in Table 19.1. The flulike symptoms generally decrease in intensity after a few months of treatment in most patients. Depression and attempted suicide were more common in the treated groups. Monitoring recommendations are also listed in Table 19.1.

Neutralizing antibodies can occur with all interferons and potentially limit the efficacy but occur half as often

Table 19.1 • Adverse Effects of DMDs for Multiple Sclerosis

Medication	Adverse Effects	Required Monitoring
Interferon beta	Injection site reaction Flulike symptoms (myalgias, low-grade fever, headache) Mildly elevated liver enzymes Lymphopenia	CBC at baseline, 1 mo, then every 3 mo LFTs (same intervals as CBC) TSH (baseline, every 6–12 mo)
Glatiramer acetate	Injection site reaction Chest pain Nausea Dyspnea	None
Natalizumab	Potential for PML	
Fingolimod	Increased risk of herpes infection Bradycardia, AV block Hypertension Macular edema Skin cancer Potential fatal varicella or herpes encephalitis	Baseline eye examination, ECG, test for VZV antibodies, LFTs
Mitoxantrone	Cardiomyopathy (dose dependent) Inhibition of menstrual cycle Leukemia	Echocardiogram or MUGA every 3 mo

Abbreviations: AV, atrioventricular; CBC, complete blood count; DMD, disease-modifying drug; ECG, electrocardiogram; LFT, liver function tests; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scanning; PML, progressive multifocal leukoencephalopathy; TSH, thyroid stimulating hormone; VZV, varicella zoster virus.

with interferon beta-1a than with interferon beta-1b (approximately 40% vs 20%). Switching from 1 preparation to the other does not change the pattern of antibody response. Low-titer neutralizing antibodies may be transient, but persistent high-titer neutralizing antibodies on 2 consecutive tests at least 6 months apart correlate with poor treatment response to interferons and could prompt a switch to a noninterferon preparation, especially if a new-onset increase in clinical and subclinical relapses develops in a patient whose condition has been stable on interferons.

Interferon beta-1b, 8 million IU administered subcutaneously every other day, is the first FDA-approved drug for MS, reducing relapse frequency by one-third (RRR, 18%; ARR, 15%; NNT, 7 patients treated over 3 years to increase the relapse-free number by 1 patient). There was a more prominent reduction in new subclinical lesion activity on MRI than the effect on clinical relapses. The severity of subsequent relapses was also decreased.

Interferon beta-1a, 30 mcg administered intramuscularly once weekly, differs from interferon beta-1b by 1 amino acid as well as by the presence of carbohydrate moieties and has the same amino acid sequence as natural interferon beta. Interferon beta-1a has a similar efficacy (RRR, 16%; ARR, 12%; NNT, 8 patients treated over 2 years to increase the number of relapse-free patients by 1) and adverse effect profile to interferon beta-1b.

High-dose interferon beta-1a, 44 mcg administered subcutaneously 3 times weekly, has a better response than half this dose (RRR, 19%; ARR, 16%; NNT, 6 patients treated over 2 years to increase the number of relapse-free patients by 1). The higher dose is more effective in limiting relapse severity, hospitalizations, MRI activity and lesion-volume accumulation, and possibly long-term disability progression in the most severely affected patients.

Glatiramer acetate, 20 mcg administered subcutaneously daily, is a noninterferon synthetic mixture of polypeptides produced by the random combinations of the 4 most common amino acids in myelin basic protein. Glatiramer acetate has the disadvantage of a slightly weaker population effect than interferons (RRR, 10%; ARR, 7%; NNT, 14 patients treated over 2 years to increase the number of relapse-free patients by 1) and the relative inconvenience of daily subcutaneous use. Glatiramer acetate also has several advantages over interferons: lack of flulike adverse effects, no known impact on depression, lack of need for regular laboratory monitoring, and no formation of neutralizing antibodies. Choice of glatiramer acetate vs low-dose interferons vs high-dose interferons as a first-line DMD in MS needs to be individually guided by disease severity and an open discussion with the patient about relative risks and benefits.

Tier 2 Medications

Tier 2 DMDs are characterized by better efficacy than tier 1 medications but because of their severe adverse effects (Table 19.1) are generally reserved for patients in whom tier 1 medications were ineffective. The exception is the onset of MS characterized by severe, recurrent relapses in a short period. In this case, an induction treatment approach may lead to initiation of tier 2 medications as first-line treatment.

Natalizumab, 200 mg infused monthly, is a humanized a_4 integrin antibody that inhibits the migration of all leukocytes (except for neutrophils) to the brain. Natalizumab reduces the number of gadolinium-enhancing lesions by 90% and the clinical relapse rate by more than 50% compared with placebo, with an annualized relapse rate reduction of 0.74 compared with the placebo group's relapse rate reduction of 0.25 (RRR, 49%; ARR, 23%; NNT, 4 patients treated over 1 year to increase the number of relapse-free patients by 1). As such, natalizumab is considerably more effective than all the previously discussed tier 1 medications.

Unfortunately, natalizumab can lead to progressive multifocal leukoencephalopathy (PML). Natalizumab is available only through the TOUCH Prescribing Program (https://www.touchprogram.com/TTP/), which is meant to provide a company-sponsored safety-monitoring system as well as a partial standardization of the frequency and nature of follow-up visits for patients on natalizumab. The frequency of PML occurrence across the board (subject to change with new data) was about 1 in 1,000 natalizumab recipients in the early studies. The risk can be stratified: the presence of anti–JC virus (JCV) antibodies and a history of prior immunosuppressant use (eg, azathioprine, methotrexate, mitoxantrone, cyclophosphamide) increase the risk to 11 in 1,000 natalizumab recipients.

The JCV antibody test is available free of charge. The result may be a false negative (3%) or may truly convert to positive later. Patients whose test results are negative initially should be rechecked periodically (eg, every 6–12 months). PML leads to death or severe disability over weeks or months. Previous exposure to methotrexate is associated with almost certain risk of death if PML develops. Symptoms of PML progress over days to weeks and include progressive weakness on 1 side of the body, clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation, which lead to confusion and personality changes.

In practice, we recommend natalizumab for patients in whom tier 1 medications fail, who test negative for JCV, and who have no history of chemotherapy exposure, with clear guidelines for monitoring. Despite a positive JCV test during monitoring, if a patient was not exposed to chemotherapy beforehand, the initial 2 years of natalizumab treatment are relatively safe. At the 2-year time point, continuation of treatment is discussed again with the patient. If a patient remains negative for JCV, we recommend continuing medication. If a patient initially tests positive for

JCV, and other medication options could not be entertained, initiation of natalizumab requires careful discussion with a properly educated patient with full understanding of the inherent risks. Biogen Idec Inc continuously updates risk estimates on their website (http://www.biogenidec.com/).

Fingolimod, 1.25 mg orally daily, is the first oral DMD approved for MS. Fingolimod inhibits lymphocyte egress from secondary lymphoid tissues and thymus by acting on the S1P1 receptor. Compared with weekly interferon beta-1a, fingolimod was superior in terms of annual relapse rate reduction (RRR, 50%; ARR, 22%; NNT, 4 patients treated over 2 years to increase the number of relapse-free patients by 1) and MRI measures.

Adverse effects are noted in Table 19.1. Because of a cardiac death within the first 6-hour monitoring period (required for all patients after first dose), fingolimod is not advised in patients with certain preexisting or recent (within last 6 months) heart conditions, baseline QTc interval of 500 ms or longer, treatment with class Ia or class III antiarrhythmic drugs, transient ischemic attack, or stroke. For patients without risk factors but deemed at high risk of bradycardia, overnight electrocardiographic monitoring is recommended. An eye examination prior to treatment, along with assessment of varicella zoster virus serum status, vaccination for seronegative patients, and pretreatment liver function tests are generally recommended.

Overall, fingolimod is more effective than at least one tier 1 medication but appears less so than natalizumab. Because of its adverse effect profile and as-yet-unclear long-term safety, it is generally reserved as a tier 2 alternative to natalizumab.

Tier 3 Medications

Cyclophosphamide and mitoxantrone can be used as tier 3 choices in very aggressive, hard-to-manage cases. These medications have been replaced largely by natalizumab, and certainly the increased PML risk following the use of chemotherapy agents dictates that natalizumab has to be tried before any chemotherapy approach is entertained.

Mitoxantrone, total lifetime dose of 140 mg/m^2 in divided doses, administered by intravenous infusion every 3 months, is an anthracenedione chemotherapeutic agent licensed for reducing neurologic disability and the frequency of clinical relapses in patients with early secondary progressive MS, progressive relapsing MS, or stepwise worsening RRMS. The common theme in all these situations is the insufficient recovery from relapses. In previous studies and in our experience, this DMD has been successful in stabilizing the disease course in the above circumstances (NNT: 11 patients with secondary progressive MS need to be treated for 2 years to prevent 1 person from worsening by 1.0 Expanded Disability Status Scale point). This modest benefit must be carefully examined in light of the risk for toxicity (Table 19.1). Since cardiomyopathy is dose dependent, we suggest the lifetime dose not exceed 96 mg/m^2 (8 doses of 12 mg/m^2).

Cyclophosphamide can be used in induction and maintenance therapy in selected cases of progressive MS. The most likely patients to respond to this treatment are the ones with ongoing MRI-detectable inflammatory activity. The protocols vary, and the evidence for use of cyclophosphamide is less robust than that for mitoxantrone. The anecdotal experience reported by some groups that use this medication extensively suggests the circumstances of use are similar to those for mitoxantrone as a tier-3 medication.

- Neutralizing antibodies can occur with all interferons and potentially limit the efficacy but occur half as often with interferon beta-1a than with interferon beta-1b (approximately 40% vs 20%).
- Persistent high-titer neutralizing antibodies on 2 consecutive tests at least 6 months apart correlate with poor treatment response to interferons and could prompt a switch to a noninterferon preparation, especially if a new-onset increase in clinical and subclinical relapses develops in a patient whose condition has been stable on interferons.
- Glatiramer acetate has several advantages over interferons: lack of flulike adverse effects, no known impact on depression, lack of need for regular laboratory monitoring, and no neutralizing antibody formation.

Table 19.2 • Symptomatic Treatment in Patients With Multiple Sclerosis

Symptom	Treatment
Fatigue	Modafinil SSRI
Spasticity	Occupational and physical therapy Baclofen Tizanidine
Paroxysmal symptoms and pain	Carbamazepine Phenytoin Gabapentin Tricyclic antidepressants OnabotulinumtoxinA for spasms
Depression	SSRI Tricyclic antidepressants
Cerebellar tremor	Clonazepam Valproic acid Isoniazid Thalamic stimulator

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

- Natalizumab reduces the number of gadolinium-enhancing lesions by 90% and the clinical relapse rate by more than 50%.
- The frequency of PML occurrence across the board (subject to change with new data) was about 1 in 1,000 natalizumab recipients in the early studies. The risk can be stratified: presence of anti–JCV antibodies and a history of prior immunosuppressant use (eg, azathioprine, methotrexate, mitoxantrone, cyclophosphamide) increase the risk to 11 in 1,000 natalizumab recipients.

Treatment of Individual Relapses and Symptoms

For patients with an acute relapse, treatment is generally 3 to 7 days of intravenously administered methylprednisolone. Plasma exchange could be considered in refractory cases. Table 19.2 lists potential treatment options for symptomatic treatment in patients with MS.

20 Mimickers of Multiple Sclerosis

JESSICA P. FLOYD, MD; ELIZABETH A. SHUSTER, MD

Introduction

Many conditions can mimic multiple sclerosis (MS) in clinical presentation and radiographic appearance (Box 20.1). The conditions that mimic MS can span a wide spectrum of causes, including non-MS inflammatory conditions, immune-mediated diseases, infectious diseases, genetic diseases, nutritional deficiencies, and even medications. The key to the correct diagnosis depends on carefully evaluating the onset and course of the disease and identifying clinical features, risk factors, and typical radiographic features. Even for the most experienced of clinicians, however, the most difficult cases may require pathologic diagnosis.

This chapter reviews the differential diagnosis of focal and multifocal presentations of diseases mimicking MS and also reviews selected diseases in more detail.

- Many conditions can mimic MS in clinical presentation and radiographic appearance.

Box 20.1 • Differential Diagnosis of Multiple Sclerosis

- Vascular
  - Stroke (thromboembolic, phospholipid antibody syndrome, mitochondrial, moyamoya, CADASIL)
  - Migraine
  - Vasculitis: isolated CNS (granulomatous) vasculitis, Susac syndrome, Eales disease
  - Intravascular lymphoma
  - Amyloid beta peptide–related angiitis
  - Spinal dural arteriovenous fistula
  - Posterior reversible encephalopathy syndrome
- Infectious
  - Human immunodeficiency virus
  - Human T-lymphotropic virus 1 (myelopathy)
  - Lyme disease
  - Syphilis
  - Progressive multifocal leukoencephalopathy
  - Subacute sclerosing panencephalitis
  - Viral myelitis
  - Whipple disease
  - Postinfectious disorders
- Inflammatory
  - Neuromyelitis optica
  - Acute disseminated encephalomyelitis
  - Systemic lupus erythematosus
  - Sjögren syndrome
  - Behçet syndrome
  - Inflammatory bowel disease

(Continued on next page)

Focal Presentations

The most common focal presentations of MS are isolated optic neuritis, transverse myelitis, and brainstem syndromes, including internuclear ophthalmoplegias, ataxia, and vertigo.

Optic Neuritis

Definition and Etiology

Optic neuritis results from inflammation of the optic nerve. This typically results in reduced visual acuity, reduced

Abbreviations: CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF, cerebrospinal fluid; CNS, central nervous system; HIV, human immunodeficiency virus; Ig, immunoglobulin; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuromyelitis optica

(Continued)

- Sarcoidosis
- Granulomatosis with polyangiitis (Wegener)

Neoplastic/paraneoplastic
- Gliomatosis cerebri
- Metastases
- Primary CNS lymphoma
- Intravascular lymphoma
- Paraneoplastic disorders

Toxic/metabolic
- Zinc toxicity
- Nitrous oxide
- Toluene and other solvents
- Vitamin B_{12} or E deficiency
- Central pontine myelinolysis
- Alcohol excess (Marchiafava-Bignami disease)
- Lead
- Carbon monoxide

Medications/drugs
- Cocaine
- Chemotherapy (5-fluorouracil-levamisole, methotrexate)
- Cyclosporine
- Phenytoin
- Metronidazole
- Tumor necrosis factor inhibitors

Degenerative
- Primary lateral sclerosis, amyotrophic lateral sclerosis
- Hereditary spastic paraparesis
- Spinocerebellar degeneration

Genetic
- Leber hereditary optic neuropathy
- Leukodystrophies
- Mitochondrial encephalopathy
- CADASIL

Trauma

Other
- Spinal cord compression
- Chiari malformation
- Syrinx

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system.

color vision, and swelling of the optic nerve (atrophy in late stages). Although MS is the most common cause, many conditions can cause optic neuritis (Box 20.2).

Optic Neuritis Due to MS

Optic neuritis associated with MS is most often unilateral. Most, but not all, patients experience periocular pain and pain on eye movement. Loss of central visual acuity is most common, and altitudinal defects are less so. Color desaturation accompanies loss of visual acuity. Ophthalmologic examination can show moderate to severe disc swelling with no hemorrhages if the anterior portion of the optic nerve is involved; the results can be entirely normal except for an afferent pupillary defect if the more posterior portion is involved (retrobulbar neuritis). Visual field defects are common and can vary from centrocecal or central scotoma to diffuse loss; rarely, altitudinal or quadrantic visual field defects are found.

When the visual loss is complete or bilateral and pain is absent, severe, or gradual, other conditions should be strongly considered.

Box 20.2 • Conditions That Cause Optic Neuritis

CNS demyelinating disorders
- Multiple sclerosis
- Neuromyelitis optica

Systemic autoimmune disease
- Sarcoidosis
- Systemic lupus erythematosus
- Sjögren syndrome
- Behçet syndrome

Infectious/parainfectious conditions
- Spirochetes: *Borrelia burgdorferi* (Lyme disease), *Treponema pallidum* (syphilis), leptospirosis
- Bacteria: β-Hemolytic streptococcal infection, *Bartonella henselae* (cat-scratch disease), *Neisseria* meningococcal infection, *Salmonella typhi, Tropheryma whipplei, Brucella, Mycobacterium tuberculosis*
- Viral: dengue fever virus, mumps virus, rubeola virus (measles), varicella zoster virus, coxsackievirus, West Nile virus, adenovirus sp, chikungunya virus
- Parasite: *Toxoplasma gondii*

Postinfectious/post-vaccination conditions
- After respiratory infections and vaccinations against tuberculosis, hepatitis B, rabies, tetanus, meningitis, anthrax, measles, rubella, influenza

Abbreviation: CNS, central nervous system.

Adapted from Hoorbakht H, Bagherkashi F. Optic neuritis, its differential diagnosis and management. Open Ophthalmol J. 2012;6:65–72. Epub 2012 Jul 24. Used under the Creative Commons License.

Treatment and Prognosis

Intravenous methylprednisolone is usually recommended and aids to improve vision faster. The prognosis is favorable for optic neuritis due to MS; up to 90% of patients achieve at least 20/40 vision or better after 1 year. In patients with isolated optic neuritis, MS may develop

within 5 years in 30%. The likelihood is higher if results of magnetic resonance imaging (MRI) are abnormal (see Chapter 18, "The Diagnosis of Multiple Sclerosis").

Brainstem and Cerebellar Presentation

Definition and Etiology

Patients may present with subacute symptoms related to the brainstem, cerebellum, or both. The differential diagnosis of disorders affecting the brainstem or cerebellum is broad (see Chapter 49, "Disorders of Cranial Nerves and Brainstem"). Bickerstaff encephalitis, celiac disease, Behçet syndrome, Alexander disease, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), and central pontine myelinolysis may all predominantly affect the brainstem and mimic demyelinating disease due to MS. These entities are described below and summarized in Table 20.1.

Brainstem and Cerebellar Symptoms Due to MS

Symptoms attributable to brainstem or cerebellum involvement in MS commonly include the following: bilateral or unilateral internuclear ophthalmoplegia, ataxia of eye movements and multidirectional nystagmus, trigeminal neuralgia, sixth nerve palsy, facial numbness, vertigo, and gait or limb ataxia. Less common symptoms include facial palsy, facial myokymia, deafness, one-and-a-half syndrome, and paroxysmal tonic spasms.

The following symptoms are atypical for MS: complete external ophthalmoplegia, vertical gaze palsies, vascular territory syndrome such as lateral medullary syndrome, third nerve palsy, progressive trigeminal sensory neuropathy, focal dystonia, or torticollis. If these are present, alternative diagnoses should be considered and investigated.

Spinal Cord Presentation

Definition and Etiology

The differential diagnosis of myelopathy is broad (see Chapter 38, "Myelopathies"). Distinguishing myelopathy due to MS from other causes includes historical features, radiographic features, and, often, additional evaluation such as spinal fluid examination and laboratory testing.

Myelopathy in MS

Spinal cord involvement in MS is typically an incomplete myelitis with dorsal column sensory features predominating. It can be associated with Lhermitte phenomenon and segmental pain that encircles the trunk, sometimes called the "MS hug." Specific spinal cord syndromes include the deafferent hand; limb numbness without weakness; numbness or pain that mimics radiculopathy; urinary urgency or incontinence; and sexual arousal or erectile dysfunction. Primary progressive MS most often presents with a progressive spastic paraplegia that is typically asymmetric.

Uncommon to MS is a spinal cord presentation with complete transverse myelitis; symmetric, either acute or progressive, spastic paraplegia; fasciculations of lower motor neuron involvement; hyporeflexia or areflexia; segmental loss of pain and temperature sensation; sparing of the posterior columns; and bowel incontinence. These features should raise the possibility for an alternative diagnosis.

Radiographically, an MS lesion of the cord typically affects one or 2 spinal cord segments. A contiguous spinal cord lesion on MRI extending 3 or more segments may be more indicative of neuromyelitis optica.

- Uncommon to MS is a spinal cord presentation with complete transverse myelitis.
- A contiguous spinal cord lesion on MRI extending 3 or more segments may be more indicative of neuromyelitis optica.

Multifocal Presentation

Disorders that present with multifocal symptoms and signs can resemble MS. The diagnostic criteria for MS rely heavily on multiple lesions seen on brain MRI, as reviewed in Chapter 18, "The Diagnosis of Multiple Sclerosis." Multifocal symptoms, and particularly multifocal lesions in the white matter in the brain, are not uncommon with aging, and determining the nature and the significance of multiple cerebral white matter lesions is one of the biggest challenges the neurologist faces. Clinical clues that should raise concern that the cause is not MS include considerable cognitive impairment, aphasia, prominent psychiatric symptoms, change in level of consciousness, seizures, severe headaches, and a time course that is subacute and progressive.

Selected Disorders and Conditions

Neuromyelitis Optica

Overview and Pathogenesis

Neuromyelitis optica (NMO) is an inflammatory demyelinating condition often misdiagnosed as MS. It was once considered a variant of MS, but it is emerging as an entirely different entity. Antibodies to aquaporin-4, a water channel, likely are involved in the pathogenesis.

Clinical Features

The classic clinical features include optic neuritis and myelopathy (most commonly cervical level). Symptoms may present simultaneously or as separate events. With NMO, the visual loss is often more severe and complete blindness is more common than with MS. Similarly, the myelopathy may be more severe with less recovery than expected in MS.

Table 20.1 • Conditions With Brainstem and Cerebellar Presentations

Disease	Clinical and MRI Findings	Diagnostic Features
Bickerstaff brainstem encephalitis	Drowsiness or coma, progressive external ophthalmoplegia, ataxia, and corticospinal tract signs History of viral illness MRI: 10%-31% with MRI changes; nonenhancing lesion in the brainstem, homogeneous CSF: increased protein	Serum anti-ganglioside GQ1b IgG antibodies present in majority of cases
Central pontine myelinolysis	Brainstem signs in setting of overcorrection of hyponatremia Risk factors: alcohol abuse, malnutrition, hospitalization, rapid correction of hyponatremia MRI: osmotic demyelination on diffusion-weighted series; definitive MRI changes may not be readily apparent CSF: normal	History of serum sodium trends plus clinical brainstem syndrome
Celiac disease	Cerebellar ataxia, peripheral neuropathy, epilepsy, dementia, depression, headache MRI: typically normal CSF: normal	Serum IgA antibodies to tissue transglutaminase to screen for disease Small bowel biopsy is diagnostic
Behçet syndrome	Young age Mediterranean origin Male > female Oral ulcers Common symptoms: headache, motor, cerebellar, brainstem MRI: large, diffuse brainstem lesions with superior and inferior extension CSF: inflammatory changes, <20% OCB	Clinical picture of systemic symptoms meeting diagnostic criteria
CLIPPERS syndrome	Episodic diplopia or facial paresthesias with subsequent brainstem with or without myelopathic symptoms MRI: symmetric curvilinear gadolinium enhancement peppering the pons with variable extension to other structures (medulla, brachium pontis, cerebellum, midbrain, spinal cord) CSF: increased OCB, mildly increased protein	Characteristic MRI appearance Favorable response to corticosteroids Biopsy possibly needed to confirm, if deemed safe
Focal brainstem glioma	Localized brainstem findings with or without hydrocephalus MRI: large brainstem lesion; typically cystic, well demarcated, noninfiltrating, typically without associated edema CSF: cytologic result possibly positive; otherwise normal	Stereotactic biopsy needed for tissue diagnosis if not able to diagnose by imaging alone Cytologic testing on CSF may be possible
Stroke	Clinical: acute onset of symptoms, vascular risk factors MRI: restricted diffusion with ADC correlate adheres to vascular territory CSF: normal	MRI is diagnostic of acute stroke
Neurosarcoidosis	Clinical: uveitis, arthritis, CNS involvement (cranial nerve 7 neuropathy is most common), peripheral lymphadenopathy, bilateral hilar lymphadenopathy on chest CT MRI: parenchymal lesions with increased T2 signal; leptomeningeal, parenchymal, and nerve root enhancement CSF: may show increased opening pressure, increased protein, decreased glucose, pleocytosis, increased immunoglobulin G index, OCBs, and ACE	Biopsies of relevant tissues are necessary for diagnosis in clinically suspected cases: skin, conjunctiva, lymph node, lung, nerve root, or nerve
Alexander disease	Childhood-adolescent presentation with variable clinical presentation: gait disorder, nystagmus, dysphagia and weight loss, hydrocephalus MRI: brainstem lesions and brainstem atrophy raise suspicion of diagnosis; extensive symmetric cerebral white matter abnormalities with frontal preponderance (extent, swelling, signal change, atrophy, cystic degeneration); periventricular rim of low signal on T2-weighted image (high on T1-weighted image); signal abnormalities with swelling or atrophy of basal ganglia or thalami; brainstem lesions; contrast enhancement of one or more of the following: ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, cerebellar cortex, brainstem	DNA diagnostics

Abbreviations: ACE, angiotensin-converting enzyme; ADC, apparent diffusion coefficient; CSF, cerebrospinal fluid; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CT, computed tomography; MRI, magnetic resonance imaging; OCB, oligoclonal bands.

Diagnosis

Clinical features may be useful in conjunction with radiographic findings. In NMO, spinal cord imaging tends to show a longitudinally extensive lesion (3 or more vertebral segments) (Figure 20.1). Results of brain imaging can be negative early on. Cerebrospinal fluid (CSF) may show pleocytosis, but oligoclonal bands are usually absent. NMO-immunoglobulin (Ig)G serum antibodies may be a specific marker for NMO.

Suggested diagnostic criteria require at least 2 of the 3 following characteristics: 1) longitudinally extensive spinal cord lesion (3 or more contiguous segments), 2) brain MRI results that do not meet MS criteria, and 3) seropositive NMO-IgG antibody.

Treatment

Early differentiation of NMO from MS is important because NMO can worsen with chronic β-interferon therapy and possibly with other MS disease-modifying agents. For acute attacks, corticosteroids and plasmapheresis are considered. For prevention of attacks, immunosuppression therapy, such as azathioprine, mycophenolate mofetil, or rituximab, is considered.

The clinical course may be monophasic, but most patients have a relapsing clinical course.

- Antibodies to aquaporin-4, a water channel, likely are involved in the pathogenesis of neuromyelitis optica.
- The classic clinical features of neuromyelitis optica include optic neuritis and myelopathy (most commonly cervical level).
- Suggested diagnostic criteria for neuromyelitis optica require at least 2 of the 3 following characteristics: 1) longitudinally extensive spinal cord lesion (3 or more contiguous segments), 2) brain MRI results that do not meet MS criteria, and 3) seropositive NMO-IgG antibody.
- Early differentiation of NMO from MS is important because NMO can worsen with chronic β-interferon therapy and possibly with other MS disease-modifying agents.

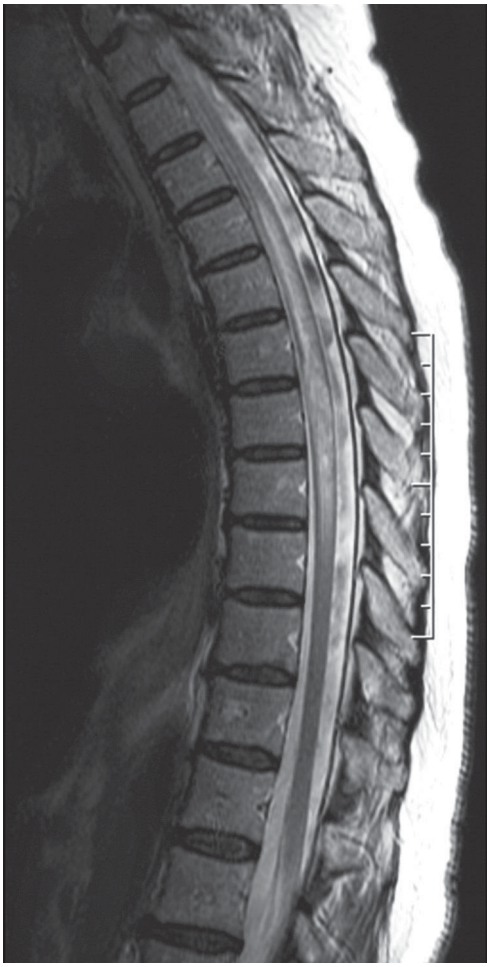

Figure 20.1 *Magnetic Resonance Imaging Findings in a Patient With Neuromyelitis Optica.*
Complete acute transverse myelitis in sagittal T2 image. T2 hyperintensity is excessive in thoracic spinal cord, extending from T3–4 to T9. (Adapted from Kantarci OH. Inflammatory and demyelinating disorders of the central nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 559–88. Used with permission of Mayo Foundation for Medical Education and Research.)

Celiac Disease

Overview

Celiac disease is an immune-mediated disease with an immune response toward various protein components of gluten. The disease affects up to 1% of the population. Many autoantibodies are associated with celiac disease, including antigliadin, antiendomysial, and antitransglutaminase antibodies. Central nervous system (CNS) involvement can be direct autoimmune or can be due to nutritional deficiencies because celiac disease affects small-bowel absorption.

Clinical Features

Like MS, celiac disease can cause relapsing neurologic deficits depending on the nutritional state. Because celiac disease can occur with MS, determining which disorder is most relevant in explaining neurologic signs and symptoms is particularly difficult. Celiac disease can present at any age with only neurologic signs. Ataxia and brainstem signs are not uncommon. (See Chapter 26, "Cerebellar Disorders and Ataxias.")

Diagnosis

MRI in patients with celiac disease may show periventricular white-matter lesions indistinguishable from those of MS, but results of CSF examination will be normal, except in the case of antigliadin antibodies in the CSF. The best screening test for celiac disease is serum IgA antibodies to transglutaminase; however, small-bowel biopsy is necessary to confirm the diagnosis.

Treatment

As with any chronic malabsorptive gastroenterologic disorder, careful monitoring of nutritional status is important for the prevention or treatment of neurologically relevant nutrient depletion.

- Ataxia and brainstem signs are not uncommon in celiac disease. (See Chapter 26, "Cerebellar Disorders and Ataxias.")

Behçet Syndrome

Overview and Epidemiology

Behçet syndrome is a multisystem, vascular inflammatory disease of unclear cause. The age at onset is similar to that for MS. Unlike MS, it is more common in men than women. Nervous system involvement most commonly presents as a brainstem syndrome or cerebral venous sinus thrombosis. Behçet syndrome is endemic to the Middle East, but it occurs worldwide.

Clinical Features

Neuro-Behçet syndrome can have a relapsing-remitting course initially and eventually have a progressive course later in the disease, much resembling the clinical course of MS. In virtually all cases of neuro-Behçet syndrome, the patient already has systemic evidence of the multisystem disease, most commonly the recurrent oral aphthous ulcers. Other systemic manifestations may include recurrent genital ulcerations that are deep and painful with irregular margins and leave scars and skin lesions ranging from folliculitis to papulopustular lesions. Acneiform lesions are more common in men, and erythema nodosum is more common in women. Eye lesions consist of a chronic relapsing posterior and anterior uveitis with blurred vision, decreased visual acuity, pain, and conjunctival hyperemia. Cardiovascular involvement is not uncommon. Cardiovascular manifestations include arterial aneurysms such as pulmonary artery aneurysms with risk of hemoptysis that can be fatal. Behçet syndrome, much like lupus and Buerger disease, can uniquely involve both the venous and the arterial vasculature. A tendency in Behçet syndrome is development of post-venipuncture venous thromboses, which would be important to screen for in the history.

Diagnosis

MRI findings in neuro-Behçet syndrome are thought to be pathognomonic (Figure 20.2), but they may not be recognized given that it is a relatively uncommon disorder in the United States. In contrast to MS, the most commonly affected region is the mesodiencephalic junction, and the pontobulbar region is the second most commonly affected. These lesions typically show an extension upward into the thalamus and basal ganglia. In contrast to MS, hemispheric lesions are uncommon; if they are present, they are almost invariably associated with the brainstem lesions or basal ganglia lesions described above. CSF examination can show pleocytosis and, infrequently, oligoclonal banding. Biopsy of mucocutaneous ulcers is definitive.

Treatment

Neuro-Behçet syndrome is usually highly responsive to corticosteroids.

- Nervous system involvement in Behçet syndrome most commonly presents as a brainstem syndrome or cerebral venous sinus thrombosis.
- In virtually all cases of neuro-Behçet syndrome, the patient already has systemic evidence of the multisystem disease, most commonly the recurrent oral aphthous ulcers.
- Eye lesions in Behçet syndrome consist of a chronic relapsing posterior and anterior uveitis.

Chronic Lymphocytic Inflammation With Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS)

Overview

CLIPPERS is an uncommon, recently recognized, presumably inflammatry CNS disorder with characteristic radiographic features.

Clinical Features

CLIPPERS is a chronic inflammatory CNS disorder that can mimic MS. Patients may present with episodic diplopia or facial paresthesias and subsequently have development of brainstem and occasionally myelopathic symptoms, including ataxia, dysarthria, diplopia, pseudobulbar affect, nausea, fatigue, dizziness, nystagmus, and paraparesis.

Diagnosis

The MRI findings all show symmetric punctate, curvilinear gadolinium enhancement, termed *peppering*, concentrated in the pons that extends variably into the medulla, brachium pontis, cerebellum, midbrain, and occasionally the cerebrum and spinal cord (Figure 20.3). The MRI

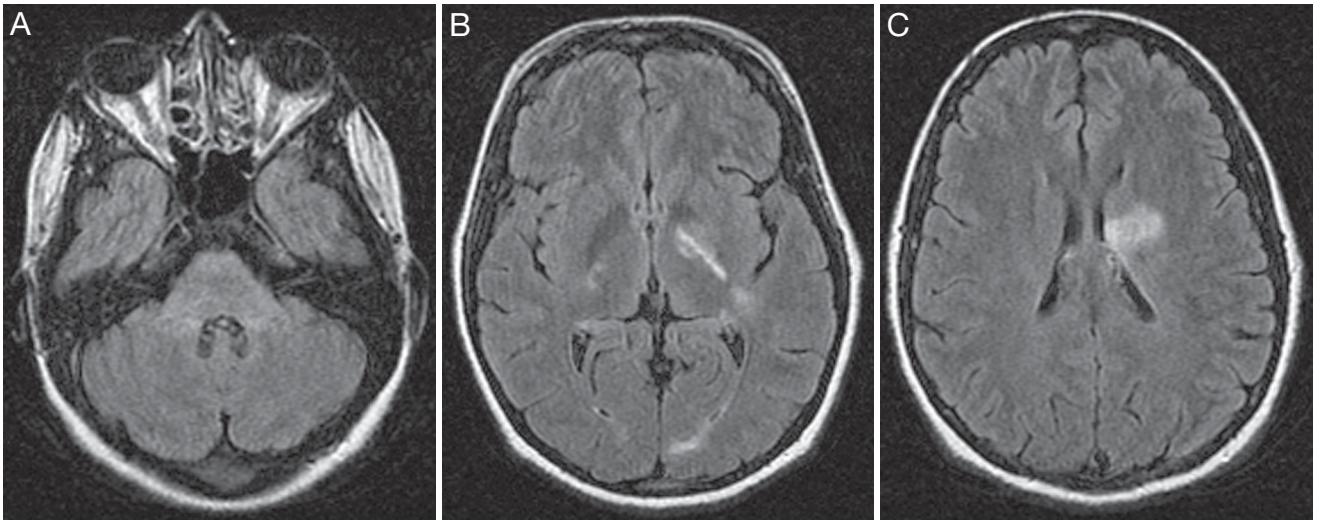

Figure 20.2 *Magnetic Resonance Imaging Findings in a Patient With Behçet Syndrome.*
Fluid-attenuated inversion recovery imaging shows multifocal T2-signal prolongation in the pons and middle cerebellar peduncles (A) and subcortical cerebral white matter (B and C).

findings, however, are not pathognomonic. Infections, neurosarcoidosis, CNS lymphoma, and CNS vasculitis can have a similar appearance. Diagnosis may require biopsy.

Treatment

The clinical symptoms and MRI lesions respond to treatment with glucocorticoids. CLIPPERS was recently reported in a patient with MS after discontinuation of treatment with natalizumab and was thought to be due to immune reconstitution syndrome.

- Patients with CLIPPERS may present with episodic diplopia or facial paresthesias and subsequently have development of brainstem and occasionally myelopathic symptoms.

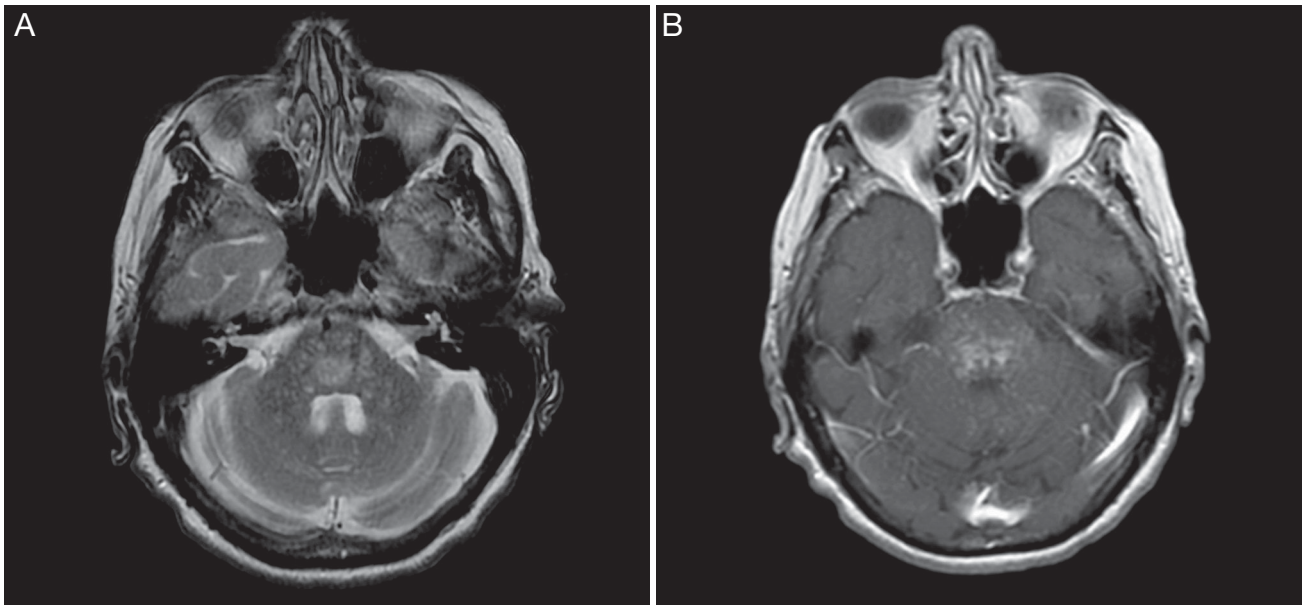

Figure 20.3 *Characteristic Magnetic Resonance Imaging Findings in a Patient With Chronic Lymphocytic Inflammation With Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS).*
T2-weighted imaging shows punctate T2-signal prolongation "peppering" the pons (A) with corresponding gadolinium-contrast enhancement (B).

Alexander Disease

Overview

Alexander disease rarely can present as a mimicker of MS, both radiographically and in clinical presentation. This disease is a rare leukoencephalopathy characterized by extensive white-matter abnormalities with frontal predominance. The mutations underlying the disease are in the glial fibrillary acidic protein and are typically de novo mutations; thus, a family history is typically negative.

Clinical Features

Patients typically present in early life to childhood, but adolescent and young adult presentations are not uncommon. Clinical presentation can be extremely broad depending on the age of the patient at time of disease manifestation. Young adults can present with cerebellar ataxia, gait problems, nystagmus, vertigo, and scoliosis.

Diagnosis

MRI findings include extensive symmetric, cerebral white-matter abnormalities with frontal preponderance (Figure 20.4). Initially the CNS involvement includes swelling of the affected structures, and this is followed by atrophy later in the disease. The proposed 2001 MRI diagnostic criteria for Alexander disease work well in typical patients; however, even patients with some but not all 5 MRI criteria should be considered for genetic testing, which will confirm the diagnosis. Before DNA diagnosis, Rosenthal fibers on brain biopsy were diagnostic of the disease.

Treatment

Patients with Alexander disease require supportive care. Comorbid seizures may be treated with antiepileptic medications. Currently, there are no accepted disease-modifying therapies.

- Young adults with Alexander disease can present with cerebellar ataxia, gait problems, nystagmus, vertigo, and scoliosis.
- Before DNA diagnosis, Rosenthal fibers on brain biopsy were diagnostic of Alexander disease.

Systemic Autoimmune Disease

Sjögren Syndrome

Sjögren syndrome is associated with serologic results that are positive for SS-A (Ro) and SS-B (La) autoantibodies. Dry eyes can be documented with the rose bengal test. Salivary gland biopsy can be performed if the diagnosis remains in question. In addition to its association with MS, Sjögren syndrome can coexist with neuromyelitis optica.

Systemic Lupus Erythematosus

Systemic lupus erythematosus and mixed connective tissue disease can be associated with diffuse systemic symptoms, including fevers, fatigue, photosensitive skin, malar rash, and arthralgias. Cytopenias are common. Serologic results may include increased titers of antinuclear antibody and double-stranded DNA autoantibodies; systemic involvement of the skin, kidneys, and hematologic systems should be sought. Scleroderma can produce a vasculopathy and subsequent focal neurologic symptoms with MRI abnormalities in the white matter. Raynaud disease, digital ischemia, and trouble with swallowing commonly occur with scleroderma. The serologic markers that are most specific are positive centromere and Scl-70 antibodies.

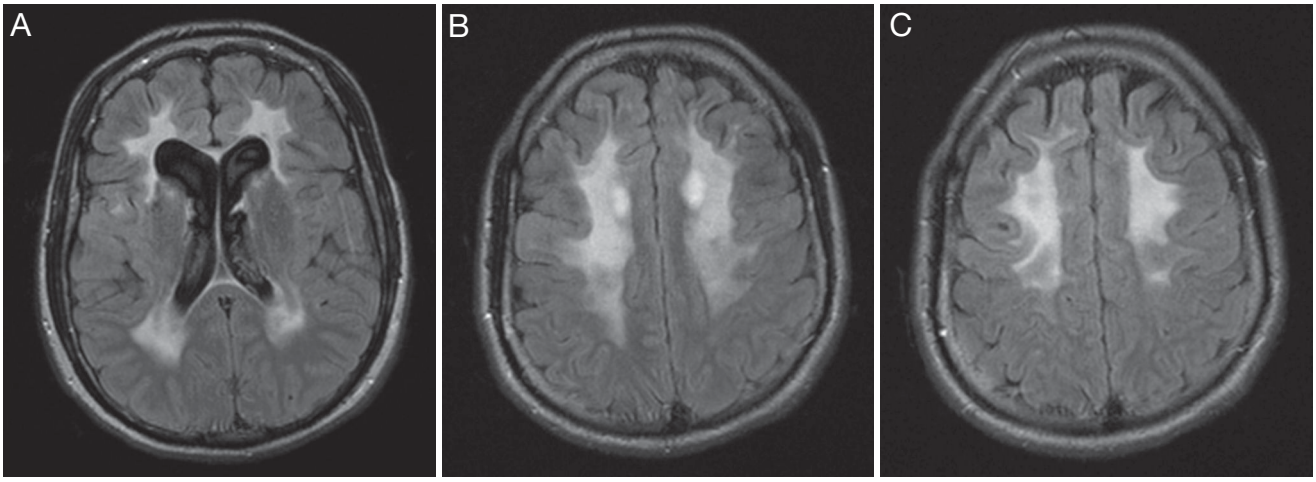

Figure 20.4 *Magnetic Resonance Imaging Findings in a Patient With Alexander Disease.*
Fluid-attenuated inversion recovery imaging shows anterior-predominant confluent T2-signal prolongation of the subcortical white matter (A–C).

Hashimoto Encephalitis

Encephalopathy with increased thyroperoxidase antibody titers, sometimes referred to as Hashimoto encephalitis, can cause a relapsing encephalopathy with focal neurologic symptoms and strokelike episodes. Patients can have prominent myoclonus.

Sarcoidosis

Overview and Epidemiology

Sarcoidosis is a multisystem, idiopathic, noncaseating granulomatous disease most prevalent in African Americans and women. Approximately 50% of patients with neurologic involvement present with neurologic disease.

Clinical Features

Common systemic manifestations include pulmonary involvement with bilateral hilar adenopathy and pulmonary infiltrates, uveitis, cutaneous manifestations such as erythema nodosum, myositis, and arthritis. Anemia occurs with bone marrow involvement. Intermittent fevers can occur.

Symptomatic nervous system involvement occurs in 3% to 5% of patients with sarcoidosis. The central nervous system, peripheral nervous system, or muscle can be involved. In some cases, the first manifestations of sarcoidosis may be related to the nervous system.

Central nervous system sarcoidosis can present as intracranial parenchymal disease due to inflammatory infiltration of the parenchyma from leptomeningeal or ependymal surfaces and as spinal cord disease manifesting as acute, subacute, or chronic myelopathy. Optic neuropathy can occur. Pituitary-hypothalamic dysfunction may lead to diabetes insipidus, somnolence, obesity, or hypopituitarism. Other features may include aseptic meningoencephalitis, hydrocephalus, and multiple cranial neuropathies due to basilar meningitis; these can occur in sarcoidosis but not MS. The most common cranial neuropathy is a facial neuropathy (lower motor neuron VII) due to meningeal inflammation.

Peripheral nervous system involvement is usually a symmetric distal polyneuropathy or, less commonly, a polyradiculoneuropathy with cauda equina leptomeningeal involvement. An asymmetric polyneuropathy due to mononeuritis multiplex may also occur.

Muscle involvement, most often asymptomatic or mild, is present in up to 50% of patients. There can be an acute or chronic myositis with pain, tenderness, and muscle weakness that is more proximal than distal. A nodular, patchy myositis can also occur.

Diagnosis

In patients with central nervous system symptoms, MRI of the brain with contrast may show parenchymal lesions with increased T2 signal and leptomeningeal and parenchymal enhancement (Figure 20.5).

Serum and urine calcium concentrations may be increased. Serum angiotensin-converting enzyme levels are increased in 30% to 70% of patients with sarcoidosis, but this finding is nonspecific. CSF examination may show increased opening pressure, mononuclear CSF pleocytosis with variable cell counts, low glucose value, and increased CSF protein level. Angiotensin-converting enzyme levels can be determined from CSF, but the impact on making the diagnosis is unclear. Chest radiography or chest computed tomography may show the characteristic hilar lymphadenopathy.

Biopsy of appropriate tissue (skin, conjunctiva, lymph node, lung, brain) is useful for diagnosis if tissue is readily accessible (Figure 20.6). It shows noncaseating granulomas and absence of any infection or lymphoma markers.

Treatment

Initially, corticosteroids are used. For long-term treatment, a steroid-sparing agent is often used, such as methotrexate, azathioprine, cyclosporine, or cyclophosphamide.

In two-thirds of patients, the disease course is monophasic. However, the remainder have a progressive or relapsing-remitting course.

- Common systemic manifestations of sarcoidosis include pulmonary involvement with bilateral hilar adenopathy and pulmonary infiltrates, uveitis, cutaneous manifestations such as erythema nodosum, myositis, and arthritis.
- In sarcoidosis, pituitary-hypothalamic dysfunction may lead to diabetes insipidus, somnolence, obesity, or hypopituitarism.
- The most common cranial neuropathy of sarcoidosis is a facial neuropathy (lower motor neuron VII) due to meningeal inflammation.
- In patients with sarcoidosis who have central nervous system symptoms, MRI of the brain with contrast may show parenchymal lesions with increased T2 signal and leptomeningeal and parenchymal enhancement (Figure 20.5).
- In sarcoidosis, CSF examination may show increased opening pressure, mononuclear CSF pleocytosis with variable cell counts, low glucose value, and increased CSF protein level.
- Biopsy in sarcoidosis shows noncaseating granulomas and absence of any infection or lymphoma markers.

Ischemic Stroke

Stroke can present with focal neurologic deficits mimicking symptoms of MS. Very acute onset, or progression over a few minutes, is characteristic of stroke; progression over hours or

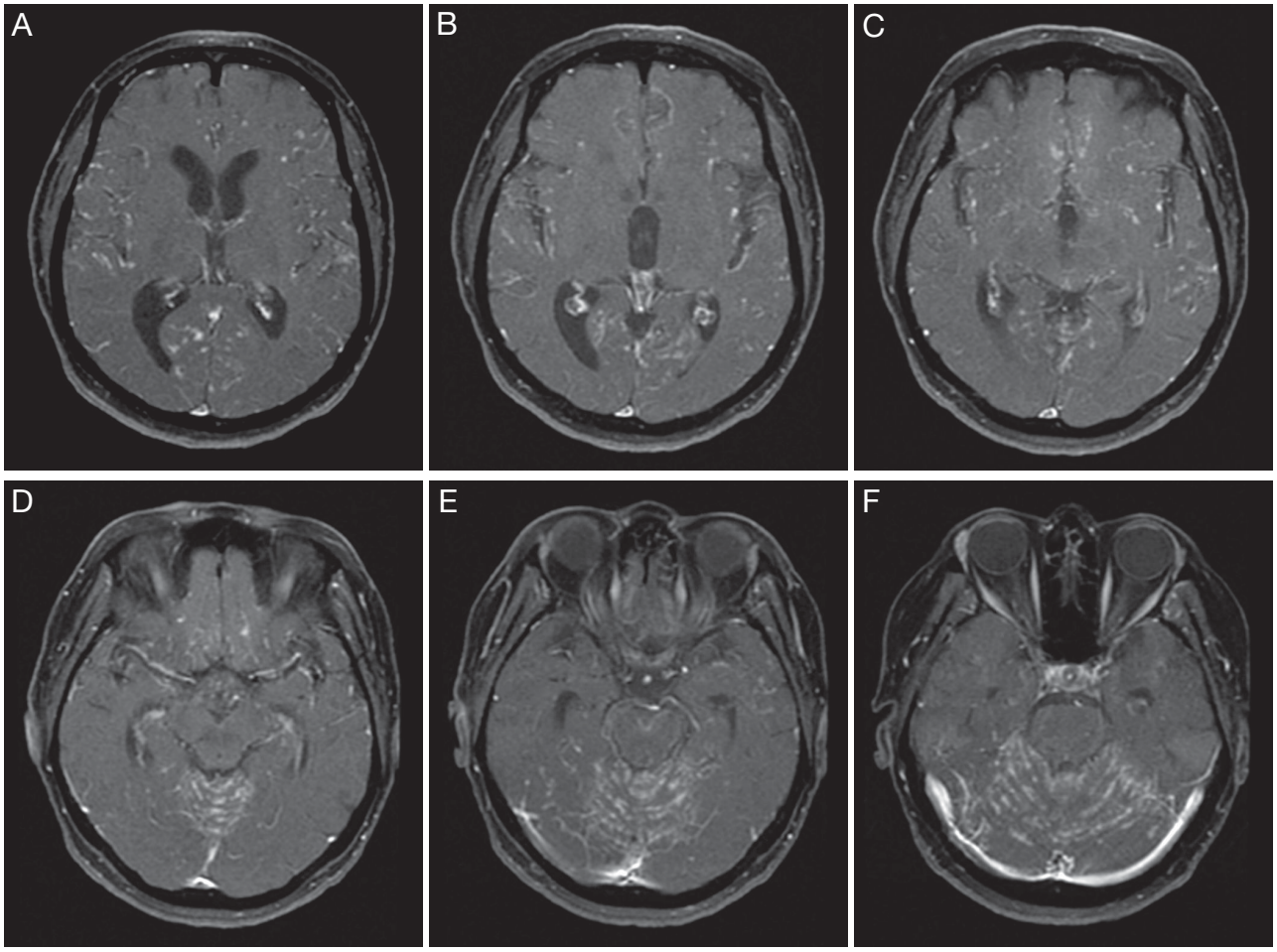

Figure 20.5 *Magnetic Resonance Imaging Findings in a Patient With Neurosarcoidosis.*
T1-weighted imaging after administration of gadolinium contrast shows diffuse cerebral (A–D) and cerebellar (D–F) leptomeningeal contrast enhancement.

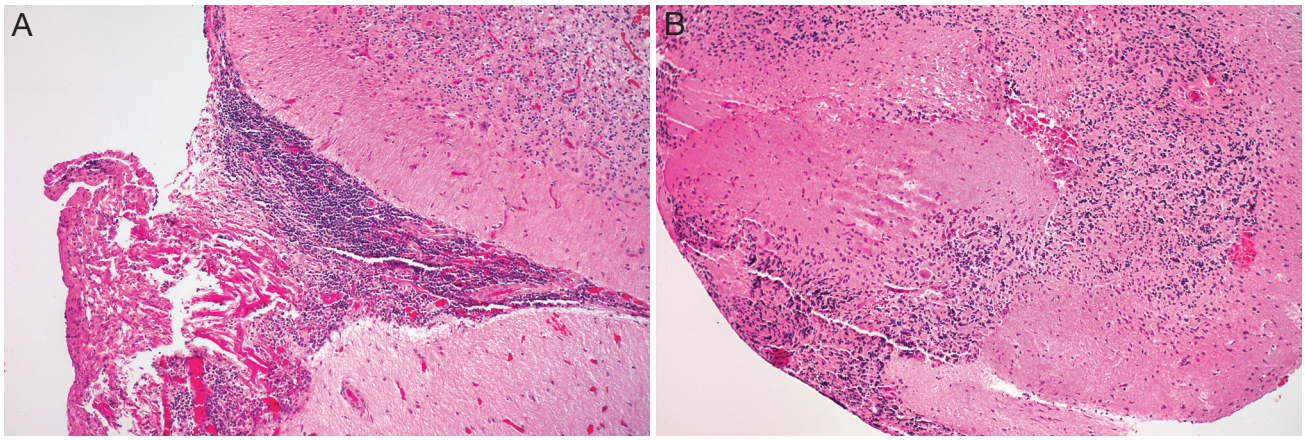

Figure 20.6 *Histopathologic Sections of Cerebellum of Patient With Central Nervous System Sarcoidosis.*
A, Leptomeningeal mononuclear infiltrates. B, Adjacent noncaseating sarcoid granulomas.
(Adapted from Kantarci OH. Inflammatory and demyelinating disorders of the central nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 559–88. Used with permission of Mayo Foundation for Medical Education and Research.)

a few days is more typical of an MS event. Gray-matter involvement, vascular territory lesions, and diffusion-weighting sequences can suggest an ischemic process. Subacute and even relapsing symptoms can occur with arteriovenous malformations, moyamoya disease, Susac syndrome, CNS vasculitis, and cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. These entities are discussed in Chapter 10, "Ischemic Stroke: Common Causes and Diagnosis," and Chapter 11, "Ischemic Stroke: Uncommon and Special Situations."

Isolated CNS Vasculitis (Granulomatous Vasculitis)

CNS vasculitis is a granulomatous vasculitis restricted primarily to the CNS (brain and spinal cord). Presenting features may include ischemic stroke, seizures, and headache.

MRI can show multifocal changes on T2 or fluid-attenuated inversion recovery sequences. Leptomeningeal enhancement may also be present. CSF examination is typically inflammatory (increased white cell count and protein value). Angiography can be helpful; however, brain biopsy is necessary for definitive diagnosis.

Treatment generally involves cyclophosphamide and corticosteroids. (See also Chapter 11: "Ischemic Stroke: Uncommon and Special Situations.")

Intravascular Lymphoma

Intravascular lymphoma (malignant angioendotheliomatosis) may present with multifocal neurologic symptoms and diffuse white-matter changes on MRI. Patients are typically elderly. CSF findings can show a predominantly lymphocytic pleocytosis and increased protein value, but they are otherwise not diagnostic. Other organs can be involved, including the spleen or skin. The diagnosis is difficult to make, and biopsy of the brain is required.

Amyloid Beta Peptide (Abeta)-Related Angiitis

Abeta-related angiitis is an unusual condition characterized by granulomatous inflammation and a β protein within affected blood vessels. The MRI appearance is that of increased T2 or fluid-attenuated recovery signal with underlying gradient-recalled echo–T2* findings of cerebral microhemorrhages (Figure 20.7).

Thiamine Deficiency

Thiamine (vitamin B_1) deficiency (Wernicke encephalopathy) causes subacute cranial nerve abnormalities,

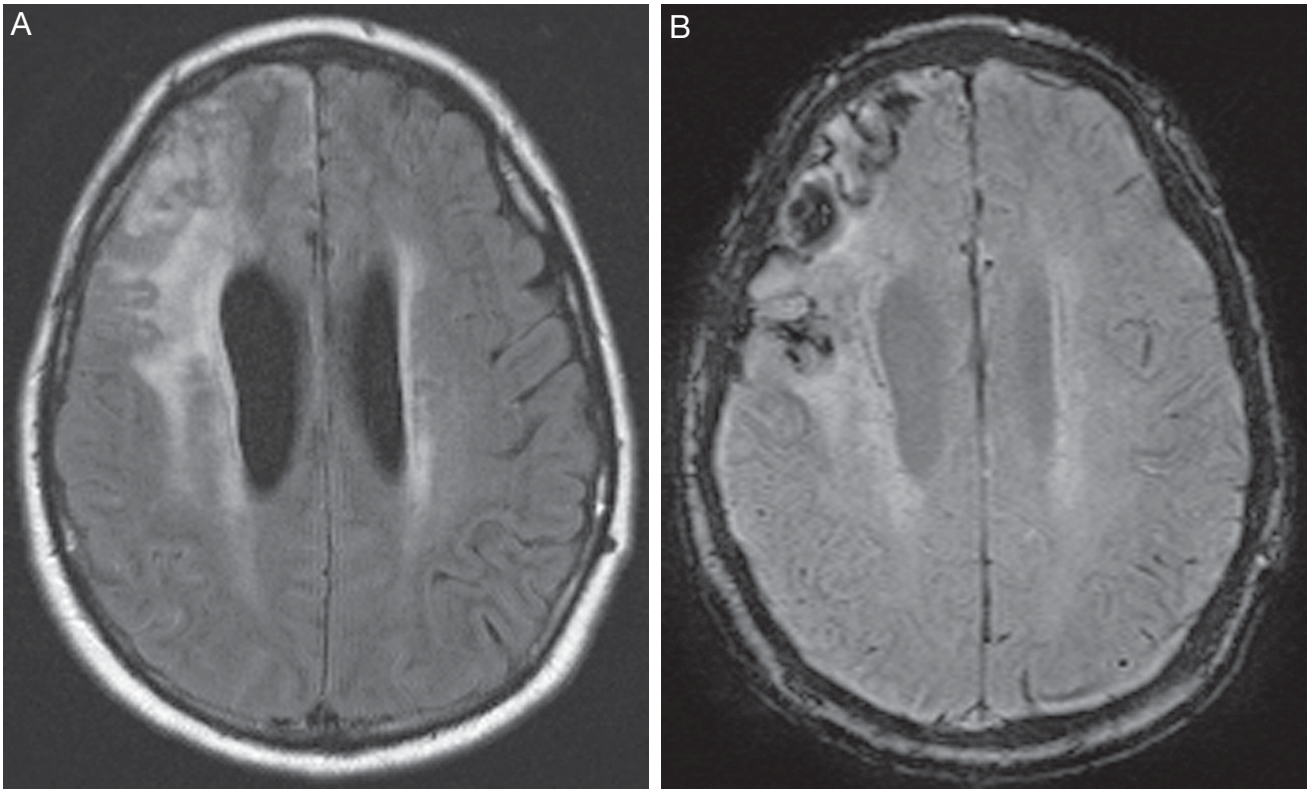

Figure 20.7 *Magnetic Resonance Imaging Findings in a Patient With Amyloid Beta Peptide-Related Angiitis. Fluid-attenuated inversion recovery imaging shows patchy, asymmetric cortical and subcortical T2-signal prolongation (A) with associated multifocal T2 shortening on gradient recovery imaging (B), indicating chronic hemorrhage.*

Table 20.2 • Genetic Diseases Mimicking Multiple Sclerosis

Disease	Clinical Features	Diagnostic Testing	MRI Findings
Adrenoleukodystrophy and adrenomyeloneuropathy (X-linked)	Progressive paresis Ataxia	Increased very long-chain fatty acids Impaired adrenal function on ACTH stimulation test	Confluent posterior predominant white-matter changes
Adult-onset autosomal-dominant leukodystrophy	Motor deficits Cerebellar deficits Early prominent autonomic dysfunction	Family history	Confluent white-matter lesions
Metachromatic leukodystrophy (autosomal recessive)	Ataxia Myelopathy	Can have IgG abnormalities on CSF Deficiency of arylsulfatase A	Symmetric, diffuse white-matter abnormalities
Krabbe globoid cell leukodystrophy (autosomal recessive)	Visual symptoms Paraparesis Neuropathy Typically occurs in infancy	Deficiency of galactocerebroside β-galactosidase	Confluent periventricular white-matter abnormalities
Fabry disease (X-linked)	Recurrent strokes in young patients Skin: angiokeratomas Renal disease Corneal opacities	Deficiency of lysosomal enzyme α-galactosidase	Widespread signal abnormalities
Mitochondrial cytopathies: MELAS MERFF	Optic atrophy Paraplegia Ataxia Seizures Dementia Recurrent focal neurologic deficits	Lactic acidosis Ragged red fibers on muscle biopsy (MERFF) DNA diagnosis	Diffuse white-matter abnormalities See also Chapter 76, "Mitochondrial Disease"
NARP	Visual and motor symptoms at a young age Sensory peripheral neuropathy	Mutation in mitochondrial gene for ATPase-6	Diffuse signal abnormality
Leber hereditary optic neuropathy	Subacute bilateral optic neuropathy Myelopathy Ataxia	DNA testing is diagnostic	Sometimes abnormal signal change
CADASIL	Migraines Multifocal neurologic symptoms Dementia	DNA testing Characteristic MRI and clinical features	Subcortical infarcts, anterior temporal lobe involvement (See also Chapter 11, "Ischemic Stroke: Uncommon and Special Situations")
HERNS	Young Chinese patients Dysarthria Hemiparesis Strong family history Renal disease Progressive dementia	Family history	Periventricular white-matter lesions

Abbreviations: ACTH, adrenocorticotropic hormone (corticotropin); ATP, adenosine triphosphate; CADASIL, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF, cerebrospinal fluid; HERNS, hereditary endotheliopathy, retinopathy, nephropathy, and stroke; Ig, immunoglobulin; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke; MERFF, mitochondrial encephalopathy with ragged red fibers; MRI, magnetic resonance imaging; NARP, neuropathy, ataxia, retinitis pigmentosa.

typically of the extraocular muscles, and cerebellar syndromes with abnormalities on MRI that can be initially mistaken for acute MS. Untreated, the condition can progress to an irreversible amnestic syndrome, so-called Wernicke-Korsakoff syndrome. Because blood levels of vitamin B_1 may not be available on an urgent basis, parenteral supplementation for patients suspected to be at risk of this disorder is crucial to their recovery. (See also Chapter 78, "Neurologic Complications of Nutritional Disorders.")

Genetic Disorders Associated With White-Matter Changes

In innumerable leukodystrophies and mitochondrial disorders, the varied presentations and radiographic findings can occasionally mimic those of MS (Table 20.2).

Infections

Several infections can mimic MS clinically or radiographically. Human immunodeficiency virus (HIV) or AIDS can be associated with a wide spectrum of neurologic symptoms, including optic neuritis, focal deficits with white matter changes on MRI, and a vacuolar myelopathy. Serologic results positive for HIV confirm the diagnosis. HIV can be associated with other infections, in particular progressive multifocal leukoencephalopathy. (See also Chapter 65, "Retroviral Infections of the Nervous System.")

Progressive multifocal leukoencephalopathy is a demyelinating disease affecting the white matter that is caused by reactivation of the latent JC virus that infects the oligodendrocytes. The JC virus can activate under other conditions of immunosuppression, including during treatment for MS with natalizumab. MRI can be helpful for suggesting the diagnosis. The DNA of the virus can be detected in the CSF in most patients. Brain biopsy is necessary in some patients. For further details, see Chapter 64, "DNA and RNA Viral Infections of the Nervous System."

Subacute sclerosing panencephalitis is a chronic inflammatory disease affecting both the white and the gray matter. It is due to latent infection with the measles virus, and patients have increased titers of antibodies to the measles virus in the serum and CSF.

Paraneoplastic Disorders

Paraneoplastic disorders can also present with symptoms that initially might suggest MS. A prior history of malignancy is not infrequently absent. Previous malignancy might be remote, and patients may not even report it without direct questioning. A history of smoking or a strong family history of malignancy should also be elicited.

Anti-Purkinje cell antibodies type 1 (anti-Yo) are associated with cerebellar and extracerebellar signs and symptoms. Women are almost exclusively affected. MRI results, when abnormal, show cerebellar atrophy, diffuse and usually symmetric abnormal signal in the brainstem or spinal cord, and even trigeminal nerve enhancement.

Anti-Ma antibody, which is associated with testicular cancer, can present with relapsing neurologic symptoms that might suggest MS.

Anti-CV2 (CRMP 5) antibodies react with oligodendrocytes and can present with optic neuritis and cerebellar and spinal cord disease. For additional details, see Chapter 62, "Paraneoplastic and Other Autoimmune Disorders."

- Anti-Purkinje cell antibodies type 1 (anti-Yo) are associated with cerebellar and extracerebellar signs and symptoms.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

III.1. Which of the following statements regarding multiple sclerosis (MS) pathology is true?
a. Lesions are rarely small, circumscribed, or ovoid
b. Lesions typically show predominant T-cell infiltration with macrophages and microglia
c. Cortical demyelination is uncommon
d. Because MS lesions are in the central nervous system, they do not demonstrate remyelination
e. Neuropathologic examination of MS lesions dates to the 1980s

III.2. A 22-year-old woman has relapsing remitting MS with continued relapses and new lesions on magnetic resonance imaging (MRI) despite ongoing use of interferon, and she wants to consider natalizumab as second-line therapy. Which of the following has *not* been associated with an increased risk of progressive multifocal leukoencephalopathy (PML)?
a. Prolonged treatment (>2 years) with natalizumab
b. Prior use of glatiramer acetate
c. Prior use of immunosuppressive medications
d. Serologic evidence of anti-JC virus antibodies
e. Previous treatment with methotrexate

III.3. A 40-year-old man with a history of uveitis would like to initiate treatment with fingolimod (Gilenya). What specific recommendation would be important for this patient?
a. Initial and annual ophthalmologic evaluations for macular edema would be necessary
b. Six-hour first-dose monitoring for heart rate would not be required
c. Interferon beta-1a intramuscularly once weekly should be suggested instead because it is superior to fingolimod in reducing the relapse rate
d. Fingolimod is contraindicated for any patient with uveitis
e. Diabetes mellitus is the only indication for annual ophthalmologic evaluation of patients treated with fingolimod

III.4. A 60-year-old man presents with a myelopathic syndrome that has progressed over 2.5 years. Which of the following is *not* a helpful diagnostic investigation to assess for a diagnosis of primary progressive MS?
a. Cerebrospinal fluid assessment for elevations in oligoclonal bands and the immunoglobulin G (IgG) index
b. MRI of the brain
c. MRI of the cervical spine
d. MRI of the thoracic spine
e. MRI of the lumbar spine

III.5. A 60-year-old man with a slowly progressive myelopathy is given a diagnosis of definitive primary progressive MS. What is the best treatment option for this patient?
a. Interferon beta-1a
b. Glatiramer acetate
c. Natalizumab
d. Aggressive physical medicine and rehabilitation therapy
e. Mitoxantrone

III.6. Which of the following statements regarding glatiramer acetate for relapsing remitting MS is true?
a. Flulike symptoms are commonly associated with this injectable treatment
b. An advantage is the lack of required regular laboratory monitoring
c. Its use does not reduce the likelihood of a second clinical attack in patients with high-risk clinically isolated syndromes of demyelination
d. It is clearly superior to interferons in reducing clinical attacks of MS
e. It is clearly superior to natalizumab in reducing new MRI lesions due to MS

III.7. Neuromyelitis optica (NMO) is associated with which of the following?
a. It is most common in white populations
b. It is more common in men than in women
c. Patients typically have mild attacks of myelitis or optic neuritis (or both)
d. It is associated with antibodies to the aquaporin-4 channel
e. It is never associated with intractable nausea, vomiting, or hiccups

III.8. According to the 2010 modified McDonald criteria for MS, dissemination of inflammation in space *cannot* be demonstrated by MRI T2 lesions in which of the following areas of the central nervous system?
a. Periventricular white matter
b. Juxtacortical white matter
c. Infratentorial white matter
d. Spinal cord
e. Optic nerve

III.9. Secondary progressive MS is characterized by which of the following?
a. Ongoing relapses are frequent
b. MRI activity with new T2- and gadolinium-enhancing T1 lesions is more common than in relapsing remitting MS
c. Currently available immunomodulatory medications have a robust effect in reversing secondary progressive MS
d. Most patients with secondary progressive MS have a progressive myelopathic clinical picture
e. Only rarely do patients with relapsing remitting MS have secondary progressive MS many years after onset

III.10. Which of the following diagnoses would *not* mimic a spinal cord manifestation of MS?
- a. Susac syndrome
- b. Subacute combined degeneration due to vitamin B_{12} deficiency
- c. Copper deficiency
- d. Paraneoplastic syndromes
- e. Syphilis

III.11. Acute disseminated encephalomyelitis is characterized by which of the following?
- a. Adults are affected more commonly than children
- b. Very few cases are associated with preceding infections or vaccinations
- c. Pathologically, inflammation is limited to the periarteriolar regions
- d. It is never associated with an altered level of consciousness
- e. It is usually a monophasic illness

Answers

III.1. Answer d.
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III.2. Answer b.
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III.3. Answer a.
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III.4. Answer e.
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III.5. Answer d.
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III.6. Answer b.
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III.7. Answer d.
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III.8. Answer e.
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III.9. Answer d.
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III.10. Answer a.
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III.11. Answer e.
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Section
IV

Movement Disorders

Bryan T. Klassen, MD,
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21 Classification and Approach to Movement Disorders

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Introduction

Movement disorders are conventionally divided into 2 major categories: 1) *Hyperkinetic movement disorders* (also called *dyskinesias*) refers to excessive, often repetitive, involuntary movements that intrude into the normal flow of motor activity. This category includes chorea, dystonia, myoclonus, stereotypies, tics, and tremor. 2) *Hypokinetic movement disorders* refers to akinesia (lack of movement), hypokinesia (reduced amplitude of movement), bradykinesia (slow movement), and rigidity. Parkinsonism is the primary hypokinetic movement disorder. In childhood, hyperkinetic disorders are common, whereas hypokinetic movement disorders are relatively uncommon.

Movement disorders may be further categorized into primary and secondary disorders. In *primary movement disorders*, the abnormal movement is the primary manifestation of the disorder. In *secondary movement disorders*, a broader structural, toxic, metabolic, or inherited etiologic factor is responsible for the symptoms.

- Movement disorders may be categorized into primary and secondary disorders.

Classification and Phenomenology

The several types of hypokinetic and hyperkinetic movements are defined on the basis of phenomenology, which includes both the spatial characteristics of the movements and their patterns of occurrence. The classification of movement disorders is reviewed here and summarized in Table 21.1.

Ataxia refers to the lack of voluntary coordination of muscle movements. This may result from an impaired spatial patterning or timing of muscle activity, a lack of proper cerebellar processing (cerebellar ataxia), or improper proprioceptive input to the cerebellum (sensory ataxia). Patients with ataxia may have generalized or localized motor coordination difficulties. Several types of eye movement abnormalities may occur, including poor fixation, oscillatory nystagmus, saccadic imprecision or overshoot, and oculomotor apraxia. Speech may be dysarthric with slow, irregularly emphasized (ie, scanning) speech. Titubation, a characteristic bobbing of the head and trunk, is a common finding. Limb movements may be imprecise or tremulous when approaching a target or performing a task. The gait may be broad based and clumsy, with slight variations between each step.

Ballism refers to large-amplitude, involuntary, flinging limb movements. They may be brief or continual, and they often fade into chorea with time. When 1 side of the body is affected, the term *hemiballism* is used. Classically, ballism results from a lesion in the contralateral subthalamic nucleus, although other causes exist.

Chorea refers to brief dancelike movements that are not rhythmic or spatially patterned and may appear to flow from 1 body part to the next. Patients with chorea may learn to disguise their movements by merging them into a purposeful movement, which is termed *parakinesia. Motor impersistence* is a negative chorea and results in difficulty maintaining tongue protrusion or grip strength (resulting in the so-called milkmaid's grip). Chorea often occurs in combination with athetosis, a slower but still quite unpredictable involuntary movement.

Dystonia is characterized by slow, sustained contractions of axial and appendicular muscles involving agonist-antagonist pairs and resulting in twisting, often

Table 21.1 • Classification of Movement Disorders

Disorder	Description
Ataxia	Lack of voluntary coordination of muscle movements (impaired spatial patterning or timing of muscle activity) Ataxic movements may occur in the extremities (appendicular) or in the truncal (axial) musculature (or both) Ataxia may affect speech, extraocular movements, and gait
Athetosis	Slow, continuous, writhing, and purposeless involuntary movements, which may flow into one another Often associated with chorea
Ballism	Large-amplitude, involuntary, flinging limb movements
Chorea	Brief, involuntary, purposeless, and nonrhythmic movements that result in unpredictable dancelike movements of the face, trunk, or extremities
Dystonia	An abnormal contraction of agonist and antagonist muscle pairs, frequently resulting in sustained twisting postures Exacerbated by voluntary movement
Myoclonus	Sudden, brief, shocklike involuntary movements of ≥1 muscle groups localizing anywhere along the neuraxis from the cerebral cortex to nerves *Positive myoclonus* usually describes sudden, quick, involuntary muscle jerks caused by muscle contraction *Negative myoclonus*, or *asterixis*, describes sudden, brief, interruption of muscle contraction
Parkinsonism	Syndrome characterized by bradykinesia, rest tremor, rigidity, and postural instability
Stereotypies	Repetitive, patterned, and purposeless movements that are often rhythmic in nature (examples of motor stereotypies in children include hand flapping and head nodding back and forth)
Tics	Sudden, repetitive, nonrhythmic, simple or complex muscle contractions or vocalizations that are preceded by an urge to perform, followed by a sense of relief, and are voluntarily suppressible for a period of time
Tremor	Involuntary, rhythmic, oscillatory movements about a fixed axis or plane Tremor may occur with action, with maintenance of posture, or at rest

repetitive postures that cannot be suppressed and often worsen with voluntary movement.

Myoclonic movements are sudden, brief, involuntary movements caused by muscular contraction *(positive myoclonus)* or inhibition *(negative myoclonus* or *asterixis)*, resulting from pathology in the cerebral cortex, subcortical regions, spinal cord, and occasionally peripheral nerves. Myoclonus is present in physiologic situations (associated with sleep, exercise, or anxiety) and pathologic situations, both epileptic and nonepileptic.

Parkinsonism is characterized by resting tremor, bradykinesia, cogwheeling rigidity, postural instability, and a characteristic shuffling gait. A patient may manifest the complete constellation of features or any subset.

Tics are repetitive, brief, recurrent, nonrhythmic, involuntary or semivoluntary movements or vocalizations that are preceded by an urge to complete the movement and are followed by a sense of relief. They are the most common movement disorder in children. Unlike many other abnormal movements, tics are voluntarily suppressible for a time, but they inevitably return and may be more severe after a period of suppression (rebound phenomenon). *Simple tics* may be a brief, purposeless movement or sound, such as a nose twitch, facial grimace, neck jerk, shoulder elevation, abdominal tensing, sniffing, and throat clearing, grunting, or coughing. *Complex motor tics* involve a more coordinated sequence of movements that appear purposeful but actually serve no purpose, such as head shaking, scratching, finger tapping, hitting, jumping, kicking, and gestures, which in some cases may be obscene (*copropraxia*). Complex vocalizations involve spoken syllables, words, or phrases, including repetition of the words of others (*echolalia*); repetition of the final syllable, word, or phrase of one's own words (*palilalia*); or shouting of obscenities or profanities (*coprolalia*).

Tremor is an involuntary, rhythmic oscillation of a body part about a fixed point or axis and is categorized according to the features of the tremor and their relation to purposeful movement. *Rest tremor* is most common in hypokinetic syndromes such as Parkinson disease. *Postural tremor* arises when a patient attempts to sustain a posture against gravity and may improve with movement or with rest supported against gravity. *Kinetic tremors* occur during directed voluntary movement, which may be evident during the entire course of movement of an extremity. An *intention tremor* is a kinetic tremor that emerges or worsens as the arm approaches an end point or target.

- The classification of movement disorders is summarized in Table 21.1.

General Approach to Diagnosis

History

The patient's age at onset, the type of onset (acute, subacute, or chronic), and the disease course (improving, static, or progressive) provide important clues to the differential

diagnosis of movement disorders. Eliciting a history of other associated symptoms or diseases may similarly be helpful. A careful review of medications, illicit drugs, or toxic exposures is important because they are potentially reversible causes of movement disorders. Family history is also important, especially in pediatric movement disorders, since several inherited conditions may result in movement disorders.

Physical Examination

The physical examination aids in classifying the movement and determining whether other neurologic deficits exist. In some situations, if the symptoms are intermittent or occur during specific triggers, review of a videotape can be useful. Useful steps in examining pediatric patients include measuring head circumference and evaluating for organomegaly and associated craniofacial abnormalities.

Differential Diagnosis and Diagnostic Testing

The differential diagnoses of primary and secondary causes of each type of movement are reviewed in other chapters. A general approach to movement disorders is reviewed in Figure 21.1. However, the approach may be quite different for pediatric patients, and it varies according to specific details obtained in the history and physical examination. Tics and stereotypies are not included in this diagram since they are typically a clinical diagnosis. It is

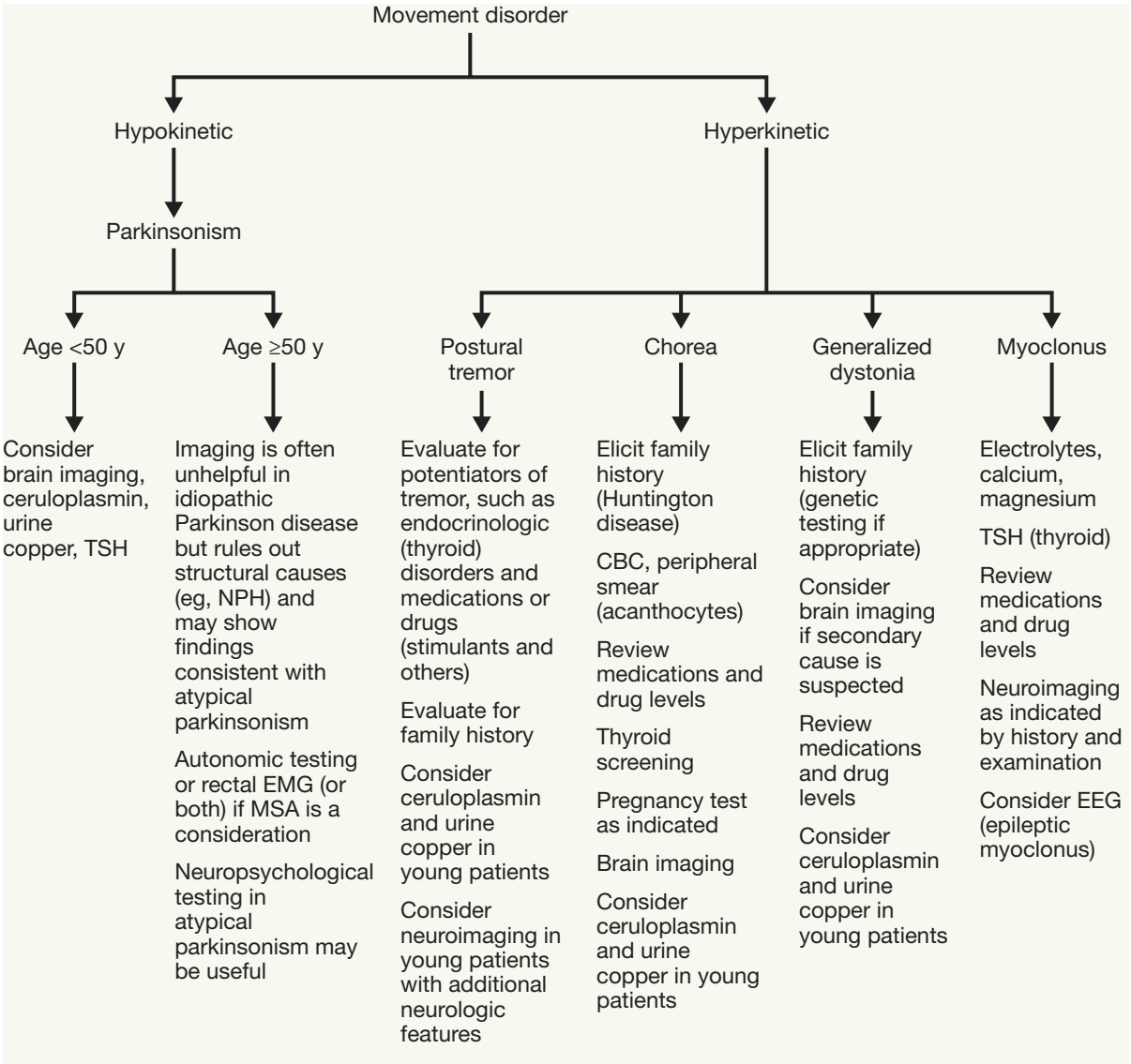

Figure 21.1 *General Approach to Movement Disorders in Adults.*
CBC indicates complete blood cell count; EEG, electroencephalogram; EMG, electromyogram; MSA, multiple system atrophy; NPH, normal pressure hydrocephalus; TSH, thyrotropin.

Box 21.1 • Paroxysmal Movement Disorders

Paroxysmal dyskinesias
Hyperekplexia
Episodic ataxia
Spasmus nutans (infants)
Tics
Stereotypies
Alternating hemiplegia of childhood

also important to keep in mind that some movement disorders are episodic (Box 21.1).

Miscellaneous Movement Disorders

Overview

Some movement disorders can be neatly classified as hyperkinetic or hypokinetic, but others cannot. Hemifacial spasm and stiff man syndrome are reviewed in this section. In addition, various medication- or drug-induced movement disorders deserve further attention because they are potentially reversible.

Hemifacial Spasm

Overview

Hemifacial spasm is characterized by involuntary, intermittent, synchronous contraction of the muscles of 1 side of the face. It is thought to result from compression of the peripheral facial nerve and thus is considered peripheral, segmental myoclonus.

Epidemiology and Causes

Most commonly, hemifacial spasm is thought to result from an aberrant blood vessel compressing the facial nerve. Rarely, an alternative structural lesion is responsible (aneurysm, vertebrobasilar artery dolichoectasia, tumor, arteriovenous malformation, or multiple sclerosis).

Clinical Features

Hemifacial spasm often starts with involuntary, episodic contractions of the orbicularis oculi muscle on 1 side. Over time, the muscle contraction may spread to involve other muscles innervated by the facial nerve ipsilaterally.

Diagnosis

The diagnosis is made clinically. Brain imaging is often performed to assess for a structural lesion.

Treatment

Medications such as baclofen, carbamazepine, and other antiseizure medications can help. However, botulinum toxin is the most commonly used medication; at least moderate improvement occurs in more than 90% of patients, but the injections must be repeated over time.

Microvascular decompression can be performed. This involves placing a tiny polytef (Teflon) pad between the facial nerve and an offending artery.

Stiff Man Syndrome

Stiff man syndrome is a disorder resulting in hypertonicity and pain thought to be due to loss of inhibitory GABAergic neurons. It is rare and may occur as a paraneoplastic syndrome or be idiopathic. It has been associated with breast cancer (anti-amphiphysin antibodies), possibly thymoma, small cell lung cancer, and lymphoma. Laboratory testing with a paraneoplastic antibody panel should be considered because anti–glutamic acid decarboxylase antibody is positive in up to 70% of cases and anti-amphiphysin antibodies are positive in up to 5%. Additional details are found in Chapter 62, "Paraneoplastic and Other Autoimmune Neurologic Disorders."

Drug-Induced Movement Disorders

Overview

Drugs, medications, and toxins can produce or worsen many movement disorders. A detailed history and consideration of a toxin screen are important when encountering movement disorders. Drug levels, if applicable, may also be considered. Many of these substances are discussed in other chapters; however, a few conditions deserve further attention here.

Acute Dystonic Reaction

A sudden dystonic posturing involving predominantly cervicocranial musculature may be the result of a medication or toxin. The posture may be painful, and sometimes the dystonia is also associated with oculogyration.

Acute dystonic reaction may be caused by common offending agents, including the neuroleptics. On neurologic wards, the offending agent may be prochlorperazine (Compazine) used for nausea. Other potential offending agents include tetrabenazine, methamphetamine, and calcium channel blockers.

Treatment is to remove the offending agent and consider benztropine mesylate (Cogentin) or diphenhydramine (Benadryl) if symptoms are severe or painful.

Tardive Dyskinesia

Tardive dyskinesia may occur 3 months to several years after treatment with a potentially offending agent (Box 21.2). There may be a genetic susceptibility to tardive dyskinesia.

Patients with tardive dyskinesia have stereotypic, episodic involuntary movements involving the oral, lingual,

Box 21.2 • Drugs Associated With Tardive Syndromes

Phenothiazines: chlorpromazine (Thorazine), prochlorperazine (Compazine), thioridazine (Mellaril), perphenazine, fluphenazine (Prolixin)
Thioxanthenes: chlorprothixene, thiothixene (Navane)
Butyrophenones: haloperidol (Haldol), droperidol
Diphenylbutylpiperidine: pimozide
Thienobenzodiazepine: olanzapine (Zyprexa)
Benzamides: metoclopramide (Reglan)
Loxapine
Risperidone
Ziprasidone
Calcium channel blockers: flunarizine, cinnarizine
Tricyclic antidepressants: amoxapine

Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.

and perioral muscles. Patients may have a chewing or smacking type movement of the mouth or occasionally a repetitive tongue protrusion. The stereotypic pattern helps distinguish this from other types of chorea. Some patients have limb involvement.

The involuntary movements may be increased by anxiety or stress. Treatment generally involves removal of the offending agent if possible. Among the neuroleptics, clozapine has the least potential for causing this syndrome. Medications for therapy have included reserpine, tetrabenazine, and clonazepam.

Tardive Dystonia

Tardive dystonia may occur days to years after exposure to an offending agent (usually a dopamine agonist). Clinical signs may include repetitive axial twisting, retrocollis, opisthotonos with elbow extension, and wrist extension. Treatment is similar to treatment of tardive dyskinesia.

Neuroleptic Withdrawal Syndrome

Abrupt withdrawal of neuroleptics may result in choreiform movements or parkinsonism. A slow taper of the offending agent may be necessary.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is discussed in Chapter 8, "Neuromuscular Disease in the Neuroscience Intensive Care Unit."

Other Miscellaneous Movement Disorders

Painful Legs and Moving Toes Syndrome

Patients with the rare disorder of painful legs and moving toes syndrome may have pain that precedes the movement disorder by days to years and is usually exacerbated by pressure on the affected limb. Movements often involve the toes and include fanning, circular movements, clawing, or other combinations of flexion and extension movements. Stress and pain may exacerbate the symptoms.

Restless Legs Syndrome

Restless legs syndrome is reviewed in Chapter 86, "Hypersomnias and Sleep-Related Movement Disorders."

- For treatment of hemifacial spasm, medications such as baclofen, carbamazepine, and other antiseizure medications can help. However, botulinum toxin is the most commonly used medication; at least moderate improvement occurs in more than 90% of patients.
- Laboratory testing with a paraneoplastic antibody panel should be considered in patients with stiff man syndrome because anti–glutamic acid decarboxylase antibody is positive in up to 70% of cases and anti-amphiphysin antibodies are positive in up to 5%.
- Acute dystonic reaction may be caused by common offending agents, including the neuroleptics. On neurologic wards, the offending agent may be prochlorperazine (Compazine) used for nausea.

22 Hypokinetic Movement Disorders: Parkinson Disease

ALEX J. NELSON, MD; BRYAN T. KLASSEN, MD

Introduction

Parkinson disease (PD) is the classic hypokinetic movement disorder and 1 of the most common and widely recognized neurodegenerative conditions. PD is distinct from parkinsonism. *Parkinsonism* refers to the syndrome of rest tremor, bradykinesia, rigidity, and postural instability. These symptoms are cardinal features of PD, but they are also present with other disorders (see Chapter 23, "Atypical Parkinsonian Syndromes").

Pathophysiology

The anatomy of basal ganglia circuitry is reviewed in Volume 1, Chapter 17, "Basal Ganglia."

The mechanism behind the progressive degeneration and cell death that result in PD is not precisely understood. Substantia nigra depigmentation occurs on a macroscopic level and loss of dopaminergic neurons and gliosis occurs on a microscopic level (Figure 22.1). Histologically, PD is characterized by Lewy bodies, which are intracytoplasmic eosinophilic inclusions composed primarily of α-synuclein and ubiquitin (Figure 22.2). Although Lewy bodies are considered the pathologic hallmark of PD, they appear in a wide range of degenerative conditions and are therefore a nonspecific finding. Because of the positive staining for α-synuclein, PD is often referred to as an α-synucleinopathy. The Braak staging system is based on a hypothesized caudal-to-rostral progression of α-synuclein pathology.

The substantia nigra depigmentation results in a paucity of dopaminergic input to the striatum and a relative activation of the indirect pathway and deactivation of the direct pathway. The net effect is an inhibition of movement resulting in motor parkinsonism.

The majority of cases of PD occur sporadically, but there is increasing evidence that even in these cases unknown environmental factors act on a polygenic predisposition. The relatively rare familial forms of PD tend to manifest at younger ages, they progress rapidly, and they are associated with several genes (Table 22.1). Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.

- Histologically, PD is characterized by Lewy bodies, which are intracytoplasmic eosinophilic inclusions composed primarily of α-synuclein and ubiquitin.

Epidemiology and Risk Factors

PD affects the general population at a rate of approximately 0.3% but increases to 1% among persons older than 60. Men are affected slightly more often than women. Several protective factors that have been suggested include nicotine use, caffeine, nonsteriodal antiinflammatory drugs, and physical activity, although their importance is controversial. Nongenetic risk factors include pesticide and heavy metal exposure (including manganese poisoning in welders), poor diet, and excess body weight.

Abbreviations: ADAGIO, Attenuation of Disease Progression With Azilect Given Once Daily; DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; DBS, deep brain stimulation; MAO-B, monoamine oxidase B; PD, Parkinson disease

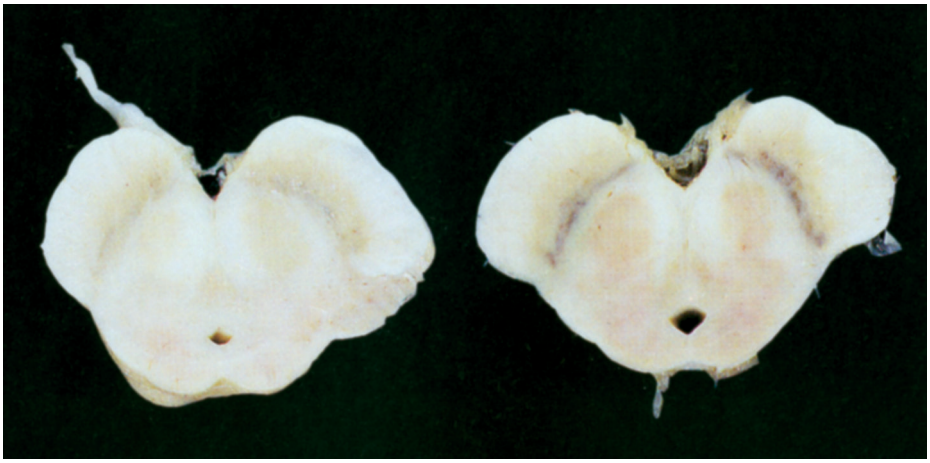

Figure 22.1 *Gross Pathology in Parkinson Disease.*
Pallor of the substantia nigra in Parkinson disease (left) compared with normal (right).
(Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 227. Used with permission of Mayo Foundation for Medical Education and Research.)

Clinical Manifestations

The cardinal features of PD include tremor, rigidity, bradykinesia, hypokinesia, and postural instability. The tremor is a characteristic pill-rolling tremor that is most pronounced at rest and is usually unilateral at onset with a frequency between 3 and 7 Hz. It typically starts in the hand but can progress to involve the tongue, jaw, lips, and legs and, rarely, the head. Tremor is the most common presenting symptom and is best elicited on examination during mental distraction or contralateral motor activation.

Rigidity is an increase in muscle tone best appreciated as a velocity-independent resistance to passive movement about the joint of a limb. Cogwheel rigidity, a jerky and ratcheting pattern of resistance and relaxation in some PD patients, is thought to be secondary to a superimposed tremor. Patients may complain of stiff joints and pain secondary to the rigidity.

Bradykinesia and hypokinesia are the most common features and the main causes of disability. Movements are not only slowed but also reduced in amplitude. Symptoms of bradykinesia and hypokinesia include hypomimia, hypokinetic dysarthria, micrographia, decreased manual dexterity with fine motor tasks, shuffling of gait, and gait freezing. Bradykinesia and hypokinesia are best assessed by observing rapid alternating movements.

Typically developing late in the disease course, postural instability results from the loss of postural reflexes, with a resultant sensation of imbalance and a tendency to fall. Postural instability is tested clinically by quickly pulling the patient backward at the shoulders (the pull test) and assessing for any retropulsion.

Many associated nonmotor features of PD often appear in later stages but may occur at any time during the course of the disease. Chief among these are cognitive dysfunction, dysautonomia (most commonly orthostatic hypotension), pain, olfactory dysfunction, psychosis, mood disorders, and several sleep disorders, including restless leg syndrome, periodic limb movements of sleep,

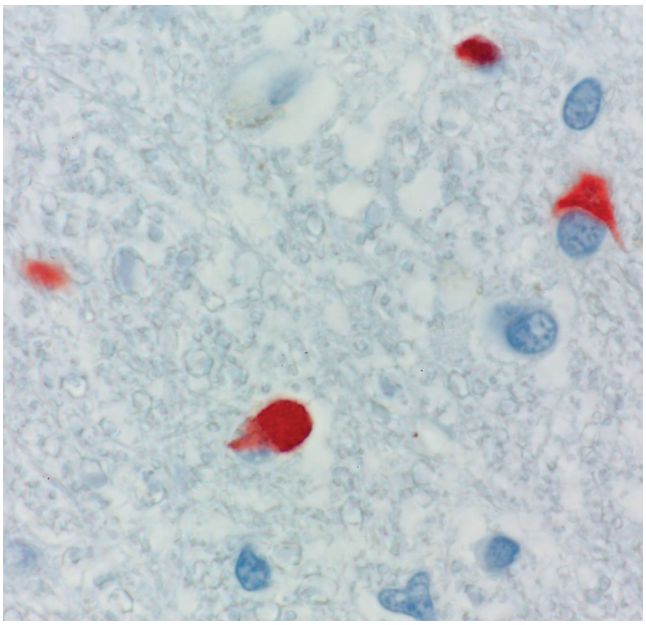

Figure 22.2 *Lewy Bodies.*
The micrograph shows cytoplasmic inclusions that stained positive for a-synuclein.
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 22.1 • Inherited Forms of Parkinson Disease

Gene (Protein)	Pattern of Inheritance	Chromosome of Gene Locus	Key Clinical Feature
PARK1 (α-synuclein)	AD	4	Dementia[a]
PARK2 (parkin)	AR	6	Dystonia[a]
PARK3	AD	4, 2p	
PARK4	AD	4p	Dementia
PARK5	AD	4p	
PARK6	AR	1p	Early-onset parkinsonism
PARK7	AR	1p, loss of DJ-1	Dystonia[a]
PARK8	AR	12	Early-onset parkinsonism
PARK9	AR	1p	
PARK10	Unknown	1p	Late-onset parkinsonism

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.
[a] Early-onset parkinsonism.

Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.

and rapid eye movement sleep behavior disorder. Virtually all patients with PD have at least a few nonmotor symptoms, which should be regarded as manifestations of the spectrum of the disease.

- The cardinal features of PD include tremor, rigidity, bradykinesia, hypokinesia, and postural instability.
- The pill-rolling tremor of PD typically starts in the hand but can progress to involve the tongue, jaw, lips, and legs and, rarely, the head.

Diagnosis

The diagnosis of PD is clinical. On physical examination, identification of the features of parkinsonism suggests a diagnosis of PD, but other conditions with similar manifestations must be ruled out. (See Chapter 23, "Atypical Parkinsonian Syndromes.") Ruling out other conditions is often difficult, particularly in the early disease with mild symptoms. Therefore, patients must be followed longitudinally. Sometimes a trial of dopaminergic therapy is helpful because a positive result strongly suggests a diagnosis of PD.

Conventional magnetic resonance imaging can be useful to rule out structural mimics such as tumors or strokes, but in their absence, no specific findings suggest PD. Striatal dopamine transporter imaging (with ioflupane iodine-123 [DaTscan] injection) has been shown to be effective for differentiating patients with parkinsonian syndromes from controls or from patients with essential tremor, but it cannot be used to distinguish between PD and atypical parkinsonian syndromes (Figure 22.3).

Olfactory testing can be a complementary tool because olfactory dysfunction is present even in early PD and is less impaired in many other parkinsonian syndromes.

- Striatal dopamine transporter imaging (with ioflupane iodine-123 [DaTscan] injection) has been shown to be effective for differentiating patients with parkinsonian syndromes from controls or from patients with essential tremor, but it cannot be used to distinguish between PD and atypical parkinsonian syndromes.

Treatment

Carbidopa-Levodopa

Pharmacotherapy is the mainstay of treatment of PD (Table 22.2). The dopaminergic agents include levodopa and dopamine agonists. Levodopa is a precursor of dopamine and is given in combination with carbidopa, a peripheral decarboxylase inhibitor that blocks the peripheral conversion of levodopa to dopamine. Carbidopa-levodopa is available in both immediate-release and controlled-release formulations. It should not be taken with a high-protein meal because amino acids compete with levodopa for transport through the blood-brain barrier and thus reduce or delay the levodopa effect.

Levodopa is initially dosed at 50 to 100 mg 3 times daily; the dose can be increased if the response is insufficient. Multiple studies have confirmed that levodopa is the most effective treatment of motor parkinsonism.

Adverse effects may include nausea, which might respond to an increase in the dose of the carbidopa

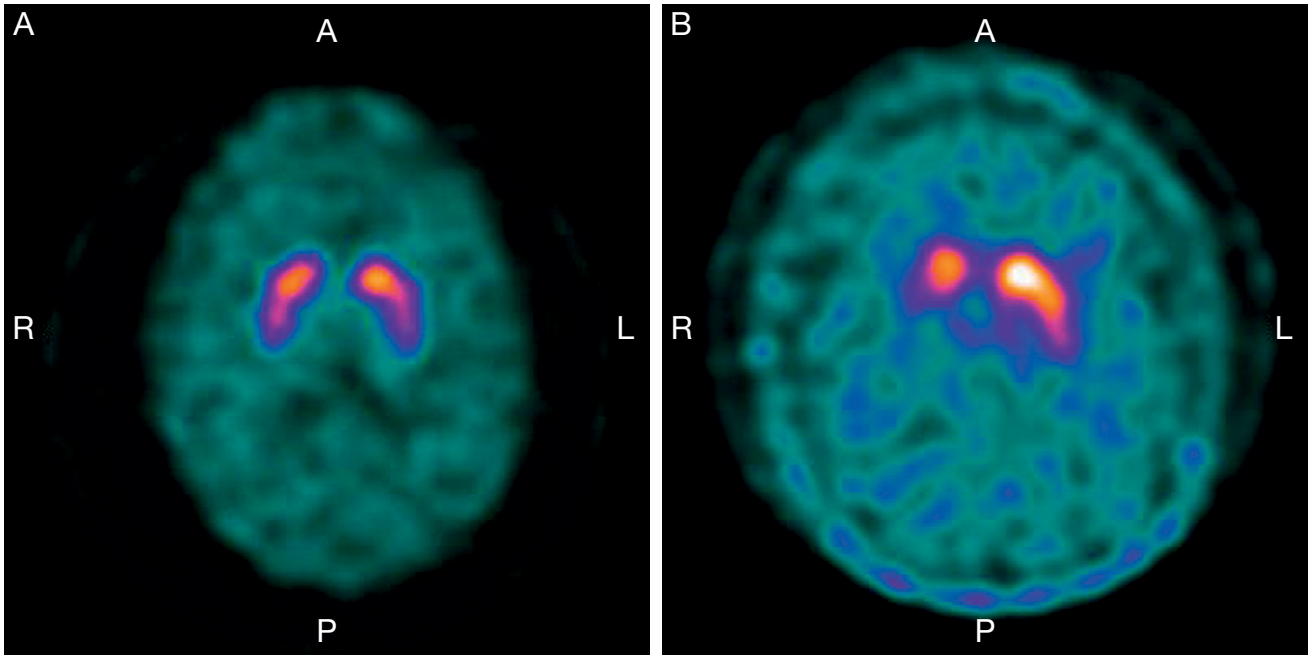

Figure 22.3 *DaTscan in Parkinsonism.*
A, Single-photon emission computed tomography (SPECT) after ioflupane iodine-123 (DaTscan) injection in a healthy patient shows robust uptake bilaterally in the caudate and putamen. B, The same technique in a patient with left hemiparkinsonism shows an absence of uptake in the right putamen and decreased uptake in the right caudate correlating with the loss of dopaminergic terminals in these locations. There is also some reduction in left putaminal uptake despite the absence of symptoms on the right in this patient. A indicates anterior; L, left; P, posterior; R, right.

Table 22.2 • Medical Treatment of Parkinson Disease

Drug	Usual Starting Dose	Maximal Dose (Usual Target Dose)	Adverse Effects
Amantadine (Symmetrel)	100 mg bid or tid	100 mg tid	Anticholinergic-like (dry mouth, urinary retention, constipation), hallucinations, livedo reticularis, insomnia
Carbidopa-levodopa	IR: 25/100 mg tid CR: 25/100 mg bid	1,500 mg daily (300–1,200 mg daily)	Nausea, orthostatic hypotension, dyskinesias, hallucinations and psychosis
Entacapone (Comtan)	One 200-mg tablet with each levodopa dose	Up to 8 doses daily	Nausea, diarrhea, prolongation of all levodopa-induced dyskinesias, and other adverse effects
Pramipexole (Mirapex)	0.125 mg tid	1.5 mg tid (3.0–4.5 mg daily)	Nausea, orthostatic hypotension, dyskinesias, vivid dreams, hallucinations and psychosis, somnolence, sleep attacks (rare)
Ropinirole (Requip)	0.25 mg tid	5 mg 5 times daily (3–25 mg daily)	Same as for pramipexole
Selegiline (Eldepryl)	5 mg bid (with breakfast and lunch)	Same as starting dose	Insomnia, vivid dreams and nightmares, potentiation of dopaminergic effects
Trihexyphenidyl	1 mg daily or bid	6 mg tid (2 mg tid)	Anticholinergic (dry mouth, urinary retention, constipation, visual blurriness, memory impairment)

Abbreviations: bid, 2 times daily; CR, controlled-release; IR, immediate-release; tid, 3 times daily.

Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.

component. Fatigue, potentiation of orthostatic hypotension, or hallucinations may also complicate therapy.

As dopaminergic neuron function continues to decrease in advanced PD, the long-duration levodopa effect may not be sustained and patients can become dependent on a short-duration response. Because of levodopa's short plasma half-life (60–90 minutes), its effect may wear off, and parkinsonian symptoms may return between doses. This problem can be addressed by shortening the levodopa dosing interval or adding adjunctive medications. Also, ongoing levodopa therapy in advancing PD may induce choreiform dyskinesia, which most often occurs at the peak of the dose. Dyskinesia in the medication "off" state or biphasic dyskinesia (occurring both when the medication effect is turning "on" and "off") may rarely occur. In some, the levodopa-induced dyskinesia may be less choreiform and more dystonic. Patients with young-onset PD (patient age <40 years at onset) are more prone to have motor fluctuations or dyskinesia (or both).

Dopamine Agonists

Available dopamine agonists include apomorphine (injectable), bromocriptine, pramipexole, ropinirole, and rotigotine. They are not as effective as carbidopa-levodopa in treating motor symptoms and generally take more time to adjust to a therapeutic dose. They have longer half-lives and are less associated with motor fluctuations and dyskinesias than levodopa. Patients taking dopamine agonists are more likely to experience adverse effects, including nausea, orthostatic hypotension, fatigue (at times, manifested as sleep attacks), hallucinations, psychosis, impulse control disorders (often pathologic gambling or shopping or hypersexuality), and compulsive use of dopaminergic drugs in a syndrome called dopamine dysregulation syndrome.

Monoamine Oxidase B Inhibitors

Selegiline and rasagaline, irreversible inhibitors of monoamine oxidase B (MAO-B), are taken once daily to attenuate the degradation of dopamine. They may provide a symptomatic benefit in PD, although they are generally less effective than the dopaminergic agents. At higher doses, these medications (particularly selegiline) can lose their MAO-B selectivity; patients are then at risk of a hypertensive crisis, particularly in the presence of certain medications (including sympathomimetic amines) or tyramine-containing foods (including fermented meats, aged cheeses, red wine, and soy products). Other possible adverse effects include nausea, headaches, and insomnia (particularly with selegiline, which has an amphetamine metabolite).

MAO-B inhibitors can be used as initial monotherapy or as add-on therapy to levodopa later in the disease course. Some have suggested that these agents may be neuroprotective, but both the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial (which studied selegiline) and the Attenuation of Disease Progression With Azilect Given Once Daily (ADAGIO) trial (which studied rasagiline) yielded controversial results; the US Food and Drug Administration's interpretation was that the trials did not provide compelling evidence of a neuroprotective effect.

Other Medications

Catechol *O*-methyltransferase inhibitors include tolcapone and entacapone. They are ineffective as monotherapy, but when used with carbidopa-levodopa, they can potentiate and prolong the effect of levodopa. They are most useful for treating patients experiencing the wearing-off phenomenon. Tolcapone is associated with hepatotoxicity and therefore requires liver function monitoring in the first 6 months of treatment.

Amantadine acts as an *N*-methyl-D-aspartate–receptor antagonist and has historically been used as monotherapy in early PD. However, it is less effective than the dopaminergic agents and its current role is as adjunctive therapy for reducing the severity of drug-induced dyskinesia. Adverse effects may include livedo reticularis and hallucinations.

Anticholinergic agents can be selectively effective for tremor and dystonia that are poorly responsive to carbidopa-levodopa. The most common formulations used in PD are trihexyphenidyl and benztropine. Dose-dependent adverse effects can be very limiting and include dry mouth, nausea, constipation, urinary retention, blurred vision, sedation, and memory impairment.

Approach to Initial Therapy

Approaches to the initial treatment of PD vary: Some favor the early use of levodopa because of its greater efficacy and ease of use, and others favor a levodopa-sparing approach, particularly for younger patients because other agents are less associated with motor fluctuations and dyskinesia. A general principle is to continue to escalate therapy until motor parkinsonism is no longer significantly affecting the patient's quality of life. The lowest equally effective dose of all medications should be used.

Motor Fluctuations and Dyskinesia

In almost all patients who have advanced PD, motor fluctuations develop with the use of levodopa. The most common is the wearing-off effect, the phenomenon in which the parkinsonian symptoms return before the next dose of levodopa. The simplest way to treat this effect is to increase the dose of levodopa (if the response is not strong enough) or to decrease the time between doses. Use of the sustained-release formulations of levodopa may also be

effective in some patients. If these strategies prove ineffective, addition of a second agent, such as a dopamine agonist, a catechol *O*-methyltransferase inhibitor, or an MAO-B inhibitor, may potentiate the effect of levodopa and improve the motor fluctuation.

Dyskinesia is any form of involuntary, abnormal movement that occurs as a direct result of treatment with levodopa. It occurs in up to 30% to 40% of patients receiving treatment for 5 years and in 60% of patients by 10 years. The most common type of dyskinesia is choreiform, manifested by jerking movements of the head, face, and extremities. Mild dyskinesia is surprisingly well tolerated by many patients; medication adjustments were required for less than 50% of patients in 1 study. The approach to treatment of dyskinesia can be complicated. Strategies include decreasing the levodopa dose, replacing a portion with a dopamine agonist, and adding amantadine. Some patients also have benefited from clozapine.

Surgical Therapies

When pharmacologic treatment proves ineffective, or motor fluctuations and dyskinesias become disabling, surgical therapies may be helpful. Lesioning procedures may be useful in treating PD. Thalamotomy improves contralateral tremor and rigidity, and pallidotomy improves most features of motor parkinsonism and reduces dyskinesia. However, these procedures (especially when performed bilaterally) can be associated with serious side effects, including dysarthria, cognitive dysfunction, and even weakness or spasticity.

Today, lesioning procedures have been largely replaced by deep brain stimulation (DBS) that targets subcortical structures. Subthalamic nucleus DBS is effective against all cardinal features of PD, it reduces the need for pharmacologic agents, and it often improves drug-induced dyskinesia. DBS targeting the globus pallidus interna results in improvement similar to what is attained with subthalamic nucleus DBS, whereas DBS targeting the ventralis intermedius nucleus of the thalamus is generally effective for only contralateral tremor. Serious complications of DBS include intracerebral hemorrhage, infection, worsening of cognition, dysarthria, behavioral dyscontrol, eyelid apraxia, and hardware complications. Despite these potential complications, DBS has proved to be an effective procedure with low morbidity for well-selected patients. Indications for DBS in PD include medication-refractory motor fluctuations and dyskinesia, medication refractory tremor, and possibly medication intolerance. DBS is less useful for treatment of midline symptoms, such as speech disturbance and gait, and imbalance or nonmotor features generally do not respond.

- Patients with young-onset PD (patient age <40 years at onset) are more prone to have motor fluctuations or dyskinesia (or both).
- The approach to treatment of dyskinesia can be complicated. Strategies include decreasing the levodopa dose, replacing a portion with a dopamine agonist, and adding amantadine. Some patients also have benefited from clozapine.
- Subthalamic nucleus DBS is effective against all cardinal features of PD, it reduces the need for pharmacologic agents, and it often improves drug-induced dyskinesia.

Prognosis

PD progression and overall prognosis vary from patient to patient. As PD advances, gait disturbance, including freezing, may become refractory to medications. Imbalance may emerge. Nonmotor symptoms such as autonomic failure or PD dementia may occur. Patients with tremor-predominant disease generally have a more favorable prognosis, including slower progression to dementia, than do those with gait-predominant disease. In patients with young-onset PD (patient age <40 years at onset), motor fluctuations and dyskinesia are more likely to develop earlier. Most studies suggest that PD patients have a nearly normal life expectancy; however, by 10 to 15 years after diagnosis, most patients have considerable disease-related disability.

- Most studies suggest that PD patients have a nearly normal life expectancy; however, by 10 to 15 years after diagnosis, most patients have considerable disease-related disability.

23 Atypical Parkinsonian Syndromes

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Introduction

The cardinal features of parkinsonism are represented in the mnemonic *TRAP*: tremor at rest, rigidity, akinesia and bradykinesia, and postural instability. The parkinsonian phenotype encompasses a broad range of clinical and pathologic disorders; the most common (about 55% of cases) is idiopathic (sporadic) Parkinson disease (PD). Rapid disease progression, poor initial response to dopaminergic therapy, or the early presence of certain other signs may suggest an atypical parkinsonian syndrome, sometimes called parkinsonism-plus syndrome. Multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) are reviewed in this chapter (Table 23.1). PD is described in Chapter 22 ("Hypokinetic Movement Disorders: Parkinson Disease"), and dementia with Lewy bodies is described in Chapter 32 ("Parkinsonian-Related Dementias").

Secondary parkinsonism refers to cases in which a specific cause is known. Certain medications, toxins, metabolic disorders, and systemic illnesses may also cause parkinsonism (Table 23.2).

Multiple System Atrophy

Overview and Epidemiology

MSA is a sporadic, adult-onset neurodegenerative disease that affects the basal ganglia, brainstem, cerebellum, and intermediolateral cell columns of the spinal cord. Medication-induced parkinsonism can occur at any age. Otherwise, the mean age at onset of MSA, 53 years, is the youngest among the parkinsonian syndromes. Median survival is 9 years. MSA includes 3 disorders that were previously considered distinct but are now recognized as having overlapping clinical and pathologic features: Shy-Drager syndrome (predominantly autonomic features), striatonigral degeneration (extrapyramidal features), and olivopontocerebellar atrophy (cerebellar features). All forms of MSA account for approximately 8% of cases of parkinsonism in autopsy series.

Clinical Features

Symptoms of autonomic failure are the presenting concerns of half of MSA patients and are present in most during the clinical course. Most common are orthostatism and urinary incontinence, followed by anhidrosis, impotence, and constipation. Hypotension manifests posturally and postprandially. Urinary incontinence results from detrusor hypofunction, denervation (loss of parasympathetic input), and hyperreflexia compounded by sphincter weakness secondary to involvement of the Onuf nucleus in the sacral spinal cord. The "cold hands sign" is another autonomic symptom that may occur in MSA.

Extrapyramidal features occur in most MSA patients during the disease course, but they are the presenting symptoms in less than half the patients. Bradykinesia and rigidity are most common; tremor is less common. In contrast to the appendicular rigidity seen in idiopathic PD, prominent axial rigidity is a hallmark of MSA. Severe postural abnormalities are also more common in MSA and may include lateral bending of the trunk, the so-called Pisa

Abbreviations: CBD, corticobasal degeneration; CBS, corticobasal syndrome; FDG, fludeoxyglucose F 18; MRI, magnetic resonance imaging; MSA, multiple system atrophy; PD, Parkinson disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; SPECT, single-photon emission computed tomography

Table 23.1 • Degenerative Causes of Atypical Parkinsonism

Cause	Clinical Features	MRI	Pathology
Multiple system atrophy	Autonomic failure (orthostatism and urinary incontinence are common) Parkinsonism with prominent axial rigidity and bradykinesia	Brain MRI may show nonspecific nigral atrophy and T2 hypointensity and atrophy of the putamen and pons Linear T2 hypointensity lateral to the putamen suggests iron deposition	α-Synucleinopathy Pathologic changes in motor cortex, basal ganglia, pons, and intermediolateral cell column of the spinal cord
Corticobasal degeneration	Alien limb or limb apraxia early in the course Dementia and visuospatial difficulties may develop later	Often normal early in the course Evolves to show asymmetric frontoparietal cortical and midcallosal atrophy, with mild T2 hypointensity in the putamen and globus pallidus	Tauopathy Pathologic changes in cerebral cortex, subcortical white matter, and substantia nigra
Progressive supranuclear palsy	Parkinsonism, oculomotor disturbances, early falls, and subcortical dementia	Atrophy of the midbrain (reduced anteroposterior diameter with "penguin" or "hummingbird" sign) and superior cerebellar peduncles, widening of the third ventricle, and T2 hyperintensity in the pontine tegmentum, midbrain tectum, and inferior olivary nucleus	Tauopathy Pathologic changes in the midbrain, pontine tegmentum, basal ganglia (globus pallidus more than putamen), and prefrontal cortex

Abbreviation: MRI, magnetic resonance imaging.

sign. The designation *MSA-P* is applied when parkinsonian features are most prominent. Other features may include severe hypophonia and postural myoclonus (jerking of outstretched hands).

Only 5% of patients with MSA present with predominantly cerebellar features (designated *MSA-C*), but cerebellar features eventually develop in 50%. Appendicular and truncal ataxia are more common than oculomotor abnormalities and may be accompanied by kinetic tremor.

Other features of MSA (all forms) include polyneuropathy; corticospinal tract signs (spasticity, hyperreflexia, and extensor plantar responses); and stridor, sleep apnea, or rapid eye movement sleep behavior disorder. Stridor in MSA is due to abductor weakness of the vocal cords and is associated with sudden nocturnal death. Cognitive dysfunction is uncommon in MSA, with a minority of patients demonstrating abnormalities in attentional tasks, working memory, processing speed, and praxis.

Evaluation

Brain magnetic resonance imaging (MRI) may show nonspecific nigral atrophy and T2 hypointensity and atrophy of the putamen. Linear T2 hypointensity lateral to the posterior putamen suggests iron deposition and supports the diagnosis of MSA (Figure 23.1). Later findings may include focal atrophy of the cerebellum, middle cerebellar peduncles, and pons. Pontine atrophy creates the "hot cross bun" sign. Fluorodopa positron emission tomography (PET) shows decreased uptake in striatonigral projections, with hypometabolism in the putamen and caudate nucleus.

Thermoregulatory sweat testing of patients who have MSA often shows segmental (progressing to complete) anhidrosis, consistent with a preganglionic sudomotor deficit originating in the intermediolateral cell column. Further autonomic dysfunction can be measured by tilt table testing and other methods. Polysomnography is indicated for evaluation of stridor. Electromyography of the external urethra or anal sphincter shows long-duration, high-amplitude (neuropathic) motor unit potentials because of denervation secondary to involvement of the Onuf nucleus.

Histopathology

MSA, like PD, is an α-synucleinopathy. Inclusions of α-synuclein (and less frequently ubiquitin, β-crystallin, and tubulins) are seen in the nucleus and cytoplasm of neurons and oligodendrocytes (glial cytoplasmic inclusions) in the motor cortex, basal ganglia, pons, and intermediolateral cell column of the spinal cord (Figure 23.2). Variable neuronal loss and gliosis occur in the inferior olivary nuclei, pons, cerebellum, intermediolateral cell column, putamen, and substantia nigra.

Treatment

No treatment cures or slows the progression of MSA or any other parkinsonism-plus syndrome, so therapies are supportive. One-third of patients may respond to levodopa, although the response is usually brief and limited. Higher levodopa doses are often necessary for MSA than for PD, but this often worsens orthostatism and may induce an early drug-induced dyskinesia or dystonia prominently involving the face.

For orthostatism, offending medications (including levodopa) should be discontinued, dietary fluid and salt should be liberalized, the head of the bed should be elevated to 30° (to increase renin secretion), and compressive elastic

Table 23.2 • Causes and Key Features of Secondary Parkinsonism

Cause of Secondary Parkinsonism	Key Feature
Vascular	
Cerebral infarction or hemorrhage (frontal)	Lower-half (ie, lower body) parkinsonism
Infectious	
Prion	May have associated dementia
HIV/AIDS	HIV risk factors
Syphilis	. . .
Postencephalitic (von Economo disease)	Worldwide epidemic in early 1900s
Inflammatory	
Lupus	. . .
Neoplastic or paraneoplastic	
Frontal or parasagittal mass	Meningioma
Metabolic or endocrine	
Wilson disease	Kayser-Fleisher rings, impaired copper metabolism
Corticobasal calcification	Parathyroid disease
Idiopathic basal ganglia calcification (Fahr disease)	Schizophrenialike psychosis (age, 20–40 years) or progressive dementia and parkinsonism (age, 40–60 years); minority of cases due to mutations on chromosomes 8, 14, and 22
GM_1 gangliosidosis or Gaucher disease	. . .
Pantothenate kinase–associated neurodegeneration (neurodegeneration with brain iron accumulation type 1; formerly called Hallervorden-Spatz disease)	MRI shows "eye of the tiger" sign; excessive intracellular and extracellular iron deposition due to autosomal recessive mutation on chromosome 20p12.3-p13
Toxin	
Carbon disulfide	Silo worker
Carbon monoxide	Hypoattenuation of globus pallidus
Cyanide	Targets globus pallidus
Mercury	Gold miners
Methanol	Targets putamen
Manganese	Miners, welders, methcathinone, patients receiving TPN or hemodialysis; targets globus pallidus and subthalamic nucleus
MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)	Designer drug whose metabolite, 1-methyl-4-phenylpyridinium, is a mitochondrial toxin
Trichloroethylene	Organic solvent and inhaled anesthetic
Medication	Symptom onset may be abrupt with new exposure or titration and is usually symmetric
Monoamine depletors: tetrabenazine, reserpine	
Antipsychotics (most except clozapine)	
Antiemetics and promotility agents: metoclopramide, chlorpromazine, prochlorperazine, fluphenazine	
Acquired	
Hydrocephalus	Gait apraxia, dementia, urinary incontinence
Pugilistic	History of chronic or repeated head trauma
ALS and PDC on Guam	. . .
Degenerative	. . .
Multiple system atrophy	
Corticobasal ganglionic degeneration	
Progressive supranuclear palsy	
Spinocerebellar ataxias (eg, Machado-Joseph disease)	
Alzheimer disease	
Huntington disease (Westphal variant)	

Abbreviations: ALS, amyotrophic lateral sclerosis; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; PDC, parkinsonism-dementia complex; TPN, total parenteral nutrition.

stockings or an abdominal binder (or both) can be worn. If conservative measures are inadequate, fludrocortisone (which has mineralocorticoid activity), midodrine (an α-adrenergic agonist), or pyridostigmine may be helpful.

For urinary incontinence, patients may progress from a bedside urinal or condom catheter (for simple urge incontinence), to intermittent self-catheterization (for urinary retention), to anticholinergic agents (oxybutynin or propantheline for detrusor hyperreflexia), to an indwelling catheter or surgery. Anhidrotic patients should avoid extreme heat (environmental heat or overheating during exercise). Stridor can be treated with continuous positive

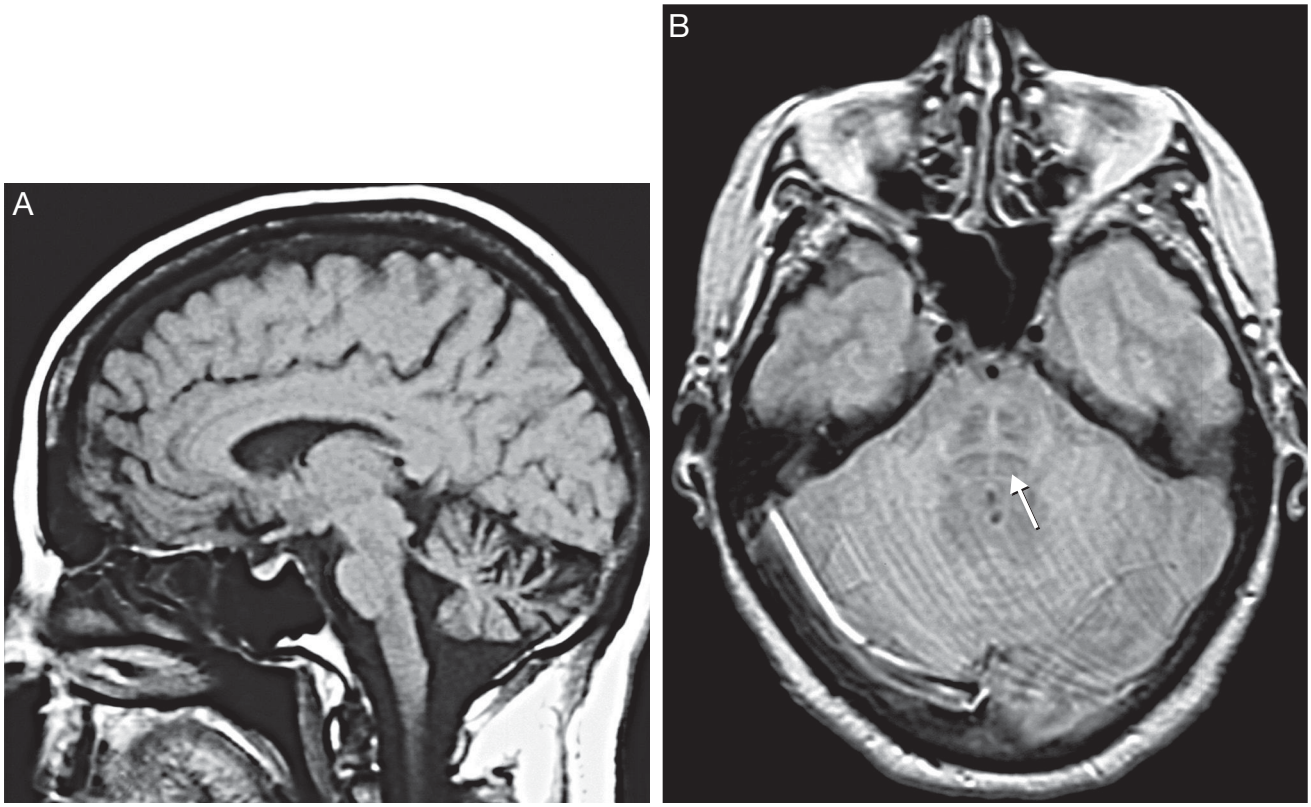

Figure 23.1 *Magnetic Resonance Imaging of Multiple System Atrophy.*
A, Atrophy of the cerebellum, pons, and lower medulla (inferior olivary nuclei) is seen best in sagittal T1-weighted images. B, The "hot cross bun" sign (arrow) results from pontine atrophy and is seen best in axial T2-weighted and proton density images.
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

airway pressure or, for refractory vocal cord paresis, tracheostomy. Physical therapy should be prescribed for all patients.

- Multiple system atrophy (MSA) is a sporadic, adult-onset neurodegenerative disease that affects the basal ganglia, brainstem, cerebellum, and intermediolateral cell columns of the spinal cord.
- The mean age at onset of MSA, 53 years, is the youngest among the parkinsonian syndromes.
- Symptoms of autonomic failure are the presenting concerns of half of MSA patients and are present in most during the clinical course.
- Prominent axial rigidity is a hallmark of MSA.
- Thermoregulatory sweat testing of patients who have MSA often shows segmental (progressing to complete) anhidrosis, consistent with a preganglionic sudomotor deficit originating in the intermediolateral cell column.
- MSA, like Parkinson disease, is an α-synucleinopathy.

Progressive Supranuclear Palsy

Overview and Epidemiology

PSP is the most common type of parkinsonism-plus syndrome, clinically manifesting as parkinsonism, oculomotor disturbances, early falls, and subcortical dementia. The combination of supranuclear vertical gaze palsy and early balance disturbance with falls distinguishes PSP from other causes of parkinsonism. Because dopaminergic, cholinergic, and adrenergic neurotransmitter systems are affected, the degenerative process is far more diffuse than in PD. Median age at onset is 63 years, and median survival is 8 years. Annual incidence in the United States is approximately 3 new cases per million, making it approximately 1% as common as PD.

Clinical Features

The chief presenting concerns of patients with PSP are stiffness and falls. Neurologic examination findings include prominent axial rigidity with a hyperextended

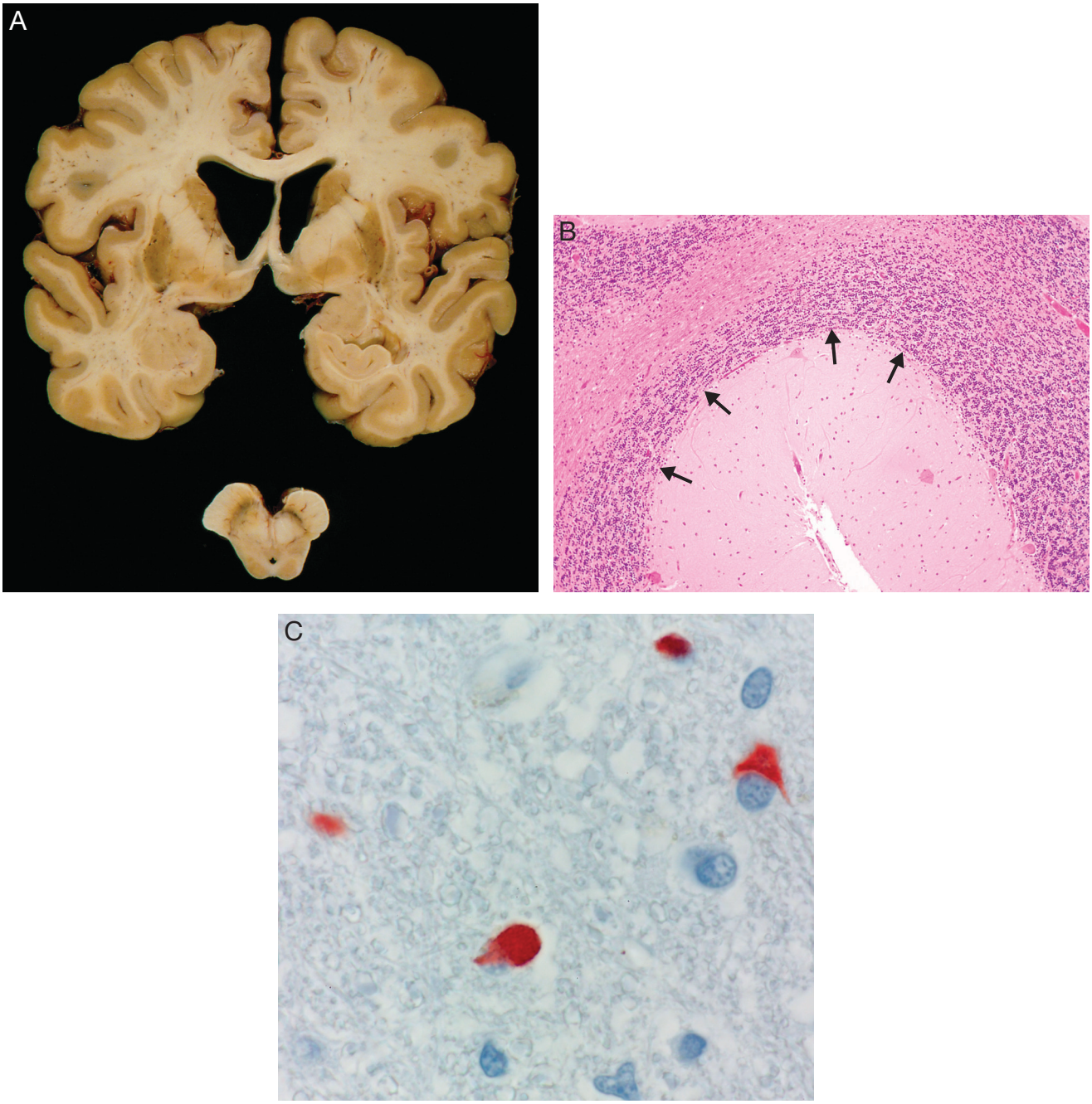

Figure 23.2 *Histopathology of Multiple System Atrophy (MSA).*
A, Macroscopically, there is often atrophy and discoloration of the putamen and pallor of the substantia nigra and locus ceruleus in the striatonigral type of MSA, in which parkinsonian features are most prominent (MSA-P). B and C, Microscopically, the disease is characterized by a loss of cerebellar Purkinje cells (arrows in B) and α-synuclein–positive cytoplasmic inclusions (C).
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

(retrocollic) posture during walking (as opposed to antecollis in PD and MSA) and early postural instability. Bradykinesia is common and generally symmetric, whereas tremor is rare.

Eye movement abnormalities are much more common in PSP than in other parkinsonian syndromes and include the breakdown of vertical saccades (slow and hypometric, especially downward) more than horizontal saccades, limitation

of convergence and a wide-eyed stare due to bilateral exophoria and lid retraction, and eventually complete bilateral ophthalmoplegia. Because the vertical ocular gaze paresis can be overcome by passive head movement (oculocephalic reflex or doll's eye reflex), it is called *supranuclear*. There may also be excess square wave jerks, saccadic intrusions on primary gaze, reduced fast component of optokinetic nystagmus, and eyelid apraxia (especially opening).

In many patients, a pseudobulbar palsy develops with drooling, dysphagia, dysarthria (spastic, sometimes hypernasal), and socially inappropriate crying and laughter (emotional incontinence). PSP is associated with frontal lobe dysfunction with impaired attention, mental slowing, executive dysfunction, personality changes (apathy, irritability, and disinhibition), and frontal release signs. Degeneration of brainstem adrenergic nuclei may cause systemic hypertension.

Evaluation

MRI of the brain of patients who have PSP shows atrophy of the midbrain (the reduced anteroposterior diameter creates the "penguin" or "hummingbird" sign) and superior cerebellar peduncles, widening of the third ventricle, and T2 hyperintensity in the pontine tegmentum, midbrain tectum, and inferior olivary nucleus (Figure 23.3). Fluorodopa PET shows reduced uptake in the caudate nucleus and putamen, with other functional imaging showing hypometabolism in the frontal lobes bilaterally (especially the premotor cortex), basal ganglia, thalamus, and upper brainstem. Polysomnography shows diminished total sleep time and rapid eye movement sleep.

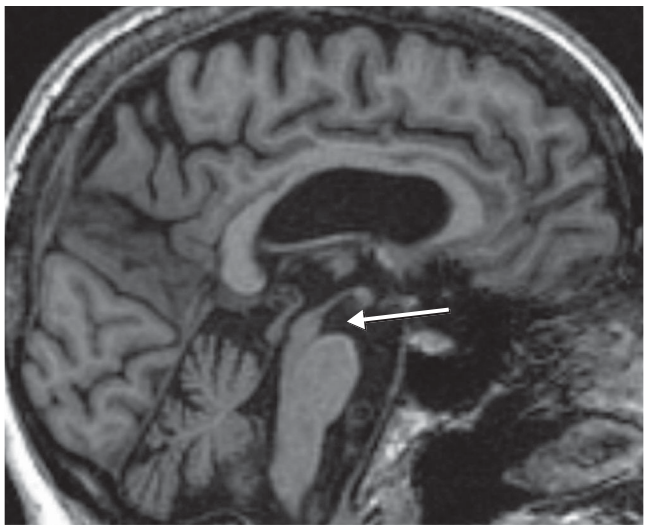

Figure 23.3 *Magnetic Resonance Imaging of Progressive Supranuclear Palsy.*
Sagittal T1-weighted image shows midbrain atrophy with reduced anteroposterior diameter (arrow) ("penguin" or "hummingbird" sign).

Histopathology

Whereas PD and MSA are α-synucleinopathies, PSP is a 4-repeat tauopathy in which histopathologic examination shows neuronal loss, gliosis, and flame-shaped and globose neurofibrillary tangles (Figure 23.4). The unusual globose bodies contain bundles of straight tau filaments (as opposed to paired helical filaments in corticobasal degeneration and Alzheimer disease). Pretangles are also seen and consist of nonfilamentous cytoplasmic tau deposits. Abnormal tau deposition creates tau-positive "tufted" astrocytes in the motor cortex and striatum. Atrophy, with neuronal loss and gliosis, may be secondary to tau deposition or result from a separate process; atrophy involves the midbrain, pontine tegmentum, basal ganglia (globus pallidus more than putamen), and prefrontal cortex. There may also be pallor of the substantia nigra and locus ceruleus and iron deposition in the globus pallidus.

Treatment

Only supportive therapy is available, but even with that, the clinical benefit is small. Levodopa and other dopaminergic agents help bradykinesia and rigidity in a minority (20%-30%) of patients with PSP for the first 1 or 2 years. Acetylcholinesterase inhibitors (donepezil or rivastigmine) and *N*-methyl-D-aspartate–receptor antagonists (memantine) are generally ineffective for slowing the cognitive decline in patients with PSP. Pseudobulbar affect may be helped by dextromethorphan in combination with quinidine (Nuedexta).

- Progressive supranuclear palsy (PSP) is the most common type of parkinsonism-plus syndrome, clinically manifesting as parkinsonism, oculomotor disturbances, early falls, and subcortical dementia.
- The chief presenting concerns of patients with PSP are stiffness and falls.
- MRI of the brain of patients who have PSP shows atrophy of the midbrain (the reduced anteroposterior diameter creates the "penguin" or "hummingbird" sign) and superior cerebellar peduncles, widening of the third ventricle, and T2 hyperintensity in the pontine tegmentum, midbrain tectum, and inferior olivary nucleus.
- PSP is a 4-repeat tauopathy in which histopathologic examination shows neuronal loss, gliosis, and flame-shaped and globose neurofibrillary tangles.
- Levodopa and other dopaminergic agents help bradykinesia and rigidity in a minority (20%-30%) of patients with PSP for the first 1 or 2 years.

Corticobasal Degeneration

Overview and Epidemiology

CBD is a pathologic diagnosis with a classic clinical presentation, corticobasal syndrome (CBS), that involves

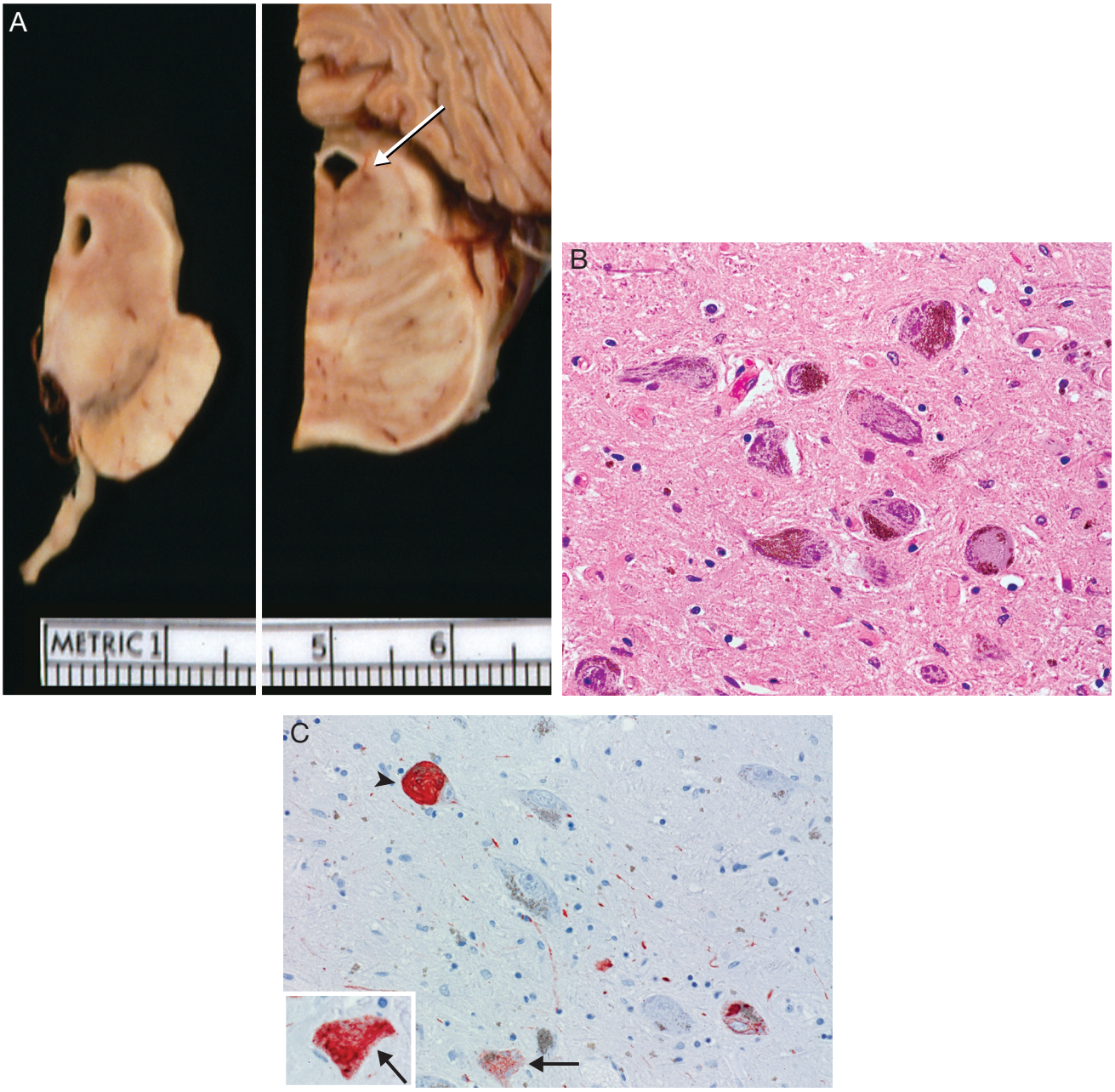

Figure 23.4 *Histopathology of Progressive Supranuclear Palsy.*
A, Macroscopically, there is atrophy of upper brainstem structures and pallor of the substantia nigra and locus ceruleus (arrow). B, The most important microscopic feature is the globose neurofibrillary tangles, which are basophilic, tau-positive, argyrophilic structures in the gray matter. C, Tau immunohistochemistry in a section of thalamus shows neuronal accumulation of tau protein, with aggregation into globose neurofibrillary tangles (arrowhead) and pretangles (arrows).
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

progressive asymmetric rigidity and cortical dysfunction. Similar histology is less often seen in evaluations of patients who present with frontotemporal dementia and progressive aphasia. Mean age at onset is 63 years, and median survival is 8 years. CBD is about as common as PSP—each is about 1% as common as PD.

Clinical Features

A defining feature of CBS is an asymmetric or focal presentation. Patients with CBS commonly have alien limb phenomenon (involuntary, uncontrollable, and semipurposeful limb movements that worsen with the eyes closed)

and ideomotor limb apraxia (inability to perform or mimic simple motor tasks in the absence of a prominent motor or sensory deficit). Limb apraxia usually involves the nondominant hand, may render a limb useless when severe, and may be masked by progressive rigidity or dystonia. The affected limb may be both rigid and spastic, and patients may have myoclonus (cortically generated, action- or stimulus-induced myoclonus) and dystonic posturing. Mirror movements, when they occur, probably result from parietal and, less often, corpus callosal degeneration. Other features include cortical sensory loss; apraxia of speech, eyelid opening, and eye movements; and dementia with psychomotor slowing, frontal-executive dysfunction, and impaired attention and concentration. Visuospatial abnormalities, including Balint syndrome (optic ataxia, ocular apraxia, and simultanagnosia), may develop.

Evaluation

MRI of the brain often shows normal findings early in the course but later shows asymmetric frontoparietal cortical and midcallosal atrophy, with mild T2 hypointensity in the putamen and globus pallidus (Figure 23.5). Central sulcus dilatation may be present because of thinning of anterior and posterior central gyri. Fludeoxyglucose F 18 (FDG)-PET shows hypometabolism of the frontoparietal cortex, lenticular nucleus, and thalamus bilaterally (usually more extensive than the MRI appearance of atrophy). Upper limb somatosensory evoked potentials may be abnormal, reflecting disruption of information processing in the parietal cortex.

Typical findings are asymmetric hypoperfusion on single-photon emission computed tomography (SPECT) and asymmetric hypometabolism on FDG-PET involving the parietofrontal cortex with or without basal ganglia; in some cases, the abnormality is remarkably focal. Asymmetric striatonigral uptake on DaTscan imaging is the rule, although DaTscan is rarely needed to solidify a clinical diagnosis of CBS. Amyloid PET imaging may be useful in distinguishing atypical Alzheimer disease from the nonamyloidopathy disorders (eg, CBD, PSP, and frontotemporal lobe degeneration characterized by TAR DNA-binding protein 43) that can underlie CBS, but it is too early to know whether this differentiation will have treatment implications in the future.

Histopathology

CBD is a 4-repeat tauopathy like PSP, although the microscopic appearances differ. Also, the tau filaments in CBD are double-stranded and paired helically as in Alzheimer disease, but they are more polymorphic. Further histopathologic examination shows asymmetric, focal frontoparietal and perirolandic cortical atrophy. Neuronal dropout and gliosis are seen in superficial cortical layers and subcortical white matter, with severe neuronal loss creating the appearance of status spongiosis in some areas. Remaining neurons may be "ballooned" with a swollen and achromatic (ie, loss of cytoplasmic staining) appearance secondary to accumulation of phosphorylated neurofilament epitopes and αβ-crystallin (Figure 23.6). The substantia nigra is generally depigmented and may contain intraneuronal, corticobasal, tau-positive, ubiquitin-negative inclusions (also in cortical layer II). Astrocytic plaques are specific for CBD (these are tau-positive, thick glial inclusions deposited in the distal processes of cortical astrocytes). The pathologic changes are severe in the white matter, where numerous tau-positive threads are seen.

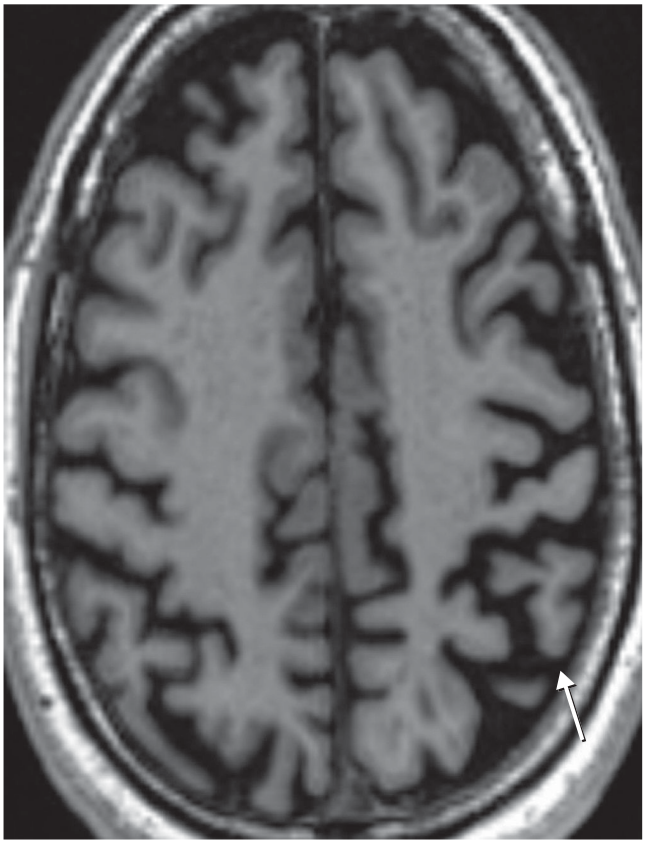

Figure 23.5 *Magnetic Resonance Imaging of Corticobasal Degeneration.*
Axial T1-weighted image shows asymmetric frontoparietal atrophy (arrow).

Treatment

Treatment is symptomatic. Levodopa may provide limited relief to a minority of patients (25%); the use of dopamine agonists or amantadine provides even less. Clonazepam may be helpful for myoclonus and dystonia; dystonia may also respond to botulinum toxin injections. Selective

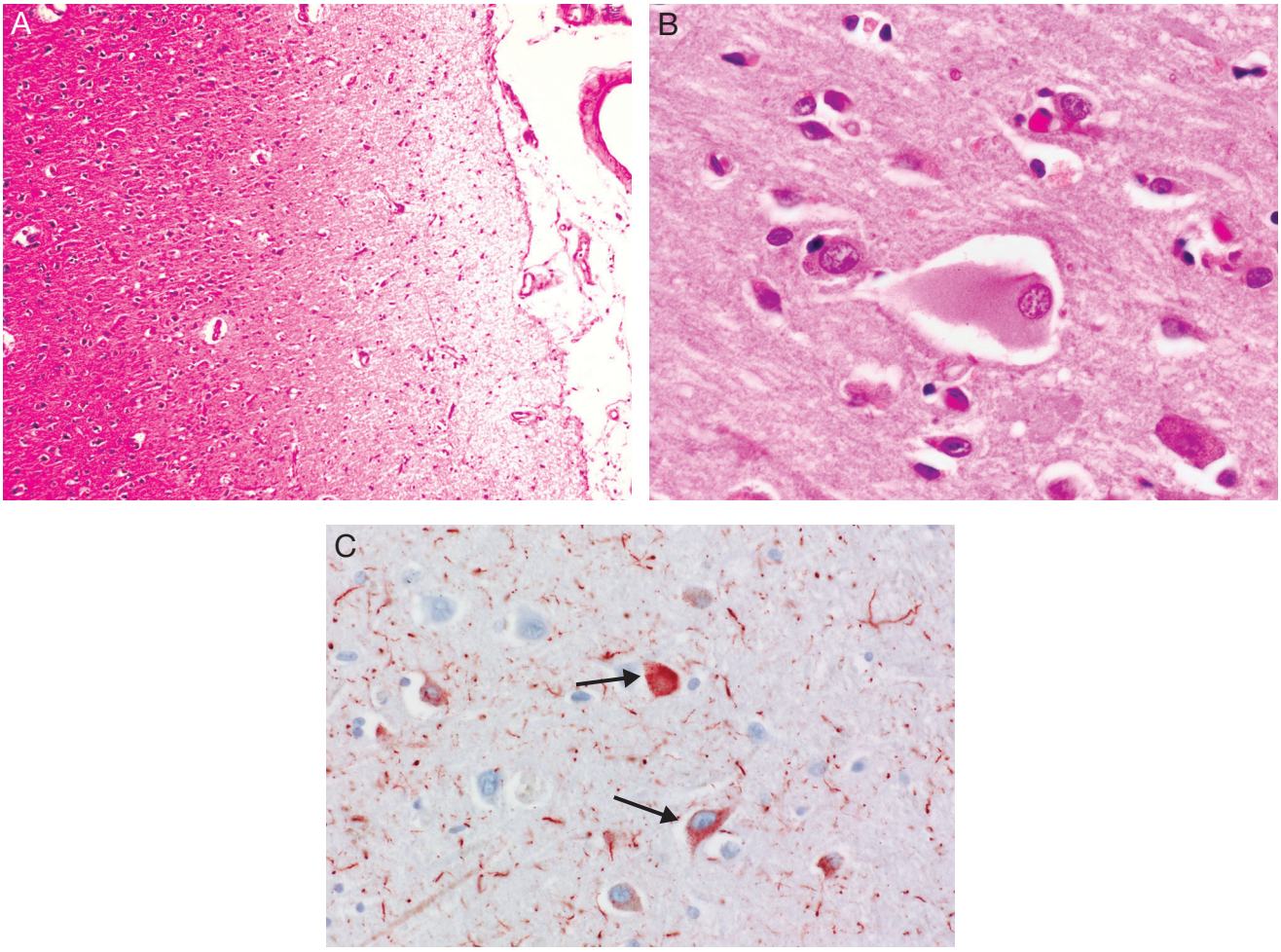

Figure 23.6 *Histopathology of Corticobasal Degeneration.*
A, The superficial layers of the cerebral cortex show neuronal loss and microvacuolation. B, Cortical neurons are characteristically swollen. C, Tau-positive intraneuronal inclusions appear as globular or angular inclusions (arrows).
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

serotonin reuptake inhibitors may help depressive symptoms. Physical therapy is important and helps to delay progression to a fixed, contracted limb.

- Corticobasal degeneration (CBD) is a pathologic diagnosis with a classic clinical presentation, corticobasal syndrome (CBS), that involves progressive asymmetric rigidity and cortical dysfunction.
- Patients with CBS commonly have alien limb phenomenon (involuntary, uncontrollable, and semipurposeful limb movements that worsen with the eyes closed) and ideomotor limb apraxia (inability to perform or mimic simple motor tasks in the absence of a prominent motor or sensory deficit).
- CBD is a 4-repeat tauopathy like PSP, although the microscopic appearances differ.

Secondary Causes of Parkinsonism

Treatable and potentially reversible causes of parkinsonism must be ruled out. In particular, young patients (<50 years) presenting with parkinsonism should undergo MRI of the brain, be tested for Wilson disease with serum copper and ceruloplasmin levels, have screening for human immunodeficiency virus and syphilis, and undergo a thorough review of family history, medications, drugs, and toxin exposures. Patients 50 years or older warrant additional testing depending on their presentation, historical features, and additional clinical symptoms.

Select secondary causes are described below. Many of the other conditions resulting in secondary parkinsonism are discussed elsewhere or are beyond the scope of the text; thus, details are not provided here.

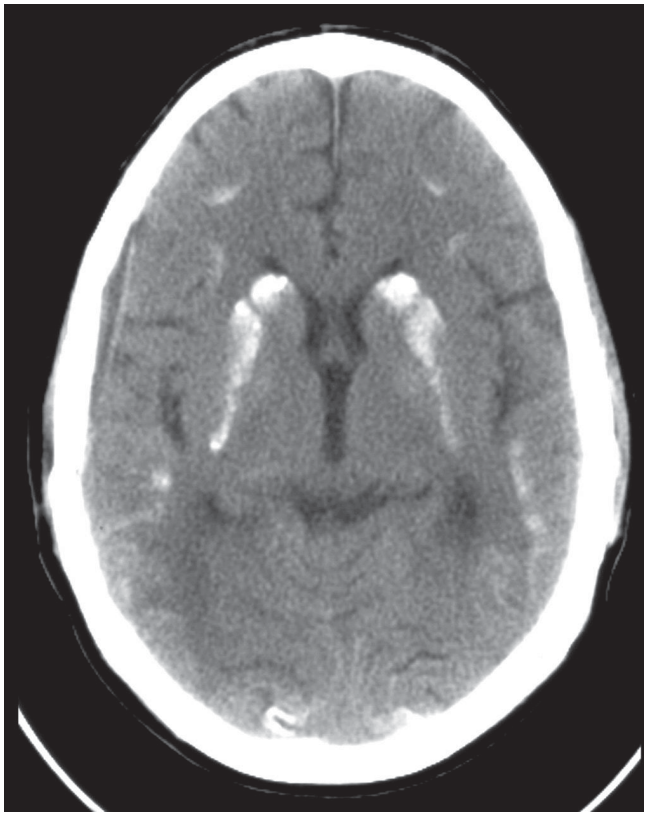

Figure 23.7 *Fahr Disease.*
Nonenhanced computed tomography shows characteristically intense calcification in the basal ganglia.
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

Vascular Parkinsonism

Vascular parkinsonism is classically a lower-half (ie, lower body) parkinsonian syndrome dominated by gait disturbance and associated with confluent subcortical white matter ischemic changes and lacunar infarcts. Dopamine transporter SPECT imaging findings are usually normal in vascular parkinsonism, distinguishing it from PD. Also, olfaction is usually preserved in vascular parkinsonism, whereas 80% of PD patients are hyposmic.

Box 23.1 • Differential Diagnosis of Symmetric Basal Ganglia Calcification

- Idiopathic
- Fahr disease
- Wilson disease
- Amyloid angiopathy
- Hypercalcemia
- Hypoparathyroidism
- Postinfectious: tuberculosis, congenital HIV, toxoplasmosis, cysticercosis
- Toxic: lead, chemotherapy agents (methotrexate), radiotherapy
- Perinatal anoxia
- Carbon monoxide intoxification
- Cockayne syndrome

Abbreviation: HIV, human immunodeficiency virus.

Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.

Fahr Disease

Patients with idiopathic calcification of the basal ganglia, also known as Fahr disease, can present with psychiatric manifestations early in life (ages 20–40 years) and with dementia and parkinsonism later (ages 40–60 years). Psychiatric manifestations may include schizophrenia or psychosis. Imaging typically shows basal ganglia, dentate, and periventricular calcification (Figure 23.7). The imaging findings alone are nonspecific (Box 23.1), but the constellation of clinical features and imaging findings are consistent with this disease.

Wilson Disease

Wilson disease is discussed in Chapter 27, "Childhood Movement Disorders."

24 Hyperkinetic Movement Disorders: Tremor and Myoclonus

MELINDA S. BURNETT, MD

Introduction

Hyperkinetic movement disorders are characterized by an excess of movement. Tremor and myoclonus are 2 common hyperkinetic movement disorders that may signify a wide variety of underlying causes or diagnoses. Other hyperkinetic movement disorders (such as chorea, dystonia, and tics) are reviewed in Chapter 25, "Hyperkinetic Movement Disorders: Chorea, Tic, and Dystonia."

Tremors

Definition and Classification

Tremor is an involuntary, repetitive, oscillatory movement of a body part. It can be distinguished from myoclonus by its regular frequency and from chorea by its stereotyped nature. The subtypes of tremor can be distinguished on the basis of their frequency, conditions of activation and relief, and associated signs and symptoms. Tremor can be *primary*, being the only manifestation of an underlying condition, or *secondary*, being symptomatic of a metabolic state or a more extensive underlying disease.

- Tremor is an involuntary, repetitive, oscillatory movement of a body part. It can be distinguished from myoclonus by its regular frequency and from chorea by its stereotyped nature.

Epidemiology

The most common primary tremor disorder is essential tremor (ET), with an estimated prevalence of about 300 per 100,000 people and an estimated age-adjusted annual incidence of 18 per 100,000 men and 17 per 100,000 women. Onset occurs most commonly between the ages of 50 to 70 (mostly sporadic ET), with a second peak at ages 15 to 20 (mostly familial ET). Other primary tremor disorders, such as primary orthostatic tremor and primary writing tremor, are rare and the prevalence has not been estimated.

Essential Tremor

Pathophysiology

The pathophysiology of ET is unknown. About 50% of patients with ET have a family history of ET, and it tends to follow an autosomal dominant pattern of inheritance. A single gene explaining the majority of ET has not been identified. Functional imaging studies implicate the establishment of a pathologic central oscillation involving the cerebellum and inferior olivary nucleus. Increased blood flow is also seen in the contralateral thalamus, globus pallidus, and sensorimotor cortex. Limited pathologic studies have described torpedoes, or Purkinje cell axonal swellings, located throughout the cerebellum in patients with ET (Figure 24.1). Furthermore, neurotransmitter studies have shown decreased γ-aminobutyric acid levels in cerebrospinal fluid and increased norepinephrine levels in some nuclei, such as the cerebellar dentate nucleus, which may explain why medications with various mechanisms are helpful in ET.

Clinical Features

ET is characterized as a rapid (4–12 Hz), regular oscillation that chiefly involves the upper extremities symmetrically.

Abbreviations: EMG, electromyographic; ET, essential tremor; MERRF, myoclonic epilepsy with ragged red fibers; PME, progressive myoclonic epilepsy

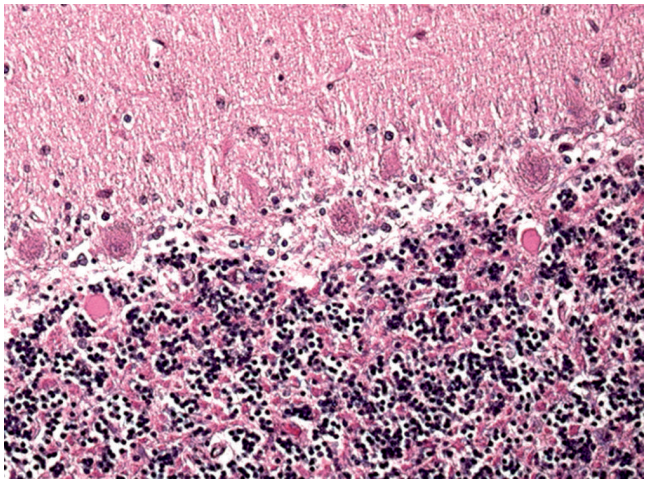

Figure 24.1 *Torpedoes in the Cerebellum of a Patient With Essential Tremor.*
(Luxol fast blue and counterstained with hematoxylin-eosin, orginal magnification ×200.)
(Adapted from Louis ED, Vonsattel JP, Honig LS, Lawton A, Moskowitz C, Ford B, et al. Essential tremor associated with pathologic changes in the cerebellum. Arch Neurol. 2006 Aug;63[8]:1189–93. Used with permission.)

Tremor frequency decreases with age. ET can also involve the head, face, voice, and lower limbs. It occurs predominantly with action and posture and diminishes with rest, although long-standing ET can have a rest component. Alcohol relieves the tremor in up to 70% of affected people. Patients' chief concerns are having difficulty drinking from cups, sipping soup from a spoon, writing, and performing other fine motor tasks (Figure 24.2).

Diagnosis

Diagnosis of ET is clinical. Anyone with an action or postural component of tremor should have thyroid function studies. A serum ceruloplasmin test, 24-hour urine copper level, and slit-lamp examination are used to rule out Wilson disease in patients younger than 50 who have ET. Magnetic resonance imaging is not necessary but could be considered if patients have unilateral symptoms or an intention component. Surface electromyographic (EMG) studies, usually available only in academic centers, can characterize the tremor and are most helpful in ruling out psychogenic disease.

Several medications and metabolic conditions can enhance any form of tremor (Box 24.1). A history of persistence and a slow progression over time can help distinguish ET from exaggerated physiologic tremor, although early in the course the distinction is difficult. Essential head tremor can be distinguished from dystonic head tremor by its consistent amplitude and persistence despite changes in head position. The presence of a prominent rest

Figure 24.2 *Spiral Figure Drawn by a Patient With Essential Tremor.*
The action-kinetic tremor is easily demonstrated with this maneuver.
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

component, bradykinesia, cogwheel rigidity, and perhaps a chin tremor argues for parkinsonism, although given the prevalence of ET, both disorders can coexist. Cerebellar tremors are typically slower in frequency and have an intention component, increasing in amplitude at the end of the movement.

Treatment

Complete tremor relief is often not possible with medical therapy, but it can improve daily function. It is estimated

Box 24.1 • Conditions that Enhance Physiologic and Pathologic Tremor

- Metabolic—hyperthyroidism, hyperparathyroidism, hypomagnesemia, hypocalcemia, hyponatremia, hypoglycemia, fever, pheochromocytoma, renal failure, liver failure, vitamin B_{12} deficiency
- Toxins or diet—nicotine, caffeine, heavy metals, alcohol withdrawal, toluene, cocaine
- Drugs—β-adrenergic agonists, tricyclic antidepressants, anticonvulsants (especially phenytoin and valproic acid), lithium, thyroxine, steroids, neuroleptics, amiodarone, mexiletine, cytostatic chemotherapy (eg, vincristine)

that only 70% of those with ET respond to medical therapy, which is more effective for limb tremor than for head and voice tremor. First-line therapy for ET involves use of long-acting β-blockers such as a long-acting form of propranolol (initially, 40 mg daily; maximum dose, 320 mg daily) in patients without asthma, heart block, bradycardia, or diabetes mellitus. A short-acting form of propranolol is sometimes used as needed. Nadolol, atenolol, and sotalol are possible alternatives. Selective β_1-blockers are less effective. Primidone is a prodrug of phenobarbital and can be administered initially at 25 mg daily and increased to a maximum dose of 250 mg 3 times daily. Adverse effects include fatigue, nausea, and gait instability. Second-line agents include benzodiazepines, such as alprazolam and clonazepam, and anticonvulsants, such as topiramate and gabapentin. Head tremor and voice tremor can respond to botulinum toxin injections. Refractory and disabling tremor can respond to deep brain stimulation of the ventral intermediate nucleus of the thalamus or stereotactic thalamotomy. Thalamotomy is typically done unilaterally, because bilateral thalamotomy results in dysarthria and other intolerable adverse effects. No medical or surgical treatment has been shown to slow or reverse the progression of the disease.

- About 50% of patients with essential tremor (ET) have a family history of ET, and it tends to follow an autosomal dominant pattern of inheritance.
- A serum ceruloplasmin test, 24-hour urine copper level, and slit-lamp examination are used to rule out Wilson disease in patients younger than 50 who have ET.
- First-line therapy for ET involves use of long-acting β-blockers such as a long-acting form of propranolol (initially, 40 mg daily; maximum dose, 320 mg daily) in patients without asthma, heart block, bradycardia, or diabetes mellitus.
- Refractory and disabling tremor can respond to deep brain stimulation of the ventral intermediate nucleus of the thalamus or stereotactic thalamotomy.

Other Tremor Disorders

Parkinsonian Tremor

The strongest component of a parkinsonian tremor is the rest component, which abates upon resumption of posture but may reemerge several seconds later. It affects the limbs asymmetrically. It does not classically affect the head or voice but can involve the jaw, lips, and tongue. This tremor is labeled *monosymptomatic resting tremor* when seen in the absence of other parkinsonian features.

Primary Orthostatic Tremor

Orthostatic tremor can be secondary and accompany other conditions, such as parkinsonism or cerebellar degeneration. The mechanism is unknown, but a cerebellar origin is suspected.

This is a rapid (13–18 Hz) tremor that occurs predominantly in the legs when standing, is relieved with rest, and diminishes with walking or leaning one's head against a wall. The "helicopter sign" is a rapid thumping noise that is heard when the patient is standing during surface EMG studies and muscle is auscultated with a stethoscope. The tremor involves the trunk and the arms to a lesser extent. Patients typically show marked anxiety while standing, and therefore they rarely fall. They stand with a wide base and curl their toes as if to grip the floor. The tremor is seen in patients older than 40 (mean age at onset, 64), and limited epidemiologic studies suggest a 2:1 female predominance.

First-line treatment includes clonazepam 0.5 mg at bedtime, increasing to a maximum of 2 mg 3 times daily. Lower-yield therapies include gabapentin, primidone, valproate sodium, and dopaminergic agents.

Dystonic Tremor

Dystonic tremor is an umbrella term that encompasses several subtypes of tremor. This category of tremor is often included in the differential diagnosis of ET, because patients with dystonia may have a rapid postural and action tremor in body parts not clinically affected by dystonia. Patients with family histories of dystonia sometimes have this kind of tremor without any other clinical evidence of dystonia. When the tremor occurs in a limb that also has dystonic contractions, the tremor is thought to result from phasic dystonia and likely responds to sensory tricks and dystonia-specific treatments. This "true" type of dystonic tremor (eg, dystonic head tremor) often has a variable amplitude and vector and a frequency that is typically less than 7 Hz. Dystonic head tremor responds to botulinum toxin injections.

Holmes Tremor

Holmes tremor has also been called rubral tremor, midbrain tremor, myorhythmia, and cerebellar outflow tremor. This wing-beating tremor affects proximal limbs more than distal limbs and is jerky and slow (<5 Hz). Unlike the more classic cerebellar tremors, this tremor can have a rest component (thought to be from interruption of the nigrostriatal tracts) that may be just as strong as the postural and intention component (thought to be from interruption of the dentatorubroolivary pathway [Guillain-Mollaret triangle] and the cerebellothalamocortical pathway). Holmes tremor has been seen when lesions affect the midbrain, cerebellum, or thalamus and can take up to 2 years to manifest after an acute event, such as a stroke. This tremor is classically described in Wilson disease.

Results with medical treatment are disappointing, and thalamic deep brain stimulation and thalamotomy provide little benefit.

Palatal Tremor

The 2 types of palatal tremor are essential (25% of cases) and symptomatic. *Essential palatal tremor* is created by movements of the tensor veli palatini muscle, produces ear clicks, stops during sleep, is seen in the absence of cerebellar signs, and is not associated with ocular oscillopsia. *Symptomatic palatal tremor* is created by movements of the levator veli palatini muscle, should not cause ear clicks, persists during sleep, is seen with cerebellar signs, and is associated with ocular oscillopsia. Symptomatic palatal tremor is caused most often by a pontine hemorrhage or infarct and arises from disruption of the Guillain-Mollaret triangle, which connects the cerebellar dentate nucleus, red nucleus, and inferior olive. Magnetic resonance imaging shows T2 hyperintensities in the contralateral hypertrophic inferior olive (the hypertrophy is due to cytoplasmic vacuolization).

Essential palatal tremor can respond to clonazepam, valproate sodium, tetrabenazine, haloperidol, trihexyphenidyl, and carbamazepine, but symptomatic palatal tremor is more difficult to treat.

Fragile X–Associated Tremor/Ataxia Syndrome

Fragile X–associated tremor/ataxia syndrome can occur in premutation carriers with 50 to 200 CGG trinucleotide repeats in the *FMR1* gene, which is on the X chromosome. Onset in men is after age 50, and penetrance increases with age. The syndrome typically begins with an intention tremor followed within 1 or 2 years by a progressive cerebellar ataxia, painful peripheral neuropathy, and some degree of autonomic failure. Various psychiatric difficulties can arise, such as anxiety and disinhibition, and, in 50% of patients, a dementia develops with memory loss and executive dysfunction. For more details, see Chapter 26, "Cerebellar Disorders and Ataxias."

Other Tremors

Other primary tremor disorders include primary writing tremor, which is a task-specific tremor (4–7 Hz) that occurs only with writing. In addition, hereditary geniospasm (chin tremor) is a rare, autosomal dominant tremor with an onset in infancy or early childhood. It consists of chin tremor episodes that last from seconds to hours and are triggered by stress, concentration, and emotion.

Other secondary tremors include the tremor of neuropathies (eg, immunoglobulin M paraproteinemic neuropathy), porphyria, or Charcot-Marie-Tooth disease (Roussy-Lévy syndrome). This type of tremor is typically a postural and action tremor of the affected limbs, but it can have a rest component. *Titubation* is a slow oscillation of the head or trunk that is seen with cerebellar disease and is most dramatic when the patient is standing.

- Symptomatic palatal tremor is caused most often by a pontine hemorrhage or infarct and arises from disruption of the Guillain-Mollaret triangle, which connects the cerebellar dentate nucleus, red nucleus, and inferior olive.

Myoclonus

Definition

In myoclonus, a body part moves in rapid, brief jerks due to muscular contraction (*positive myoclonus*) or inhibition of contraction (*negative myoclonus* or *asterixis*). It can be distinguished from tremor by its irregular, nonrhythmic activation (Figure 24.3).

Diagnosis

Myoclonus can be characterized by its location (focal, multifocal, segmental, or generalized), provoking factors (spontaneous or reflex), and context of activation (resting, action, postural, or orthostatic). Describing myoclonus in this way can, to a limited extent, help localize the site of origin as cortical, subcortical, spinal, or peripheral. These categories can then guide diagnosis and therapy. However, often electrophysiologic tests such as surface EMG and electroencephalography are required for full characterization of myoclonus.

Myoclonus is usually a secondary phenomenon, and therefore its presence should prompt a thorough search for underlying metabolic, infectious, and inflammatory causes (Box 24.2). The workup can include electrolyte and blood glucose levels, liver and kidney function tests, thyroid function tests, brain and spinal magnetic resonance imaging, and electroencephalography. Additional tests (eg, paraneoplastic antibody screens and spinal tap for lactate) are done as the clinical context dictates.

Cortical Myoclonus

Cortical myoclonus, consisting of short-duration and "lightning" jerks, can be focal, multifocal, or generalized. It is prominent in the hands and face, is typically stimulus sensitive, and is activated by touch, action, and sometimes visual stimuli. Focal cortical myoclonus originates from a hyperexcitable inflammatory, neoplastic, or vascular lesion of the sensorimotor cortex. Multifocal cortical myoclonus can be seen in posthypoxic myoclonus (Lance-Adams syndrome), progressive myoclonic epilepsy, progressive myoclonic ataxia, and neurodegenerative conditions such as Creutzfeldt-Jakob disease, parkinsonism, and Lewy body dementia. Surface EMG of cortical myoclonus records bursts lasting less than 70 ms, and jerk-locked back-averaging of simultaneous electroencephalographic recordings can sometimes localize the origin of focal cortical myoclonus. Giant somatosensory evoked potentials and enhanced long-loop reflexes can be seen.

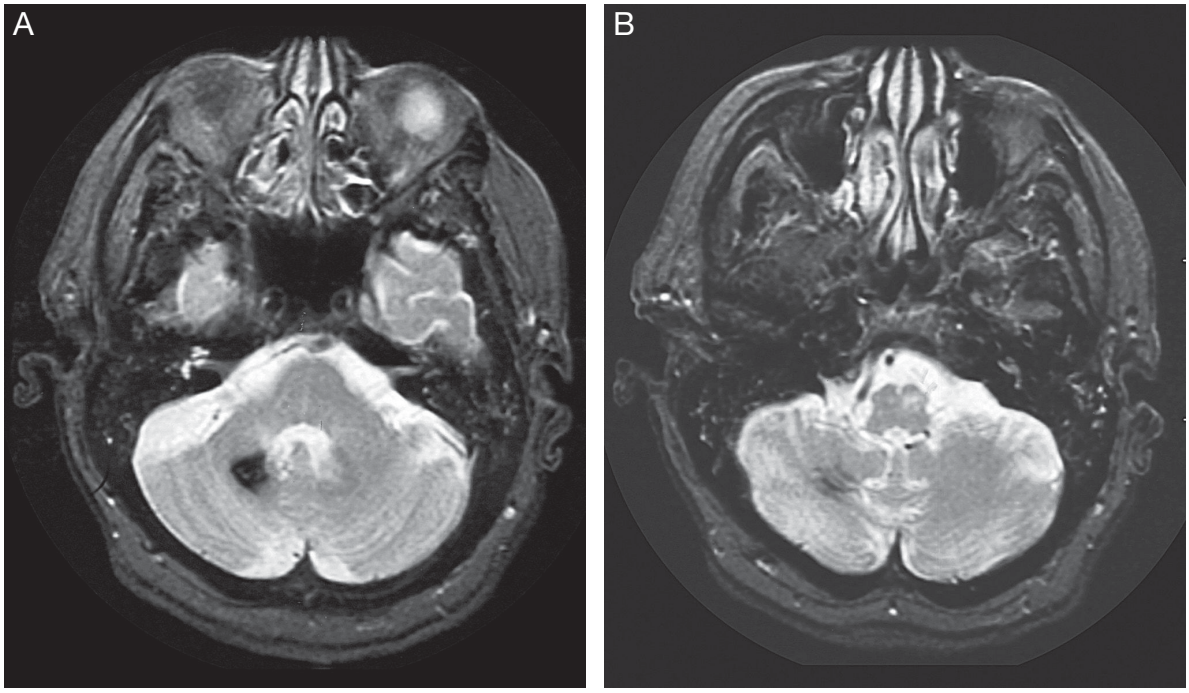

Figure 24.3 *Axial T2-Weighted Magnetic Resonance Images From a Patient With Palatal Myoclonus.*
A, Hemorrhage occurred in the right dentate nucleus (area of low T2 signal intensity and hemosiderin deposition from old hemorrhage). B, The lesion affected predominantly dentatorubroolivary pathway outflow, leading to hypertrophic olivary degeneration (abnormal signal in the ventral left medulla), with sparing of the olivocerebellar projections.
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

Treatment includes valproate sodium (1,200–2,000 mg daily), clonazepam (up to 15 mg daily), piracetam, or levetiracetam (up to 3,000 mg daily). Zonisamide, primidone, acetazolamide, and phenobarbital provide less benefit.

Subcortical Myoclonus

Subcortical myoclonus is usually nonsegmental. The normal startle response is an example of nonsegmental subcortical myoclonus. The startle is sensitive to auditory stimuli, touch of the upper body, and visual stimuli and propagates through the body in a rostral-caudal manner. The pathologic startle response (hyperekplexia) does not habituate on repeated stimuli and can be seen in stiff person syndrome, brainstem encephalitis, vascular lesions, and multiple sclerosis. The genetic form of hyperekplexia is autosomal dominant and results from a mutation in the α_1 subunit of the glycine receptor. People who have this syndrome may have seizures and low intelligence and may have episodes of myoclonic jerks, falls, and even apnea.

Another form of nonsegmental subcortical myoclonus is brainstem reticular reflex myoclonus, which is generalized and sensitive to stimulation of the lower half of the body. This is seen in brainstem encephalitis, uremia, and the posthypoxic state. The myoclonus of myoclonic dystonia (described below) is also thought to be subcortical in origin.

Box 24.2 • Conditions That Enhance Myoclonus

Metabolic—hyperthyroidism, hyperparathyroidism, hypomagnesemia, hypocalcemia, hyponatremia, hypoglycemia, renal failure, liver failure, biotin deficiency

Toxins or diet—mercury, oven cleaner, marijuana, tetanus toxoid

Drugs—selective serotonin reuptake inhibitors, tricyclic antidepressants, MAO inhibitors, buspirone, anticonvulsants (especially phenytoin, carbamazepine, lamotrigine, and vigabatrin), lithium, antibiotics (eg, penicillin), narcotics, anesthetics (including midazolam), calcium channel blockers and antiarrhythmics, antihistamines, pseudoephedrine, metoclopramide

Abbreviation: MAO, monoamine oxidase.

Adapted from Caviness JN. Myoclonus. Mayo Clin Proc. 1996 Jul;71(7):679–88. Used with permission of Mayo Foundation for Medical Education and Research.

Palatal myoclonus can occur as a result of a lesion in the dentatorubroolivary pathway (Figure 24.3).

Surface EMG of subcortical myoclonus records bursts of duration longer than 70 ms with a rostral-caudal pattern of spread that begins in the face or neck. It can occur at rest. No signs of cortical hyperexcitability are found. Compared with cortical myoclonus, subcortical myoclonus responds less often to antiepileptic drugs, but clonazepam has been helpful.

Spinal Myoclonus

Spinal myoclonus can be spontaneous, it can persist during sleep, and it has variable stimulus sensitivity. It can be segmental or propriospinal, in which the myoclonus spreads through several segments. *Segmental spinal myoclonus* involves only 1 or 2 myotomes and consists of bursts lasting up to 1,000 ms and occurring from 1 to 200 times per minute. It usually reflects an underlying spinal lesion such as syringomyelia, myelitis, trauma, infarct, or neoplasm.

Propriospinal myoclonus also consists of long-duration bursts, but it involves more myotomes than does segmental spinal myoclonus and produces axial flexion jerks 1 to 6 times per second. Unlike brainstem myoclonus, it spares the face and can be provoked by hammer tap of involved muscles and tendons rather than noise. Focal spinal lesions are a rare cause, and most cases are psychogenic.

Much like subcortical myoclonus, spinal myoclonus does not respond as well to antiepileptic drugs, but high-dose clonazepam and levetiracetam may help.

Peripheral Myoclonus

Peripheral myoclonus is usually diagnosed in the presence of a known nerve, root, or plexus lesion. Carbamazepine sometimes helps when patients have this rare form of myoclonus. However, it is not as helpful in hemifacial spasm, the most common form of peripheral myoclonus. *Hemifacial spasm* consists of frequent, unilateral facial contractions that are usually caused by vascular compression of the origin of the seventh cranial nerve. (See also Chapter 21, "Classification and Approach to Movement Disorders.") During facial nerve conduction studies, hemifacial spasm can produce a "lateral spread" response, which is characterized by a delayed contraction of muscles innervated by 1 branch of the facial nerve when a separate branch is stimulated. Botulinum toxin injections are the most effective therapy.

Disorders With Prominent Myoclous

Essential Myoclonus and Myoclonic Dystonia

Essential myoclonus and myoclonic dystonia are autosomal dominant disorders that occur with mutations in the ε-sarcoglycan gene (*DYT11*).

Essential myoclonus, which also occurs sporadically, consists solely of generalized, multifocal, unilateral, or segmental myoclonus. The myoclonus is predominant in the upper body and may be action induced. Onset occurs during the first or second decade of life, and men and women are equally affected. An alcohol response, sometimes prominent, may be present, and an essential-type tremor develops in some patients. Treatment includes clonazepam and 5-hydroxytryptophan.

Myoclonic dystonia is similar to essential myoclonus except that myoclonic dystonia affects the limbs as well. In addition, myoclonic dystonia patients can have comorbid psychiatric disease such as obsessive-compulsive disorder, anxiety, and depression. Clonazepam, valproate sodium, and tetrabenazine help, and γ-hydroxybutyric acid may help patients who have severe symptoms and a strong alcohol response. Affected patients have a normal life span.

Chronic Posthypoxic Myoclonus (Lance-Adams Syndrome)

Chronic posthypoxic myoclonus follows an anoxic insult such as cardiorespiratory arrest or drug overdose that was severe enough to produce coma and often seizures. It is usually cortical but can have components of brainstem-origin myoclonus. Patients often have cerebellar ataxia as well. This myoclonus can be disabling because it can be action induced and consists of negative as well as positive components. First-line treatment of chronic posthypoxic myoclonus usually involves a combination of clonazepam, valproate sodium, piracetam, or levetiracetam. Selective serotonin reuptake inhibitors give partial relief in some cases.

Progressive Myoclonic Epilepsy Syndromes

The progressive myoclonic epilepsy (PME) syndromes are rare, and most are genetic metabolic diseases. In general, these syndromes consist of progressive epileptic myoclonus (persistent, cortical-origin myoclonus), generalized seizures, ataxia, and dementia. Myoclonus in PME is typically of multifocal origin, is present with posture and action, and has reflex sensitivity to light, sound, or touch. Like most cortical myoclonus, it is more prominent in the face and distal limbs. Common causes of PME include neuronal ceroid lipofuscinosis, Lafora disease, Unverricht-Lundborg disease (Baltic myoclonus), myoclonic epilepsy with ragged red fibers (MERRF) syndrome, sialidoses, dentatorubropallidal atrophy, storage diseases such as Gaucher disease type 3 and GM_2 gangliosidoses, juvenile neuroaxonal dystrophy, and juvenile Huntington disease.

Treatment is symptomatic and syndrome specific, but phenytoin can exacerbate Unverricht-Lundborg disease and valproate sodium should not be used in patients with mitochondrial disorders (eg, MERRF syndrome) because of the risk of hepatic failure.

Progressive Myoclonic Ataxia (Ramsay Hunt Syndrome)

Progressive myoclonic ataxia is a milder version of PME in which ataxia accompanies myoclonus, and epilepsy and dementia are mild or absent. Some causes are similar to those of PME, such as Unverricht-Lundborg disease, mitochondrial encephalomyopathies, storage disorders, and some other progressive neurodegenerative diseases. However, the differential diagnosis also includes acquired syndromes such as paraneoplastic syndromes, viral encephalitis, human immunodeficiency virus, opportunistic infections (eg, JC polyomavirus infection), and celiac disease. Vitamin E deficiency can also produce this symptom complex.

- Multifocal cortical myoclonus can be seen in posthypoxic myoclonus (Lance-Adams syndrome), progressive myoclonic epilepsy, progressive myoclonic ataxia, and neurodegenerative conditions such as Creutzfeldt-Jakob disease, parkinsonism, and Lewy body dementia.
- *Hemifacial spasm* consists of frequent, unilateral facial contractions that are usually caused by vascular compression of the origin of the seventh cranial nerve.
- Chronic posthypoxic myoclonus follows an anoxic insult such as cardiorespiratory arrest or drug overdose that was severe enough to produce coma and often seizures.
- First-line treatment of chronic posthypoxic myoclonus usually involves a combination of clonazepam, valproate sodium, piracetam, or levetiracetam.
- Common causes of PME include neuronal ceroid lipofuscinosis, Lafora disease, Unverricht-Lundborg disease (Baltic myoclonus), MERRF syndrome, sialidoses, dentatorubropallidal atrophy, storage diseases such as Gaucher disease type 3 and GM_2 gangliosidoses, juvenile neuroaxonal dystrophy, and juvenile Huntington disease.

25 Hyperkinetic Movement Disorders: Chorea, Tic, and Dystonia

ELIZABETH A. COON, MD; JAMES H. BOWER, MD

Introduction

As described in Chapter 24, "Hyperkinetic Movement Disorders: Tremor and Myoclonus," hyperkinetic movement disorders are characterized by an excess of movement. This chapter outlines the classification, causes, and treatment of chorea, tic disorders, and dystonia.

Chorea

Overview

The term *chorea* refers to dancelike irregular, arrhythmic, rapid, involuntary movements that appear to flow from 1 muscle group to another. *Athetosis*, a slower and twisting dystonic-like movement, may be superimposed with chorea, leading to choreoathetosis. *Ballism* is a form of high-amplitude and proximal chorea that has a flailing appearance.

Chorea may be a manifestation of either inherited or acquired diseases (Box 25.1). Huntington disease and drug-induced chorea are the most common causes of adult-onset chorea. Sydenham chorea is the most common cause of childhood chorea.

Clinical Manifestations

Chorea can involve any part of the body and lead to grimacing and abnormal respiratory sounds. Although choreiform movements are erratic, the patient may disguise them by incorporating the movements into deliberate acts, termed *parakinesia*. When chorea is subtle, the patient may appear

Box 25.1 • Causes of Chorea

- Inherited disorders
  - Nonprogressive
    - Benign hereditary chorea
    - Senile chorea
  - Progressive
    - Huntington disease
    - Huntington disease–like illnesses
    - Wilson disease
    - Pantothenate kinase–associated neurodegeneration (PKAN)
    - Dentatorubral-pallidoluysian atrophy (DRPLA)
    - Neuroacanthocytosis syndromes
    - Paroxysmal choreoathetosis syndromes
- Acquired disorders
  - Immune mediated
    - Sydenham chorea
    - Systemic lupus erythematosus
    - Paraneoplastic disorders
    - Anticardiolipin antibodies
    - Central nervous system vasculitis
  - Infectious
  - Metabolic disorders, vitamin deficiencies
  - Vascular
  - Drug induced
  - Hormonal

Abbreviations: BTX, botulinum toxin; FDA, US Food and Drug Administration; HDL, Huntington disease–like

fidgety or restless. On examination, the inability to maintain tone leads to "milkmaid's grip" on handgrip testing and "fly-catcher's tongue" on tongue protrusion. The speech is characterized by a hyperkinetic dysarthria with poor intelligibility due to imprecise and inconsistent articulation, irregular rhythm, and abnormal breathing patterns. Patients are often hypotonic with pendular reflexes that, when superimposed on a choreiform movement, give a "hung-up" reflex. Chorea affects gait by causing random limb and trunk movements, which can cause a lurching quality.

Pathophysiology

The mechanism behind chorea is not entirely clear but is likely due to imbalance in the direct and indirect pathways of the basal ganglia (see Figure 17.3 in Volume 1, Chapter 17, "Basal Ganglia"). Disruption of the indirect pathway leads to loss of pallidal inhibition and hyperkinetic movements. Excess dopaminergic activity in the striatum is also hypothesized to have a role.

- Huntington disease and drug-induced chorea are the most common causes of adult-onset chorea.

Hereditary Causes of Chorea

Huntington Disease

Overview and Genetics. Huntington disease is an autosomal dominant disorder due to a trinucleotide (CAG) repeat in the *htt* (huntingtin) gene on chromosome 4. The presence of more than 36 expanded CAG repeats leads to an unstable polyglutamine tract and disease, with the expansion size inversely related to the age at onset. The expanded repeat tends to increase in subsequent generations, termed *anticipation*, particularly if it is paternally inherited (exaggerated anticipation with spermatogenesis). The expanded huntingtin protein causes disease through both toxic gain-of-function and loss-of-function effects. Mutated huntingtin protein impairs many intraneuronal processes, such as vesicular transport, calcium homeostasis leading to excitotoxicity, and release of trophic factors (eg, brain-derived neurotrophic factor). Cleavage products of expanded huntingtin protein lead to intranuclear and cytoplasmic aggregates that are not directly toxic, but they impair axonal transport, sequester normal proteins, and disrupt the ubiquitin-proteasome pathway.

Epidemiology. The prevalence of Huntington disease is 4 to 8 per 100,000 people. Repeat length influences the onset of Huntington disease, but most commonly onset occurs between 35 and 40 years of age.

Clinical Features. Huntington disease is a progressive disorder characterized by the triad of motor dysfunction, cognitive impairment, and psychiatric disturbance. Chorea, the hallmark of Huntington disease, may be preceded by depression and personality changes. Chorea typically progresses in a distal-to-proximal manner, with progressive dysphagia and dysarthria. Eye movement abnormalities are common and include slowing of saccades and prolonged latency. Other motor symptoms of rigidity, myoclonus, and ataxia may be present, with dystonia tending to occur late in the course of the disease. Cognitive dysfunction, inevitable as the disease progresses, is manifested by deficits in executive function, attention, concentration and verbal fluency. Observed evidence of frontal lobe dysfunction includes apathy, disinhibition, abulia, changes in sexual behavior, and increased antisocial tendencies. Patients who have Huntington disease have other psychiatric disturbances, including psychosis, delusions, and an increased risk of suicide.

Patients present with clinical variability, which can be related to age. Patients with the juvenile-onset form of Huntington disease, termed Westphal variant, have prominent motor features of bradykinesia and rigidity with behavioral issues and early dementia. The clinical manifestation of late onset of Huntington disease may be solely chorea.

Genetic Testing. Guidelines for genetic testing of patients who have Huntington disease outline 3 clinical situations when testing is useful: for confirmation of clinically suspected disease, for predictive testing in an asymptomatic patient at high risk of carrying the gene, and for prenatal testing. The essential components of predictive Huntington disease genetic testing are genetic counseling, informed consent, psychological assessment, review of the potential impact of the test with disclosure of results in person, and follow-up.

Imaging. Neuroimaging reveals caudate and putamen atrophy on magnetic resonance imaging (Figure 25.1), but bilateral caudate hypometabolism on positron emission tomography is an earlier and more sensitive marker.

Neuropathology. Neuropathologic evaluation of patients with Huntington disease reveals gross atrophy of the caudate nucleus and putamen (Figure 25.1) with selective loss of medium spiny neurons and gliosis. Microscopically, there are intranuclear and intracytoplasmic inclusions of ubiquitinated mutant huntingtin protein in striatal and cortical neurons.

Treatment. No therapies are known to slow or delay Huntington disease. Physical therapy, occupational therapy, and speech therapy are therapeutic mainstays; symptomatic treatments are aimed at motor and psychological dysfunction.

Pharmacologically, chorea is treated with dopamine receptor blockers and dopamine-depleting agents. Dopamine-depleting agents include reserpine and tetrabenazine (the only US Food and Drug Administration [FDA]-approved medication for chorea), but tetrabenazine

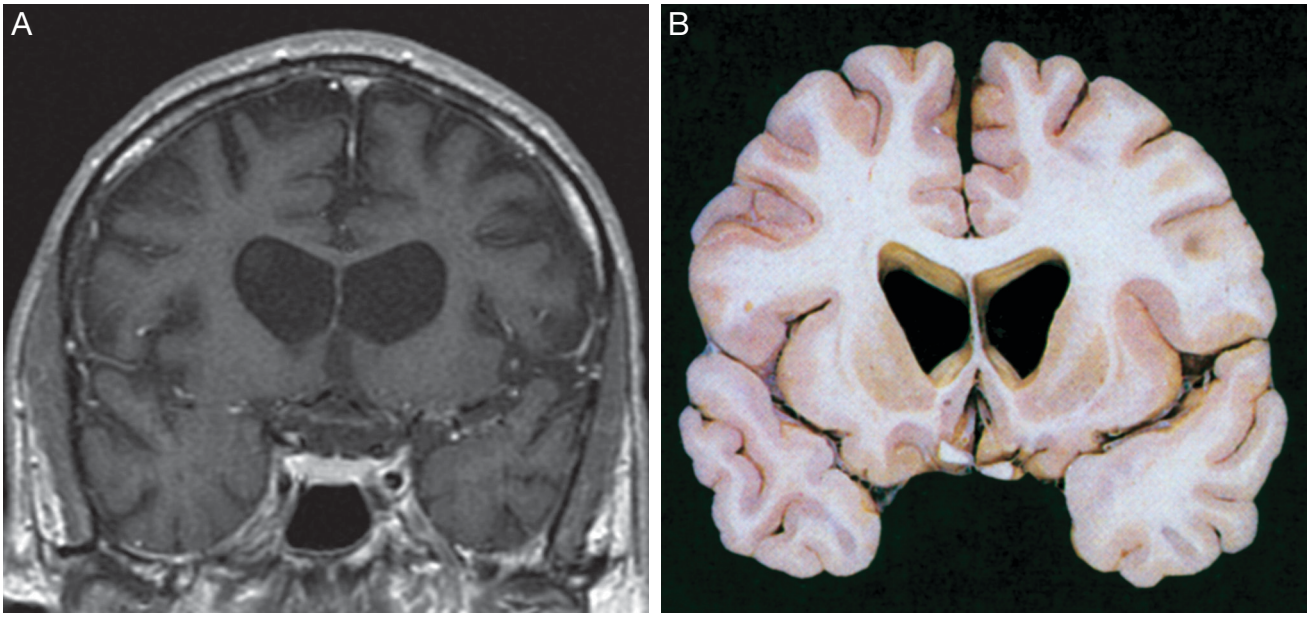

Figure 25.1 *Huntington Disease.*
A, Coronal T1-weighted magnetic resonance imaging from a patient with Huntington disease shows severe atrophy of the caudate nucleus and a concave appearance of the lateral ventricles. B, Marked caudate atrophy is also prominent on a gross pathology specimen from a different patient with Huntington disease.
(B is adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 226. Used with permission of Mayo Foundation for Medical Education and Research.)

must be used with caution because the most common adverse effect is depression. Atypical antipsychotics are better tolerated than dopamine receptor blockers and carry less risk of extrapyramidal side effects; olanzapine is more effective for motor and psychiatric symptoms, and clozapine is effective for psychosis but not chorea. Selective serotonin reuptake inhibitors are first-line agents in treating depression in patients with Huntington disease and may suppress chorea and aggression. Valproate may be useful for behavioral and psychiatric symptoms. Striatal stem cell transplants and pallidotomies have had disappointing results.

- Huntington disease is a progressive disorder characterized by the triad of motor dysfunction, cognitive impairment, and psychiatric disturbance.
- Patients with the juvenile-onset form of Huntington disease, termed Westphal variant, have prominent motor features of bradykinesia and rigidity with behavioral issues and early dementia.
- Chorea is treated with dopamine receptor blockers and dopamine-depleting agents. Dopamine-depleting agents include reserpine and tetrabenazine (the only FDA-approved medication for chorea), but tetrabenazine must be used with caution because the most common adverse effect is depression.

Huntington Disease–like Syndromes

Patients with Huntington disease–like (HDL) syndromes present clinically like those with Huntington disease, but gene testing is negative for the large number of CAG repeats that cause Huntington disease. Autosomal dominant disorders include HDL1, HDL2, and HDL4 (also known as spinocerebellar ataxia 17). HDL1 results from a mutation in the prion protein. HDL2 is usually seen in African Americans and results from a CTG/CAG repeat expansion on the junctophilin-3 gene. HDL3 is an autosomal recessive variant.

Dentatorubral-Pallidoluysian Atrophy

Dentatorubral-pallidoluysian atrophy (Haw River syndrome) is an autosomal dominant polyglutamine disorder due to an unstable trinucleotide repeat in the *ATN1* gene. More than 48 repeats cause disease, and the repeat size is inversely correlated with the age at onset. Typically, patients present in their 20s and have anticipation and exaggerated anticipation with spermatogenesis. The clinical presentation depends on the age at onset. Children have behavioral changes, progressive intellectual dysfunction, epilepsy, and myoclonus. Adults are more likely to have ataxia, chorea, and dementia. Neuropathologic examination shows degeneration of the dentate nucleus, pallidum, red nucleus, and subthalamic nucleus with neuronal loss and intranuclear neuronal inclusions. For further details, see Chapter 26, "Cerebellar Disorders and Ataxias."

Neuroacanthocytosis

Acanthocytes are erythrocytes with spicules and are associated with a group of heterogeneous neurodegenerative

Table 25.1 • Neuroacanthocytosis Syndromes

Syndrome	Neurologic Findings	Systemic Findings	Additional Features
Hereditary choreoacanthocytosis	Predominantly chorea with feeding and gait dystonia, parkinsonism, axonal neuropathy, myopathy, seizures, dementia, psychosis, and personality changes	. . .	Autosomal recessive (locus 9q21, *VPS13A* gene)
McLeod syndrome	Older age at onset with axonal neuropathy, myopathy, chorea, seizures, cognitive impairment, and psychiatric symptoms	Hemolytic anemia, cardiomyopathy, splenomegaly, hypobetalipoproteinemia, and cancers (sarcoma)	X-linked recessive (mutation in Kell group erythrocyte antigens)
Amyotrophic choreoathetosis with acanthocytosis	Chorea, orofacial dyskinesias, tics, dystonia, and parkinsonism with muscular weakness and atrophy (predominantly lower extremities); cognitive impairment, psychiatric manifestations, and seizures are possible	Elevated creatine kinase level	Electromyographic findings mimic those with ALS
Pantothenate kinase–associated neurodegeneration (PKAN)	Orofacial and limb dystonia, choreoathetosis, and spasticity	Pigmentary retinopathy	NBIA
Abetalipoproteinemia (Bassen-Kornzweig syndrome)	Progressive ataxia	Pigmentary retinopathy and severe malabsorption of fat-soluble vitamins	. . .
Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP syndrome)	Prominent orofacial dyskinesias, progressive dystonia	Atypical retinitis pigmentosa	NBIA with abnormal lipoproteins

Abbreviations: ALS, amyotrophic lateral sclerosis; NBIA, neurodegeneration with brain iron accumulation.

disorders (Table 25.1). Inheritance is variable, and the mean age at onset is in the 30s. Chorea, orofacial dystonia, and lingual dystonia are prominent; features may also include myopathy, elevated creatine kinase, and seizures. The caudate nucleus and putamen typically show abnormalities on imaging and neuropathologic examination.

Benign Hereditary Chorea

Benign hereditary chorea is an autosomal dominant disorder. Onset is in early childhood, and the severity peaks in the teenage years. It is nonprogressive and is not associated with other neurologic abnormalities. (See Chapter 27, "Childhood Movement Disorders.")

Nonhereditary Causes of Chorea

Sydenham Chorea

Sydenham chorea is an autoimmune form of chorea that occurs after group A β-hemolytic streptococcal infections. This condition typically manifests in childhood and early adolescence with generalized chorea and personality changes, including obsessive-compulsive disorder and irritability. (See Chapter 27, "Childhood Movement Disorders.")

Other Immune-Mediated Types of Chorea

Generalized chorea or hemichorea is an uncommon and generally late manifestation in systemic lupus erythematous and antiphospholipid antibody syndrome. Paraneoplastic disorders can cause chorea, particularly because of anti-Hu and CRMP5 antibodies, and are associated with small cell lung carcinoma, lymphomas, renal cell carcinoma, and thymoma. Chorea may be a manifestation of central nervous system vasculitis, including primary central nervous system angiitis, polyarteritis nodosa, Henoch-Schönlein purpura, and Behçet syndrome, or it may be associated with anticardiolipin antibodies.

Other Causes of Chorea

Infectious chorea may occur with the sudden onset of encephalitis or bacterial, tubercular, or aseptic meningitis. In AIDS, toxoplasmosis may cause hemichorea or hemiballism. Chorea may be seen after a stroke, particularly with infarction of the subthalamic nucleus. Chorea is recognized after pediatric cardiac surgery, and postpump chorea occurs after extracorporeal circulation. Chorea may be caused by metabolic derangements such as abnormal glucose or sodium levels, hypomagnesemia, hypocalcemia, hepatic or renal failure, hypothyroidism, and hypoparathyroidism with hypocalcemia. Chorea may also be caused by hormonal alterations such as those that occur during pregnancy or with the use of oral contraceptives. Toxins that trigger chorea include toluene, manganese, and carbon monoxide.

Drug-Induced Chorea

Drug-induced chorea is most commonly caused by levodopa and dopaminergic agonists, but it also occurs with anticonvulsants (eg, lamotrigine), lithium, methadone, cocaine, and amphetamines.

- Sydenham chorea is an autoimmune form of chorea that occurs after group A β-hemolytic streptococcal infections.
- Sydenham chorea typically manifests in childhood and early adolescence with generalized chorea and personality changes, including obsessive-compulsive disorder and irritability.
- Drug-induced chorea is most commonly caused by levodopa and dopaminergic agonists, but it also occurs with anticonvulsants (eg, lamotrigine), lithium, methadone, cocaine, and amphetamines.

Ballism

Ballism is typically unilateral (hemiballism) and results from a contralateral lesion of the subthalamic nucleus or its projections. Causes of ballism are similar to those of chorea, especially the vascular, neoplastic, or structural causes. When ballism is bilateral, a metabolic derangement such as nonketotic hyperosmolar hyperglycemia may be the cause.

Tic Disorders

Tics are defined by stereotypy and irresistibility. Movements are often described as a semivoluntary movement in response to an involuntary urge to perform the movement. They may manifest as simple or complex motor movements or as vocalizations. *Simple motor tics* may be rapid (clonic type), such as blinking, or slower (dystonic), such as neck stretching. *Coordinated motor tics* are stereotypical acts that often serve a purpose, such as head shaking. *Simple vocal tics* include sniffing or coughing; *complex vocal tics* include *palilalia* (repeating one's own words), *echolalia* (repeating another's words), and *coprolalia* (vocalizing obscenities). Tics may be voluntarily suppressed for a brief period, which is frequently followed by an overflow of excessive tics. Tics worsen with stress and are alleviated by rest; they also may attenuate when the patient is strongly focused on another task.

Tourette syndrome is a common primary cause of tics in young patients. This syndrome is discussed in Chapter 27, "Childhood Movement Disorders."

Dystonia

Classification and Causes

Dystonia involves involuntary and sustained cocontraction of agonist and antagonist muscle groups, leading to an abnormal posture or repetitive movements. The movements are typically slow but may be rapid and are often exacerbated by stress, anxiety, or fatigue. Dystonia may be alleviated with rest or a sensory trick (called a *geste antagoniste*). When elicited by voluntary movements, dystonia is called *action dystonia* and may be task specific (writer's cramp).

Dystonia is classified according to cause, as primary or secondary, and according to distribution, as focal (1 body region), multifocal (≥2 noncontiguous regions), hemidystonia (≥2 ipsilateral regions), segmental (adjacent regions), or generalized (involving both lower extremities *or* 1 lower extremity and the trunk *and* another region).

Primary focal dystonia is typically sporadic and has an adult onset. *Primary generalized dystonia* usually has a genetic cause and a childhood onset. In *young-onset dystonia* (age <26 years), dystonia typically starts in a lower extremity and evolves into generalized dystonia. In *adult-onset dystonia* (age ≥26 years), onset is typically in the upper extremities or neck and rarely evolves. Initial symptoms may be noticeable during activity and less apparent with rest. Later, dystonia becomes more apparent at rest and involves other body regions. Gait becomes affected, and when dystonic postures are constant at rest, the patient may become nonambulatory.

Secondary dystonia encompasses a number of conditions. The differential diagnosis for secondary dystonia includes perinatal cerebral injury, kernicterus, drug-induced disorders, trauma, infectious diseases, postinfectious or immune-mediated encephalopathies, toxin-induced disorders, and metabolic causes. *Posttraumatic dystonia* may emerge after an episode of hemiparesis resolves and may occur shortly after trauma or years later. The prognosis tends to be poorer than for other forms of secondary dystonia, but posttraumatic dystonia may respond to botulinum toxin (BTX) or surgery.

Inherited Dystonias

With advances in molecular genetics, the inherited dystonias have been further characterized (Table 25.2). Dystonia syndromes are numbered according to the order in which they were identified, but they can be classified into primary dystonia, dystonia plus (including parkinsonism and myoclonus), and paroxysmal dyskinesias.

Primary Torsion Dystonia

Primary torsion dystonia (*DYT1*) is the most common early-onset primary dystonia. It results from a triplet (GAG) deletion in the *TOR1A* gene encoding for torsinA, a member of the AAA+ adenosine triphosphatase family of proteins. TorsinA is involved in the nuclear envelope, cytoskeleton, and secretory pathway, with mutant protein accumulating in perinuclear inclusions. The characteristic phenotype is a childhood onset of limb dystonia and subsequent generalization, usually with sparing of the craniocervical muscles. (See Chapter 27, "Childhood Movement Disorders.")

Table 25.2 • Inherited Dystonias

Gene (Locus)	Syndrome	Inheritance	Common Age at Onset	Protein	Clinical Characteristics
DYT1 (9q24)	Early-onset primary torsion dystonia	AD	Child	TorsinA (ATP-binding protein)	Often starts in a limb and spreads to other regions
DYT2	AR primary torsion dystonia	AR	Child	. . .	Early onset; generalized or segmental
DYT3 (Xq13)	X-linked dystonia-parkinsonism (lubag syndrome)	X-linked	Adult	*TAF1*/*DYT3* gene transcription factor	Segmental or generalized dystonia; parkinsonism in approximately 50% of cases; myoclonus; chorea
DYT4	Whispering dysphonia	AD	. . .	. . .	Reported in an Australian family
DYT5a (14q22)	Dopa-responsive dystonia	AD	Child	GTP cyclohydrolase I	Dystonia with parkinsonism and diurnal worsening
DYT5b (11p15.5)	Segawa syndrome	AR	Child	Tyrosine hydrolase	Marked response to levodopa
DYT6 (8p)	Adolescent-onset torsion dystonia of mixed type	AD	Teenager, adult	THAP1	Cranial or cervical onset; mostly segmental; rarely generalizes
DYT7 (18p11)	Adult-onset focal torsion dystonia	AD	Adult	. . .	Focal dystonia (torticollis, writer's cramp, blepharospasm, dysphonia)
DYT8 (2q)	Paroxysmal nonkinesigenic dyskinesia	AD	Child	Probable hydrolase PNKD	Attacks of dystonia or choreoathetosis are precipitated by stress, fatigue, alcohol, and chocolate
DYT9 (1p)	Paroxysmal choreoathetosis with episodic ataxia and spasticity	AD	Child	. . .	Attacks of dystonia, ataxia, paresthesias, double vision precipitated by exercise, stress, and alcohol; spastic paraparesis occurs between attacks
DYT10 (16)	Paroxysmal kinesigenic choreoathetosis	AD	Child	. . .	Dystonia or choreoathetosis triggered by sudden movements
DYT11 (7q)	Myoclonus-dystonia	AD	Child	ε-Sarcoglycan	Rapid, jerklike movements with variable dystonia; responsive to alcohol
DYT12 (19q)	Rapid-onset dystonia-parkinsonism	AD	Teenager, adult	Sodium-potassium–ATPase α3	Acute or subacute onset of generalized dystonia with parkinsonism
DYT13 (1p)	Multifocal or segmental dystonia	AD	Teenager	. . .	Craniocervical or upper limb onset of focal or segmental dystonia with mild course
DYT15 (18p)	Myoclonus-dystonia	AD	Child, teenager	. . .	Rapid, jerklike movements or tremor in the first or second decade of life; variable response to alcohol
DYT16 (2p)	Young-onset dystonia-parkinsonism	AR	Child, teenager	PRKRA stress-response protein	Early-onset and progressive dystonia may involve axial and oromandibular muscles, occasionally with parkinsonism
DYT17 (20)	AR primary torsion dystonia	AR	Teenager	. . .	Identified in a Lebanese family
DYT18 (1p)	Paroxysmal exertion-induced dyskinesia 2	AD	Child	SLC2A1 glucose transporter	Episodic abnormal movements accompanied by epilepsy, mild developmental delay, decreased cerebrospinal fluid glucose concentration and hemolytic anemia
DYT19 (16q)	Episodic kinesigenic dyskinesia 2	AD	. . .	. . .	. . .
DYT20 (2q)	Paroxysmal nonkinesigenic dyskinesia 2	AD	Child	. . .	Episodic involuntary movements occurring at rest or precipitated by stress, caffeine, or alcohol
DYT21 (2q)	Uncategorized	AD	. . .	. . .	. . .

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; GTP, guanosine triphosphatase.

Dystonia Plus Syndromes

X-linked dystonia-parkinsonism was described in the Philippines and termed lubag syndrome. The disorder heterogeneously affects men in their 30s to 50s with parkinsonism, dystonia, tremor, chorea, or myoclonus. The response to levodopa is typically poor, but some patients may respond.

Rapid-onset dystonia-parkinsonism is an autosomal dominant disorder with low penetrance. Age at onset ranges from adolescence to adulthood. Symptom onset may occur over hours to weeks, and symptoms plateau after the initial period. The onset of dystonia may be precipitated by fever, physiologic or psychologic stress, or excessive alcohol intake. Affected persons have dystonia with prominent cranial involvement and parkinsonism. The response to dopaminergic medications is generally poor.

Other dystonia plus syndromes that predominantly present in childhood are discussed in Chapter 27, "Childhood Movement Disorders."

Paroxysmal Dyskinesias

Paroxysmal kinesigenic dyskinesia is an autosomal dominant disorder characterized by attacks of choreoathetosis and dystonia. It manifests in childhood and adolescence with a male predominance. *Paroxysmal nonkinesigenic dyskinesia* is an autosomal dominant disorder characterized by attacks of paroxysmal choreoathetosis, dystonia, or ballism. These disorders are discussed in Chapter 27, "Childhood Movement Disorders."

Primary Focal Dystonia

Cervical Dystonia

The most common form of dystonia affects the neck (*idiopathic cervical dystonia* or *torticollis*). Women are more often affected with onset occurring between the ages of 30 and 50. The muscle spasms may be more pronounced on 1 side, leading to rotation and partial extension (*rotational torticollis* or *laterocollis*). When posterior and anterior musculature is involved, the head may become hyperextended (*retrocollis*) or, rarely, flexed (*anterocollis*). Symptoms often worsen throughout the day, and the effectiveness of sensory tricks tends to diminish as the disease progresses. Spontaneous remission occurs in 20%, although the recurrence rate is high.

Cranial Dystonia

Blepharospasm results from spasm of the orbicularis oculi, leading to bilateral repetitive blinking or prolonged eyelid closure. The movements may be induced or aggravated by bright light, wind, specific activities (watching television or reading), or stress and may be alleviated by sensory tricks. Blepharospasm can be associated with dystonic facial movements involving the jaw, tongue, and oral and pharyngeal muscles; essential blepharospasm involves only the eyelids. *Meige syndrome* is a form of craniocervical dystonia with forceful opening or closing of the jaw, retraction or pursing of the lips, spasm of the platysma, and possibly tongue protrusion. *Oromandibular dystonia* refers to dystonia primarily affecting the jaw muscles and resulting in jaw opening, trismus, bruxism, or jaw deviation, occasionally with involvement of the tongue, lips, or platysma. *Spasmodic dysphonia* affects the laryngeal muscles and may begin as a task-specific dystonia affecting talking or singing. Voice tremor may be the presenting symptom. The adductor variety accounts for 90% of cases and causes a strained voice due to excessive contraction of the thyroarytenoids. The abductor variety leads to a breathy voice as the vocal cords are separated because of excessive contraction of the posterior cricoarytenoids.

Limb and Trunk Dystonia

Limb dystonia is the least common form of focal dystonia and may be part of a segmental dystonia. *Action dystonia* typically involves an upper extremity and may be task specific, such as "writer's cramp" or "musician's cramp." *Trunk dystonia* describes repetitive and stereotyped movements of exaggerated lordosis, kyphosis, scoliosis, or opisthotonic posturing that may improve with sensory tricks, running, or walking backward.

Treatment of Focal and Generalized Dystonia

BTX injection is first-line treatment of adult-onset focal dystonia and is effective in up to 95% of cases. The toxin is taken up by motor nerve endings and prevents release of acetylcholine from the presynaptic membrane into the neuromuscular junction. The mechanism of action is related to the type of BTX: BTX-A cleaves the synaptosome-associated protein SNAP-25, a type of SNAP receptor protein; BTX-B and BTX-F cleave synaptobrevin (also called the vesicle-associated membrane protein VAMP); and BTX-C cleaves syntaxin. Resistance, which may develop to a specific type of toxin, warrants switching types, typically to BTX-B. Oral pharmaceutical agents are effective in a smaller number of patients. The anticholinergic agents trihexyphenidyl and benztropine may be effective. Other possibly useful agents are baclofen, levodopa, dopaminergic antagonists or depleting agents, clonazepam, carbamazepine, and gabapentin. Surgical treatment includes deep brain stimulation and denervation procedures by cervical rhizotomy or peripheral nerve lysis.

- In *young-onset dystonia* (age <26 years), dystonia typically starts in a lower extremity and evolves into generalized dystonia. In *adult-onset dystonia* (age ≥26 years), onset is typically in the upper extremities or neck and rarely evolves.
- *Meige syndrome* is a form of craniocervical dystonia with forceful opening or closing of the jaw, retraction or pursing of the lips, spasm of the platysma, and possibly tongue protrusion.
- BTX injection is first-line treatment of adult-onset focal dystonia and is effective in up to 95% of cases.

26 Cerebellar Disorders and Ataxias

ANHAR HASSAN, MB, BCH

Introduction

Disorders of the cerebellum or its connections can result in ataxia characterized by imbalance and incoordination of gait, limbs, speech, and eye movements. The pathologic changes may be confined to the cerebellum or simultaneously affect other parts of the central nervous system or peripheral nervous system. Ataxias are generally classified as acquired, inherited, or sporadic. The differential diagnosis is broad and daunting; however, a detailed history and examination can rapidly narrow the list. Key information includes age at onset (Table 26.1); rate of disease progression (Table 26.2); family history; presence of pure cerebellar syndrome or other neurologic signs; other systemic features; and imaging findings (Table 26.3). A general guide to the approach to cerebellar ataxia is shown in Figure 26.1 and Table 26.4.

Acquired Cerebellar Disorders

Acquired cerebellar disorders are summarized in Table 26.5.

Vascular

Vascular causes of ataxia include cerebellar or brainstem infarctions, intracerebral hemorrhage, and vascular malformations. Patients with a vascular cause of ataxia generally present with acute symptoms. A vascular cause may be easily seen on magnetic resonance imaging (MRI).

Infectious and Parainfectious

Infections may cause an acute or subacute cerebellar syndrome or be present as part of a diffuse encephalomyelitis. Idiopathic infections are the most common. Viral,

Table 26.1 • Differential Diagnosis of Cerebellar Disorders and Ataxias According to Age at Onset

Age at Onset	Acquired Disease or Causative Factor	Genetic Disease or Causative Factor
Infancy	Ataxic cerebral palsy, intrauterine insult	Inherited congenital ataxias (eg, Joubert syndrome, Gillespie syndrome)
Childhood	Acute cerebellitis, abscess, posterior fossa tumor, AVM, congenital malformation (eg, Dandy-Walker malformation), toxic disorder, immune-mediated disorder	FA, other recessive ataxias, EA, mitochondrial disease, DRPLA, SCA types 2, 7, and 13
Young adulthood	Infection, tumor, HIV, vascular disease, autoimmune disease, toxic disorder, metabolic disorder	FA, SCAs
Older adulthood	All conditions applicable to other ages except congenital disorders; MSA, ataxia with anti-GAD antibodies, SREAT	SCA6, benign SCAs

Abbreviations: AVM, arteriovenous malformation; DRPLA, dentatorubral-pallidoluysian atrophy; EA, episodic ataxia; FA, Friedreich ataxia; GAD, glutamic acid decarboxylase; HIV, human immunodeficiency virus; MSA, multiple system atrophy; SCA, spinocerebellar ataxia; SREAT, steroid-responsive encephalopathy associated with autoimmune thyroiditis.

Abbreviations: ADCA, autosomal dominant cerebellar ataxia; DRPLA, dentatorubral-pallidoluysian atrophy; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; SCA spinocerebellar ataxia

Table 26.2 • Differential Diagnosis of Cerebellar Disorders and Ataxias According to Rate of Disease Progression

Rate of Progression	Acquired Disease or Causative Factor	Genetic Disease or Causative Factor
Sudden	Stroke	. . .
Acute (hours to days)	Wernicke encephalopathy, autoimmune (Miller Fisher syndrome, MS), parainfectious or infectious disease, toxic disorder	. . .
Subacute (weeks)	Paraneoplastic, gluten, GAD, SREAT, tumors, posterior fossa mass, infection (HIV, CJD), metabolic (vitamin B_1 or B_{12} deficiency, hypothyroidism)	. . .
Chronic (months to years)	Structural lesion (stroke, tumor), craniovertebral junction lesion, alcohol abuse, idiopathic cerebellar MSA, OPCA	Autosomal recessive ataxias (FA, AT, other), SCAs
Episodic	. . .	EA types 1–4, inborn errors of metabolism

Abbreviations: AT, ataxia-telangiectasia; CJD, Creutzfeldt-Jakob disease; EA, episodic ataxia; FA, Friedreich ataxia; GAD, glutamic acid decarboxylase; HIV, human immunodeficiency virus; MS, multiple sclerosis; MSA, multiple system atrophy; OPCA, olivopontocerebellar atrophy; SCA, spinocerebellar ataxia; SREAT, steroid-responsive encephalopathy associated with autoimmune thyroiditis.

bacterial, and prion infections may result in ataxia (Box 26.1). Localized abscesses or cysts (cystericercosis) in the cerebellum may also result in ataxia.

Viral

Children aged 5 to 6 years may have acute cerebellitis, more commonly after varicella than after infection with coxsackievirus group A or B, echovirus, or poliovirus. Teenagers may have acute cerebellitis after Epstein-Barr virus infection or after vaccinations. Spinal fluid analysis may show elevated protein and mononuclear pleocytosis; polymerase chain reaction is used for viral identification. Viral infections are usually benign, with MRI signal density changes, but occasionally cerebellar swelling or herniation necessitates decompression.

Bickerstaff brainstem encephalitis typically follows an upper respiratory infection, with diplopia and gait ataxia at onset, followed by altered consciousness, ophthalmoplegia, ataxia, lower cranial neuropathies, hyperreflexia, and extensor plantars. It is associated with anti-GQ1b immunoglobulin G antibodies (for further details, see Chapter 20, "Mimickers of Multiple Sclerosis").

Human immunodeficiency virus (HIV) or its complications (toxoplasmosis, progressive multifocal leukoencephalopathy, and lymphoma) may cause ataxia. Cerebellar ataxia precedes dementia in about 30% of patients with HIV dementia. In some HIV patients, a rapidly progressive cerebellar ataxia is associated with cerebellar atrophy and marked granular cell loss.

Table 26.3 • Differential Diagnosis of Cerebellar Disorders and Ataxias According to Imaging Clues

Imaging Finding	Disease or Causative Factor
Cerebellar mass	Tumor (glioma, meningioma), abscess
Abnormal craniovertebral junction	Arnold-Chiari malformation, Alexander disease, basilar invagination
Vascular lesion	Stroke (infarct, hemorrhage), AVM
Signal change, cerebellum	MS, acute cerebellitis
Signal change, MCP	FXTAS
Pure cerebellar atrophy	Pure cerebellar syndrome: SCA types 5 and 6, idiopathic cerebellar atrophy, toxic disorder, vitamin deficiency, autoimmune disease, paraneoplastic disease
Cervical cord atrophy	FA, AVED
Pontocerebellar atrophy	SCA types 1–4, 7, and others; sporadic OPCA; MSA-C
Cerebral WM changes	Leukodsytrophy, MS

Abbreviations: AVED, ataxia with vitamin E deficiency; AVM, arteriovenous malformation; FA, Friedreich ataxia; FXTAS, fragile X–associated tremor/ataxia syndrome; MCP, middle cerebellar peduncle; MS, multiple sclerosis; MSA-C, multiple system atrophy, cerebellar type; OPCA, olivopontocerebellar atrophy; SCA, spinocerebellar ataxia; WM, white matter.

Bacterial and Other Infectious Agents

Borrelia burgdorferi (Lyme disease), *Mycoplasma, Mycobacterium tuberculosis, Plasmodium falciparum* (malaria), and *Taenia* (cysticercosis) can all produce cerebellar dysfunction.

Tropheryma whippeli produces multisystem Whipple disease, with weight loss, diarrhea, and abdominal pain. The central nervous system manifestation is ataxia in 45% of patients. Less common are the pathognomonic oculomasticatory and oculofacial-skeletal myorhythmias. (See Chapter 66, "Bacterial Infection of the Nervous System.")

Inflammatory and Autoimmune

Demyelinating Disease

Multiple sclerosis and other demyelinating diseases may result in ataxia because of involvement of the cerebellum

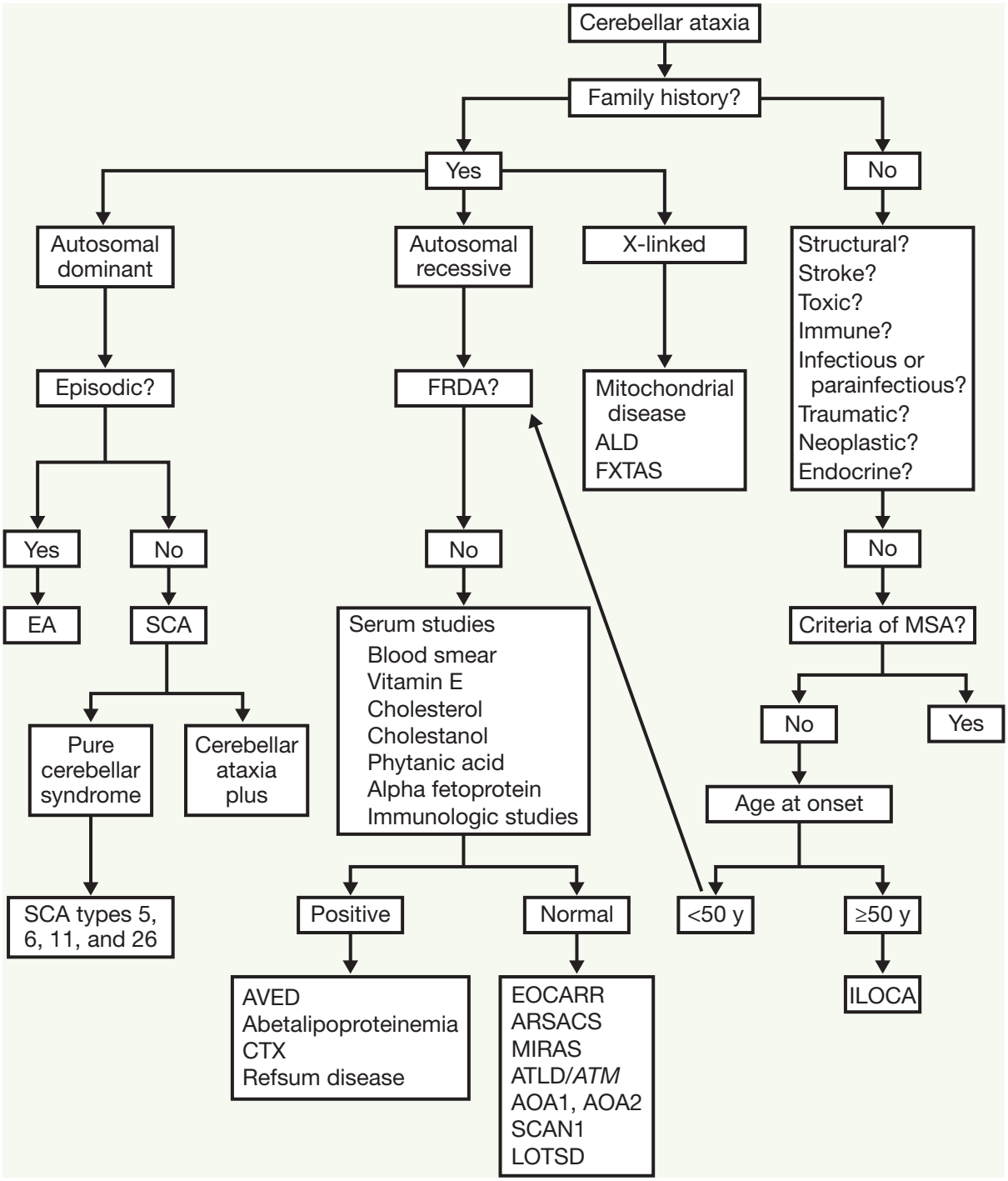

Figure 26.1 *Diagnostic Algorithm for Cerebellar Ataxias.*
See text for details, and see Table 26.4 for details specifically related to cerebellar ataxia plus. ALD indicates adrenoleukodystrophy; AOA, ataxia with oculomotor apraxia; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; ATLD, ataxia-telangiectasia-like disorder; ATM, *ataxia-telangiectasia mutated gene; AVED, ataxia with vitamin E deficiency; CTX, cerebrotendinous xanthomatosis; EA, episodic ataxia; EOCARR, early-onset cerebellar ataxia with retained reflexes; FRDA, Friedreich ataxia; FXTAS, fragile X–associated tremor/ataxia syndrome; ILOCA, idiopathic late-onset cerebellar ataxia; LOTSD, late-onset Tay-Sachs disease; MIRAS, mitochondrial recessive ataxia syndrome; MSA, multiple system atrophy; SCA, spinocerebellar ataxia (types 1–30); SCAN1, spinocerebellar ataxia with axonal neuropathy.*
(Adapted from Manto M, Marmolino D. Cerebellar ataxias. Curr Opin Neurol. 2009 Aug;22[4]:419–29. Used with permission.)

Table 26.4 • Clinical Presentations of Spinocerebellar Ataxia (SCA)

Presentation	Disorder
Childhood	SCA types 2, 7, and 13; DRPLA
Young adulthood	SCA types 1–3 and 21
Older adulthood	SCA6
Pure cerebellar features	SCA types 5, 6, 11, and 26
Cerebellar ataxia plus features	
Cognitive impairment and behavioral symptoms	SCA types 1–3, 10, 12–14, 17, 19, and 21; DRPLA
Seizures	SCA types 10 and 17; DRPLA
Eye and oculomotor deficits	
Slow saccades	SCA types 1–3, 7, and 28
Downbeat nystagmus	SCA6
Ophthalmoplegia	SCA types 1–3, 28, and 30
Ocular dyskinesia	SCA10
Pigmentary retinopathy	SCA7
Movement disorders	
Parkinsonism	SCA types 1–3, 12, 17, and 21
Dystonia	SCA types 3, 14, and 17
Tremor	SCA types 8, 12, 16, 19, and 20
Myoclonus	SCA types 2, 14, and 19; DRPLA
Chorea	SCA types 1 and 17; DRPLA
Myokymia	SCA5
Corticospinal tract	SCA types 1–4, 7, 8, 10–15, 28, and 30
Peripheral neuropathy	SCA types 1–4, 6, 8, 12, 18, 22, and 25

Abbreviation: DRPLA, dentatorubral-pallidoluysian atrophy.

Adapted from Manto M, Marmolino D. Cerebellar ataxias. Curr Opin Neurol. 2009 Aug;22(4):419–29. Used with permission.

Table 26.5 • Acquired Causes of Ataxia

Disease	Potential Testing
Vascular	Brain imaging
Cerebellar ischemia or hemorrhage	
Cerebellar vascular malformation	
Vertebrobasilar dolichoectasia	
Infectious	
Cerebellar abscess, cyst, focal infection	Brain imaging
Cerebellitis (see Box 26.1)	Brain imaging, CSF, HIV, Lyme titer
Brainstem encephalitis (Bickerstaff brainstem encephalitis)	Anti-GQ1b immunoglobulin G antibody
Inflammatory	
Demyelinating disease	Brain imaging, CSF
Celiac disease	Antigliadin antibodies, antitissue transglutaminase antibodies, jejunal biopsy
Neoplastic and paraneoplastic	
Primary cerebellar tumor or metastases	Brain imaging
Paraneoplastic	Paraneoplastic panel, tumor screening
Metabolic and endocrine	
Thyroid or parathyroid disease	Thyrotropin, calcium, serum parathyroid hormone
Vitamin E deficiency	Vitamin E level
Thiamine deficiency	Thiamine level, clinical history
Medications and drugs	
Anticonvulsants	Drug levels
Alcohol	Toxicology screen, alcohol
Chemotherapeutic agents	Historical
Degenerative	
Sporadic cerebellar ataxia	Rule out other causes
Multiple system atrophy	Autonomic testing
Congenital	
Arnold-Chiari malformation	Brain imaging
Dandy-Walker malformation	Brain imaging
Other	
Superficial siderosis	Brain imaging, assessing for cause
Trauma	History, brain imaging
Foramen magnum compression	Brain imaging
Hydrocephalus	Brain imaging

Abbreviations: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

or cerebellar circuits. Demyelination typically causes unilateral signs of cerebellar dysfunction often accompanied by a Holmes tremor.

Ataxia With Gluten Sensitivity

Gluten sensitivity is an autoimmune disease that may manifest as celiac disease and potentially affect the cerebellum. Gliadin, a gluten protein in wheat, can provoke an immune-mediated response that leads to jejunal villi flattening and malabsorption. Cerebellar ataxia, which has been reported for some patients, may relate directly to antigliadin and antitissue transglutaminase antibodies or vitamin deficiency. One study reported that up to 50% of patients with idiopathic sporadic ataxias had gluten sensitivity, although numerous other studies found that the prevalence of antigliadin and antitissue transglutaminase antibodies was zero to low. These antibodies are also found in hereditary ataxias and healthy controls, thus creating controversy over the diagnosis. Ataxia is usually slowly progressive with hyperreflexia and peripheral neuropathy.

Pathology shows Purkinje cell loss, T-lymphocyte infiltration, and posterior column degeneration. Jejunal biopsy

Box 26.1 • Infectious and Parainfectious Causes of Ataxia

- Viral
  - Varicella-zoster virus
  - Coxsackievirus groups A and B
  - Echovirus
  - Poliovirus
  - Human immunodeficiency virus
- Bacterial
  - *Borrelia burgdorferi* (Lyme disease)
  - *Mycoplasma*
  - *Mycobacterium tuberculosis*
- Protozoan
  - *Plasmodium falciparum* (malaria)
- Tapeworm
  - *Taenia* (cysticercosis)
- Prion
  - Creutzfeld-Jakob disease
  - Gerstmann-Sträussler-Scheinker syndrome

findings can be typical for celiac disease or normal, creating a diagnostic conundrum. If celiac disease is confirmed (by antigliadin antibodies, antitissue transglutaminase antibodies, and jejunal biopsy), a gluten-free diet may reverse the ataxia.

Neoplastic and Paraneoplastic

Primary brain neoplasms or metastases affecting the cerebellum or cerebellar circuits may result in ataxia. Primary tumors preferentially affecting the cerebellum include pilocytic astrocytoma, cerebellar hemangioblastoma, medulloblastoma, choroid plexus papilloma, and ependymoma.

Paraneoplastic cerebellar degeneration is a subacute rapidly progressive pancerebellar syndrome. Severe ataxia may occur with dysarthria, oscillopsia, and vertigo. The most common associated cancers are ovarian cancer, lung cancer, and lymphoma. (For details, see Chapter 62, "Paraneoplastic and Other Autoimmune Neurologic Disorders.")

Ataxia and Anti–Glutamic Acid Decarboxylase Antibodies

Progressive ataxia, typically in middle-aged women with type 1 diabetes mellitus and other autoimmune disease antibodies (thyroid, parietal cell, and pancreatic islet cell), has been associated with anti–glutamic acid decarboxylase antibodies. The antibody titers are higher than in type 2 diabetes mellitus and may affect presynaptic γ-aminobutyric acid nerve terminals of Purkinje cells. Peripheral neuropathy, slow saccades, and stiff person syndrome may co-occur. Intravenous immunoglobulin or immunosuppressants may improve symptoms.

Metabolic and Endocrine

Hypothyroidism may cause impaired balance or gait related to pathologic changes in the midline cerebellum. Replacement therapy leads to improvement.

Hypoparathyroidism may cause cerebellar ataxia, accompanied by extrapyramidal symptoms and cataracts. Diagnosis is with parathyroid hormone, calcium, and phosphate levels and with computed tomography of the brain demonstrating cerebellar calcification.

Vitamin E deficiency may result in ataxia, myopathy, or neuropathy. Patients may have ataxia with hyporeflexia and loss of large-fiber sensation. Vitamin E deficiency is rare but may occur in patients with poor fat absorption, such as occurs in severe cirrhosis, celiac disease, cystic fibrosis, and other bowel or liver disease. (See also Chapter 78, "Neurologic Complications of Nutritional Disorders.")

Patients with Wernicke encephalopathy, which is due to thiamine deficiency, present with the triad of encephalopathy, ataxia, and ocular abnormalities. (See Chapter 78, "Neurologic Complications of Nutritional Disorders.")

Toxic

Alcohol

Acute alcohol intoxication produces reversible ataxia. Cerebellar degeneration can occur from direct chronic alcohol toxicity or thiamine deficiency (or both). Atrophy of the superior and anterior vermis causes a midline cerebellar syndrome with progressive, prominent truncal and gait ataxia and relative sparing of other cerebellar signs. Pathologic findings include loss of Purkinje cells, molecular layer thinning, and proliferation of Bergmann glia. Abstinence can improve gait ataxia over 1 year.

Heavy Metals

Organic mercury, which is toxic to granule cells and the visual cortex, causes ataxia, paresthesia, and visual field deficits. Patients with *lead poisoning* can present with cerebellar signs, encephalopathy, and abdominal pain. Chelation therapy can reverse the syndrome. *Bismuth toxicity* (due to excessive bismuth subsalicylate [Pepto-Bismol]) can cause ataxia, myoclonus, and confusion, which resolve over months after cessation. *Thallium* may also cause ataxia.

Solvents

Toluene abuse (from inhaling the fumes of spray paint or paint thinners) produces chronic ataxia, with cognitive impairment and spasticity.

Medications and Drugs

Chemotherapeutic Agents

Fluorouracil at typical doses produces cerebellar ataxia in patients with dihydropyrimidine dehydrogenase deficiency; at higher doses, it causes a general acute to

subacute cerebellar syndrome. *Cytosine arabinoside* causes a cerebellar syndrome with loss of Purkinje and dentate neurons, gliosis, and spongiform changes, necessitating immediate cessation. *Piperazine* may also cause ataxia.

Anticonvulsants

Acute reversible ataxia can result from supratherapeutic levels of anticonvulsants, especially *phenytoin*. Long-term use of phenytoin can cause cerebellar atrophy with Purkinje cell loss, although the changes may be clinically mild. Possible causes include direct toxicity, seizure-induced repeated hypoxia or Purkinje cell discharges, or a congenital or inherited disorder that produces both seizures and cerebellar atrophy, such as spinocerebellar ataxia (SCA) type 10. Several second-generation anticonvulsants (lamotrigine, oxcarbamezepine, pregabalin, tiagabine, topiramate, and zonisamide) also produce dose-dependent ataxia, but gabapentin and levetiracetam do not.

Neurodegenerative

Sporadic Ataxias

Sporadic ataxias are progressive cerebellar ataxias that resemble SCA (see the sections on inherited ataxias below) but without a clear genetic cause. These are typically ataxias with onset after age 50. Imaging and blood tests can be used to rule out most acquired and structural causes of ataxia. A small percentage of patients have a gene mutation. In 1 study, the most common mutations were in genes involving SCA6 (6%), Friedreich ataxia (4%), SCA1 (2%), and SCA2 (1%).

Multiple System Atrophy

The cerebellar type of multiple system atrophy is a common cause of late-onset sporadic progressive cerebellar ataxia (see Chapter 23, "Atypical Parkinsonian Syndromes"). Patients are older than 30 and have progressive cerebellar ataxia with dysautonomia or parkinsonism.

MRI shows brainstem and cerebellar atrophy and a characteristic "hot cross bun" sign (Figure 26.2). Additional autonomic testing (thermoregulatory sweat test, autonomic reflex screen, and sphincter electromyography) can be helpful in making the diagnosis. Single-photon emission computed tomography dopamine transporter imaging can be abnormal even without parkinsonism. Polysomnography is indicated to assess for stridor, a preventable cause of respiratory arrest and sudden death. Rapid eye movement sleep behavior disorder supports a diagnosis of multiple system atrophy.

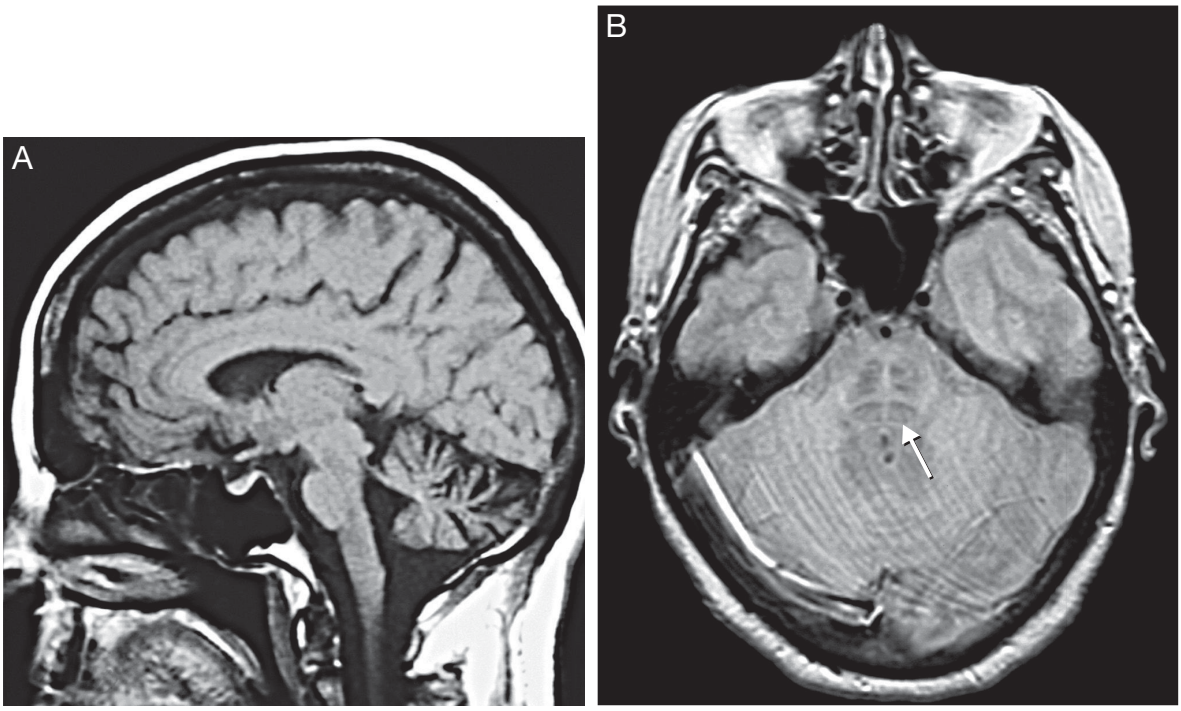

Figure 26.2 *Magnetic Resonance Imaging Characteristics of Multiple System Atrophy.*
A, Atrophy of the cerebellum, pons, and lower medulla (inferior olivary nuclei) are seen best in sagittal T1-weighted images. B, The "hot-cross-bun" sign (arrow) may result from pontine atrophy; it is seen best in axial T2-weighted and proton density images.
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

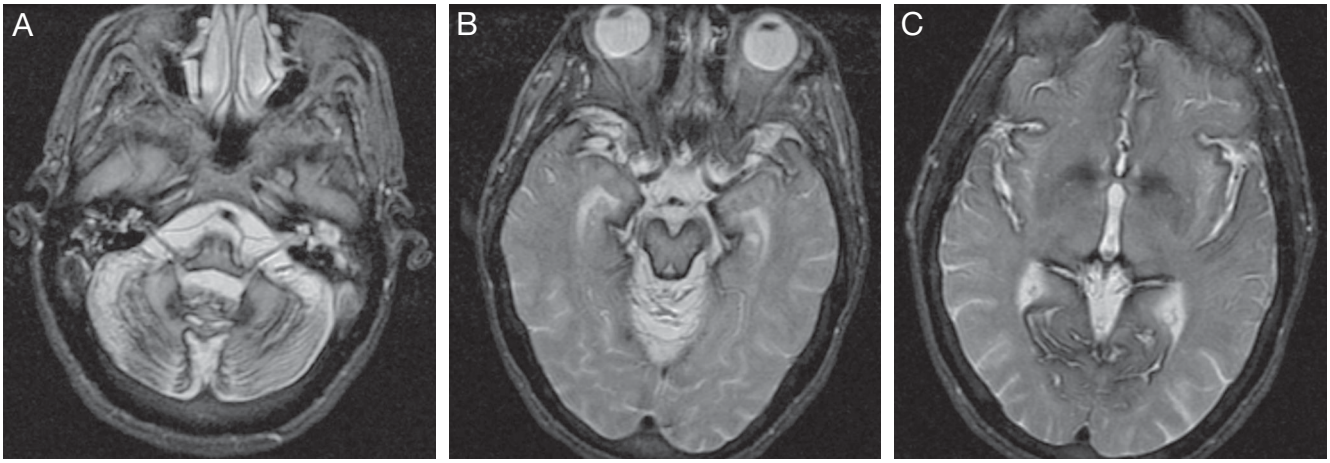

Figure 26.3 *Superficial Siderosis.*
T2-weighted sequence from magnetic resonance imaging of the brain shows areas of hemosiderin deposition along the cerebellar folia (A), surrounding the brainstem (B), and along the sulci (C).

Congenital

Arnold-Chiari Malformation

Chiari malformations may result in ataxia. (See Chapter 70, "Malformation of the Brain, Skull, and Spine.")

Dandy-Walker Malformation

Dandy-Walker malformation manifests in infancy and may be sporadic or autosomal recessive in inheritance. It is described below in the section on autosomal recessive inherited ataxias.

Other

Superficial Siderosis

Iron and hemosiderin, often from surreptitious bleeding, are deposited on pial and subpial brain surfaces. Ataxia, deafness, and cognitive impairment can occur. MRI shows low signal intensity on T2-weighted imaging, with a black rim on posterior fossa structures (Figure 26.3). Cerebrospinal fluid xanthochromia with siderophages are seen. Identification of the bleeding source and halting of the bleeding will arrest the disease. Iron chelation is ineffective.

- If celiac disease is confirmed (by antigliadin antibodies, antitissue transglutaminase antibodies, and jejunal biopsy), a gluten-free diet may reverse the ataxia.
- Progressive ataxia, typically in middle-aged women with type 1 diabetes mellitus and other autoimmune disease antibodies (thyroid, parietal cell, and pancreatic islet cell), has been associated with anti–glutamic acid decarboxylase antibodies.
- *Fluorouracil* at typical doses produces cerebellar ataxia in patients with dihydropyrimidine dehydrogenase deficiency; at higher doses, it causes a general acute to subacute cerebellar syndrome.

Autosomal Recessive Inherited Ataxias

Overview

There are several autosomal recessive inherited ataxias (Table 26.6). Select disorders are described below, and clinical features of the more common disorder are summarized in Table 26.7.

Friedreich Ataxia

Epidemiology and Genetics

Friedreich ataxia is the most common autosomal recessive inherited ataxia, affecting 1 in 50,000 whites.

Friedreich ataxia and its variants are caused by mutations in the frataxin gene. There is an unstable expansion of a trinucleotide (GAA) triplet repeat in the first intron of the *FRDA* gene (chromosome 9q13q21.1). This expansion (66–1,000 repeats) is present on both alleles in more than 95% of affected persons, but the size can differ on each allele. The expansion leads to impaired transcription and less frataxin protein. Frataxin is located in mitochondria; thus, deficiency leads to excess mitochondrial iron and resultant oxidative stress. Decreased frataxin levels have been reported in skeletal muscle, heart, pancreas, liver, kidney, and the central nervous system. Repeat length correlates with disease severity, cardiomyopathy, and diabetes mellitus. Repeat length correlates inversely with age at onset and is modified by other genetic or environmental triggers. Somatic mosaicism of the repeat size in different tissues also influences the phenotype. About 5% of patients with clinical Friedreich ataxia signs have a single allele with GAA expansion, but the other allele has a point mutation. Thus, the unexpanded allele must be sequenced to identify this. Point mutations in the carboxy end have a typical phenotype, and those at the amino terminal have a milder phenotype.

Table 26.6 • Autosomal Recessive Cerebellar Ataxias

Type	Protein	Gene Locus
Degenerative ataxias		
Friedreich ataxia	Frataxin	9q13
Coenzyme Q_{10} deficiency with cerebellar ataxia	. . .	. . .
Spastic ataxia of Charlevoix-Saguenay	Sacsin	13q12
Early-onset cerebellar ataxia with retained tendon reflexes (EOCARR)	. . .	13q11–12
Mitochondrial recessive ataxia syndrome (MIRAS)	Polymerase γ	. . .
Marinesco-Sjögren syndrome	SIL1	5q32
Congenital ataxias		
Joubert syndrome (JBTS)		
JBTS1	. . .	9q34
JBTS2	AHI1	11p12-p13.3
JBTS3	. . .	6q23
JBTS4	. . .	2q13
JBTS5	Nephrocystin-6	12q21.32
Cayman ataxia	Cayataxin	19p13.3
Metabolic ataxias		
Ataxia with isolated vitamin E deficiency (AVED)	Alpha-tocopherol transfer protein (α-TTP)	8q13
Refsum disease	Phytanoyl-CoA hydroxylase	10pter-p11.2
	Peroxisomal biogenesis factor 7	6q22-q24
Cerebrotendinous xanthomatosis (CTX)	Sterol 27-hydroxylase	2q33-qter
Abetalipoproteinemia	Microsomal triglyceride transfer protein	4q22-q24
Metachromatic leukodystrophy	Arylsulfatase 1	22q13
Niemann-Pick disease type C	NPC1 protein	18q11–121
GM_1 gangliosidosis	β-galactosidase	3p21.33
GM_2 gangliosidosis (Tay-Sachs disease)	Hexosaminidase 1	15q23–24
Chorea-acanthocytosis	Chorein	9q21
Wilson disease	ATPase copper-transporting β-polypeptide	13q14–21
Aceruloplasminemia	Ceruloplasmin	3q23-q24
Ataxias with DNA repair defects		
Ataxia telangiectasia	ATM	11q22.3
Ataxia with oculomotor apraxia 1 (AOA1)	Aprataxin	9p13
Ataxia with oculomotor apraxia 2 (AOA2)	Senataxin	9q34
Ataxia-telangiectasia-like disorder (ATLD)	MRE11A	11q21
Spinocerebellar ataxia with axonal neuropathy (SCAN1)	Tyrosyl-DNA phosphodiesterase 1	14q31

Abbreviation: ATPase, adenosine triphosphatase.

Adapted from Manto M, Marmolino D. Cerebellar ataxias. Curr Opin Neurol. 2009 Aug;22(4):419–29. Used with permission.

Clinical Features

Classic features are onset before age 20, progressive gait and leg clumsiness, and scoliosis. Dysarthria and upper limb ataxia emerge later. Examination findings include gait and limb ataxia, large-fiber sensory loss (vibration and proprioception) with sensory ataxia, and areflexia. Typically, pyramidal signs are present (positive Babinski sign initially, followed by lower limb weakness, atrophy, and spasticity) with bulbar signs and square wave jerks.

Skeletal abnormalities include scoliosis (Figure 26.4), pes cavus, pes planus, and talipes equinovarus. Cardiac disorders (T-wave inversion, hypertrophic cardiomyopathy [in 50% of patients], and dilated cardiomyopathy with atrial fibrillation) and diabetes mellitus (10%) often occur. Optic atrophy (25%) and deafness (10%) are possible.

The phenotype has expanded with the advent of genetic testing. About 75% of patients have classic Friedreich ataxia, and the remaining 25% fit 1 of several patterns: adult onset of classic signs (ie, late-onset or very late-onset Friedreich ataxia); early onset of classic signs but with hyperreflexia (ie, Friedreich ataxia with retained reflexes); late-onset Friedreich ataxia with spastic paraparesis; or chorea. Because of the broad spectrum, Friedreich ataxia should be considered in older patients who have sporadic ataxia but no family history of Friedreich ataxia.

Diagnosis

Nerve conduction studies show reduced or absent sensory nerve action potentials, consistent with axonal sensory neuropathy, and normal compound motor action potentials. MRI shows upper cervical cord atrophy and possible dorsal column signal change, with a normal cerebellum. Pathologic studies show relative sparing of the cerebellum and degeneration of the dorsal columns, lateral corticospinal tracts (lumbar more than cervical), dorsal root ganglia, and myelinated peripheral nerve fibers (Figures 26.5 and 26.6). Ultimately, genetic testing is confirmatory.

Table 26.7 • Comparison of Select Autosomal Recessive Ataxias

Disorder	Genetics	Age at Onset	Clinical Features	Other Findings
Friedreich ataxia	Frataxin gene Chromosome 9 GAA expansion	≥1 y	Progressive gait ataxia Large-fiber sensory loss Scoliosis	Cardiomyopathy, which can result in death
Ataxia telangiectasia	*ATM* gene Chromosome 11	1–12 mo	Progressive truncal ataxia, slurred speech Conjunctival telangiectasias (age ≥5 y)	Immunodeficiency with recurrent sinopulmonary infections and tendency toward malignancies Increased levels of AFP Decreased levels of immunoglobulins
Abetalipoproteinemia (Bassen-Kornzwieg syndrome)	*MTTP* gene Chromosome 4	<1 y	Cerebellar ataxia Reduced reflexes	Low levels of soluble vitamins, including vitamin E
Marinesco-Sjögren syndrome	*SIL1* gene	1–12 mo	Ataxia Cataracts Myopathy Mental retardation	. . .
Refsum disease	Phytanoyl-CoA hydroxylase gene Peroxin 7 gene	≥13 y	Ataxia Pigmentary retinal degeneration Neuropathy	May also have cardiac disease Organic acid testing shows increased phytanic acid
Mitochondrial recessive ataxia syndrome	Polymerase γ (*POLG*) gene	≥1 y	Cerebellar ataxia Reduced reflexes Painful axonal neuropathy May have cognitive issues or seizures (or both)	Reported in Finland and other European countries
Dandy-Walker malformation	Autosomal recessive or sporadic Chromosome 3	1–12 mo	Ataxia, poor head control and feeding Nystagmus or cranial neuropathies Symptoms associated with hydrocephalus May have delayed motor and cognition May have seizures	Cystic dilatation of the fourth ventricle with cerebellar vermal dysplasia Corpus callosal agenesis, cortical heterotopies, syringomyelia
Joubert syndrome type 1	Chromosome 9	1–12 mo	Ataxia or hypotonia Developmental delay Apnea Oculomotor apraxia, nystagmus	May have other organ involvement (liver, kidney, eye) MRI shows hypoplastic or dysplastic cerebellar vermis

Abbreviations: AFP, alpha fetoprotein; MRI, magnetic resonance imaging.

Treatment of Friedreich ataxia is symptomatic with multidisciplinary rehabilitation and close monitoring for cardiac abnormalities, diabetes mellitus, scoliosis, and hearing loss. Idebenone benefits cardiac hypertrophy and neurologic function. Coenzyme Q_{10} and vitamin E may improve cardiac and skeletal function. Iron chelation therapy may have a role. Experimental treatments include gene replacement, erythropoietin, and therapies to improve frataxin transcription.

Clinical Course

Progression is slow, with wheelchair dependence 15 years after onset, and patients usually die in their late 30s (or in their 50s or 60s with milder phenotypes). Patients may die of cardiac disease.

- Friedreich ataxia and its variants are caused by mutations in the frataxin gene. There is an unstable expansion of a trinucleotide (GAA) triplet repeat in the first intron of the *FRDA* gene (chromosome 9q13q21.1).
- In Friedreich ataxia, repeat length correlates with disease severity, cardiomyopathy, and diabetes mellitus. Repeat length correlates inversely with age at onset and is modified by other genetic or environmental triggers.
- Nerve conduction studies of patients with Friedreich ataxia show reduced or absent sensory nerve action potentials, consistent with axonal sensory neuropathy, and normal compound motor action potentials.

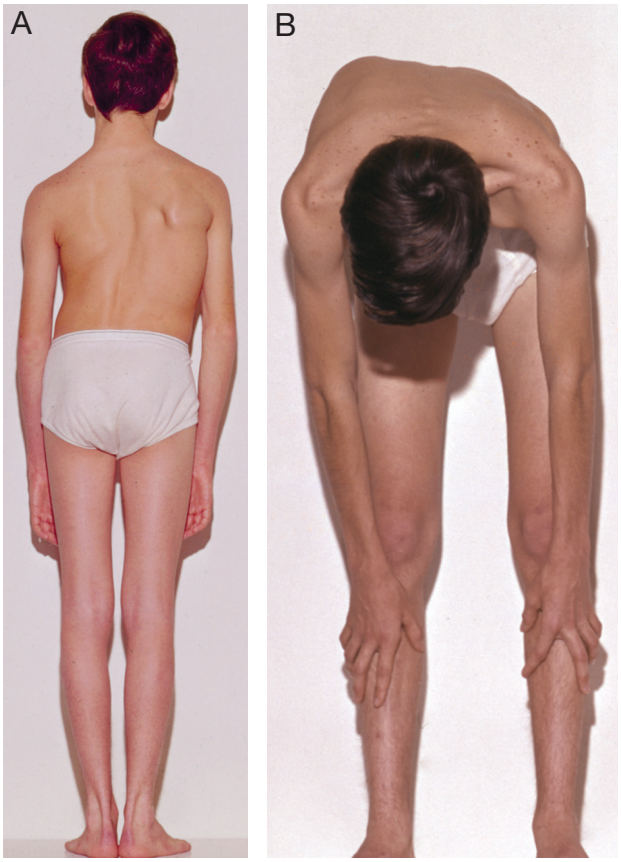

Figure 26.4 *Friedreich Ataxia.*
A and B, Kyphoscoliosis in a patient with Friedreich ataxia. (Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

- Treatment of Friedreich ataxia is symptomatic with multidisciplinary rehabilitation and close monitoring for cardiac abnormalities, diabetes mellitus, scoliosis, and hearing loss.

Ataxia-Telangiectasia

Epidemiology and Genetics

Ataxia-telangiectasia is the most common infantile-onset cerebellar ataxia. The prevalence is 1 per 20,000 to 1 per 100,000 persons.

Over 300 mutations are described for the *ATM* gene, located on chromosome 11q22-q23. The *ATM* gene codes for a kinase that is located mainly in the nucleus and has a role in cell cycle control and mitogenic signal transduction.

Clinical Features

The usual age at onset of ataxia-telangiectasia is 1 to 2 years, with truncal ataxia followed by clumsy hands and slurred speech. Conjunctival telangiectasias appear after ataxia, at about age 5, but these may fade with age (Figure 26.7). They may also occur on earlobes and popliteal fossae. Oculomotor apraxia (head thrust followed by lagging eye movement to fixate on an object) is a key eye sign. Jerky pursuit with loss of optokinetic nystagmus, upgaze palsy, and slow saccades with long latency may also occur.

Choreoathetosis and dystonia are notable. Later, distal muscle atrophy, areflexia, and large-fiber sensory neuropathy emerge. Other features may include immunodeficiency (in 60% of patients) and frequent sinopulmonary infections, T-cell deficiency, and an absent or small thymus gland. The risk of neoplasia, mainly leukemia or β-cell lymphoma, and solid malignancies increases after age 20.

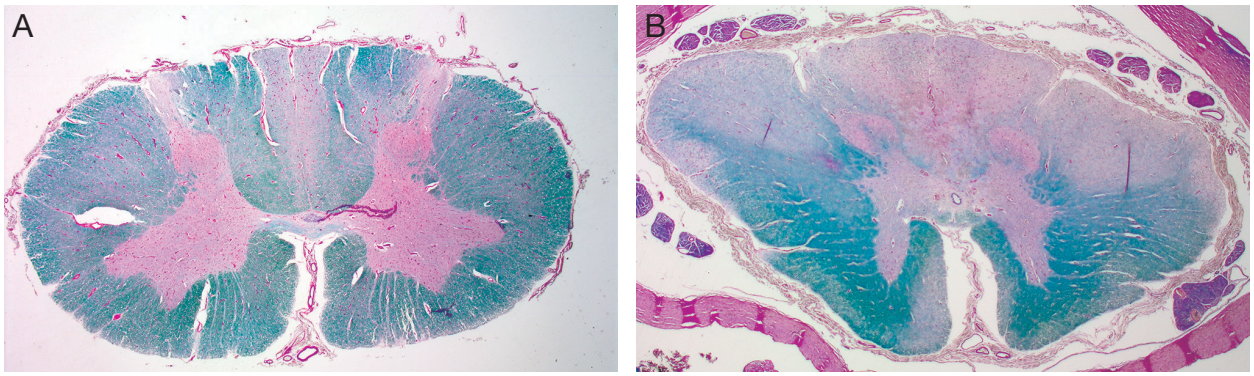

Figure 26.5 *Spinal Cord Sections From a Patient With Friedreich Ataxia.*
A, Cervical. B, Thoracic. Degeneration is more prominent in the gracile fasciculus than in the cuneate fasciculus. The thoracic section (B) shows degeneration of the spinocerebellar tracts and the lateral and anterior funiculi, the location of the corticospinal tracts. The corticospinal tracts are often spared at the cervical level (A), as shown here. (Luxol fast blue.)
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

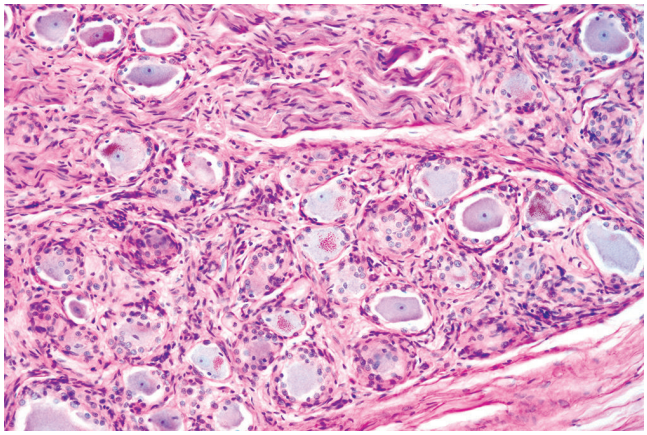

Figure 26.6 *Friedreich Ataxia.*
Degeneration of the dorsal root ganglion is indicated by dense clusters of cells called the nodules of Nageotte.
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

Diagnosis and Treatment

Patients with ataxia-telangiectasia usually have an increased alpha-fetoprotein level and low serum immunoglobulin levels. Chromosomal abnormalities, especially a 7;14 translocation, are common on karyotyping. Testing for genetic confirmation is limited to a few laboratories.

Pathologic studies show cerebellar atrophy (especially in the vermis); cell loss in the inferior olivary nucleus, dentate nucleus, Purkinje cells, and granule cells; spinal cord degeneration of the posterior and lateral columns and anterior horn cells (Figure 26.8); and demyelinating peripheral neuropathy.

Treatment is supportive with rehabilitation. Monitoring for infection and malignancy has improved survival to more than 25 years. Other important steps include screening for and treating endocrinopathies and diabetes mellitus and avoiding radiation.

- The usual age at onset of ataxia-telangiectasia is 1 to 2 years, with truncal ataxia followed by clumsy hands and slurred speech. Conjunctival telangiectasias appear after ataxia, at about age 5, but these may fade with age.
- Patients with ataxia-telangiectasia usually have an increased alpha-fetoprotein level and low serum immunoglobulin levels.

Ataxia-Telangiectasia-Like Disorder

Ataxia-telangiectasia-like disorder results from mutations encoding MRE11, a double-stranded DNA repair enzyme.

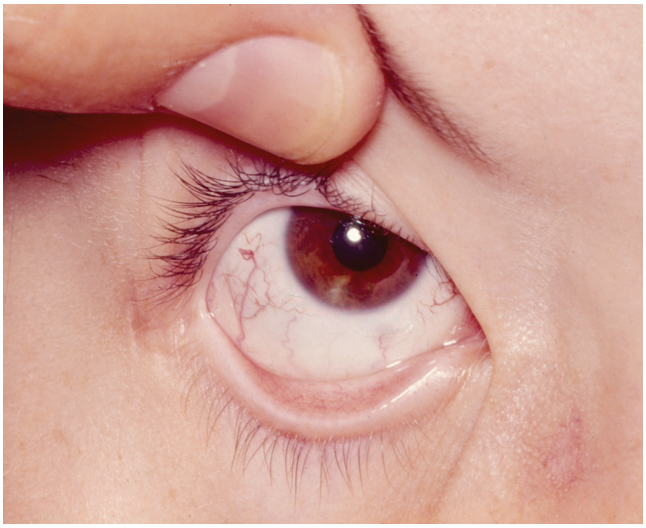

Figure 26.7 *Ocular Telangiectasia in a Patient With Ataxia-Telangiectasia.*
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

Clinical findings are similar to those in mild ataxia-telangiectasia without telangiectasia or an elevated alpha-fetoprotein level.

Ataxia With Isolated Vitamin E Deficiency

Ataxia with vitamin E deficiency is a rare, recessive, progressive ataxia resembling Friedreich ataxia but with low or undetectable vitamin E levels. It is caused by mutations of the α-tocopherol transfer protein gene on chromosome 8q13.1-q13.3. The role of the protein is to transport vitamin E into chylomicrons in the liver; thus, impaired hepatic processing rather than malabsorption underlies the vitamin E deficiency.

Onset is usually in childhood with large-fiber sensory loss, areflexia, extensor plantars, ataxia, dysarthria, head titubation, and dystonia. Cardiac involvement is less than in Friedreich ataxia. Retinopathy and visual loss may occur.

Vitamin E levels are usually less than 1.8 mg/L. Diagnosis is confirmed by detecting the α-tocopherol transfer protein mutation. Treatment is high-dose vitamin E, which may stabilize the syndrome.

Abetalipoproteinemia (Bassen-Kornzweig Syndrome)

Abetalipoproteinemia is a rare disorder. Patients present with neonatal- and infantile-onset diarrhea and malabsorption, followed by a slow deterioration in neurologic

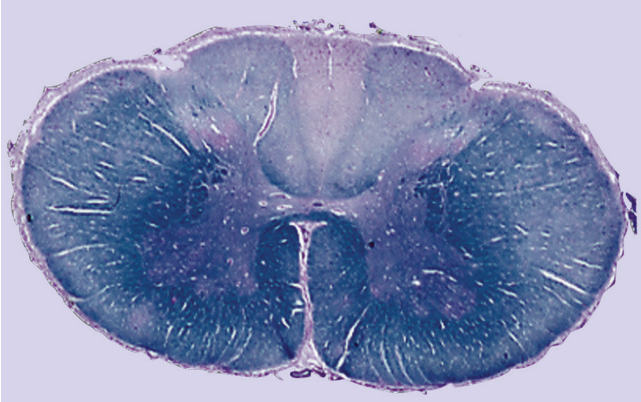

Figure 26.8 *Ataxia-Telangiectasia.*
This section through the cervical spinal cord from a patient with ataxia-telangiectasia shows marked degeneration of the posterior columns (more prominent in the gracile fasciculus) and less severe degeneration in the lateral funiculi. (Luxol fast blue.)
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

status with ataxia resembling that of isolated vitamin E deficiency. Mutations in the gene for microsomal triglyceride transfer protein (on chromosome 4q24) are implicated. Loss of the protein leads to impaired intestinal lipid absorption and, thus, to impaired absorption of fat-soluble vitamins.

Patients with abetalipoproteinemia have low serum levels of cholesterol and vitamins A, D, E, and K; no apolipoprotein B; and peripheral blood acanthocytes. Liver function test results may be abnormal, with an elevated international normalized ratio. Serum lipoprotein electrophoresis confirms the diagnosis. Treatment with a low-fat diet and replacement of vitamins A, D, E, and K may slow disease progression.

- Patients with abetalipoproteinemia have low serum levels of cholesterol and vitamins A, D, E, and K; no apolipoprotein B; and peripheral blood acanthocytes.

Ataxia With Oculomotor Apraxia Type 1

Ataxia with oculomotor apraxia type 1 is a childhood-onset, slowly progressive ataxia, similar to ataxia-telangiectasia, followed by oculomotor apraxia and a severe axonal motor and sensory neuropathy. Mental retardation is common, but there is no increased risk of immunodeficiency, neoplasia, or radiation sensitivity. It is common in Japan and Portugal from a mutation in the aprataxin gene (*APTX*) on chromosome 9. Aprataxin is a nuclear protein that is probably involved in base strand repair on single-stranded DNA. Investigations show elevated creatine kinase and cholesterol levels and hypoalbuminemia.

Ataxia With Oculomotor Apraxia Type 2

Ataxia with oculomotor apraxia type 2 is the most frequent autosomal recessive ataxia after Friedreich ataxia in Europe. Progressive ataxia starts in the mid-teenaged years, and patients are wheelchair bound by age 30. Oculomotor apraxia occurs in 50% of patients. Other signs are pyramidal signs (20%), dystonia, chorea, head tremor, and strabismus. The condition is caused by senataxin gene (*SETX*) mutations, which probably affect DNA and RNA helicase repair. Investigations show elevated levels of alpha fetoprotein (which should suggest the diagnosis), axonal polyneuropathy, and marked cerebellar atrophy. There is no malignancy, immunodeficiency, or radiation risk.

Other Ataxias With DNA Repair Defects

Spinocerebellar ataxia with axonal neuropathy is a rare, late-childhood–onset ataxia with peripheral neuropathy and areflexia. It is caused by mutations affecting tyrosyl-DNA phosphodiesterase 1, a DNA repair enzyme. There are no typical features of ataxia-telangiectasia or ataxia-telangiectasia-like disorder.

Cockayne syndrome (autosomal recessive [chromosome 5] or autosomal dominant [chromosome 10]) and *xeroderma pigmentosum* are caused by DNA excision repair defects. Both are characterized by ataxia with mental retardation, microcephaly, seizures, pyramidal and extrapyramidal signs, and photosensitivity. The differences are the finding of basal ganglia calcification on computed tomography in Cockayne syndrome and the presence of skin tumors in xeroderma pigmentosum.

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay

Autosomal recessive spastic ataxia of Charlevoix-Sanguenay is named after the Quebec province where it was first described in consanguineous French-Canadian families. Affected patients have early-childhood onset of spasticity, ataxia, and amyotrophy of distal muscles. The condition progresses slowly, and patients have an expected life span into the sixth decade. It is linked to a point mutation in a gene on chromosome 13, resulting in loss of sacsin, which may act as a chaperone in protein folding.

Marinesco-Sjögren Syndrome

Marinesco-Sjögren syndrome is a rare multisystem disorder with infancy-onset ataxia, early cataracts, mental retardation, and myopathy. The syndrome is caused by

mutations in the *SIL1* gene, which encodes a nucleotide exchange factor for the Hsp70 chaperone protein.

Refsum Disease

Onset of Refsum disease is in the second to third decade. Refsum disease is characterized by a relapsing-remitting course of early pigmentary retinal degeneration and night blindness, demyelinating sensorimotor polyneuropathy, sensorineural deafness, ataxia, ichthyosis, and cardiac arrhythmias. Deficiency in the peroxisomal enzyme phytanoyl-CoA hydroxylase prevents alpha-oxidation of phytanic acid, leading to accumulation of phytanic acid and neurotoxicity. Organic acid testing shows increased plasma and urine phytanic acid, and cultured fibroblasts are less able to oxidize phytanic acid. Treatment is dietary reduction in phytanic acid to help the neuropathy.

- Onset of Refsum disease is in the second to third decade. Refsum disease is characterized by a relapsing-remitting course of early pigmentary retinal degeneration and night blindness, demyelinating sensorimotor polyneuropathy, sensorineural deafness, ataxia, ichthyosis, and cardiac arrhythmias.

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis, an autosomal recessive disorder, stems from a defect in liver bile acid synthesis (27-hydroxylase), which impairs the formation of cholic acid. The capacity to remove excess cholesterol from peripheral tissues is decreased so that cholesterol accumulates in tissues and cerebellar white matter.

Clinically, affected patients have tendon xanthomas, xanthelasma, and cataracts, with slowly progressive ataxia, pyramidal signs, peripheral neuropathy, and cognitive impairment. They may have seizures, palatal myoclonus, and pseudobulbar palsy.

Neuroimaging may show cerebellar and cerebral atrophy. Treatment with cholic acid and chenodeoxycholic acid compensates for deficient bile acids in the hepatic pool and decreases cholestanol synthesis. Simvastatin or lovastatin decrease cholesterol synthesis and cholestanol levels.

Vanishing White Matter Leukoencephalopathy

Vanishing white matter leukoencephalopathy is a childhood-onset ataxia with central nervous system hypomyelination. Affected patients have chronic progressive ataxia, seizures, cognitive deficit, spasticity, and optic atrophy. Episodic deterioration may follow stress or fever, with episodes of coma. Mutations occur in any 1 of the 5 genes coding for translation initiation factor 2b. MRI findings are shown in Figure 26.9. Pathologic changes are confined to the white matter, which shows diffuse leukoencephalopathy with astrocytic dropout and "foamy" oligodendrocytes, and the

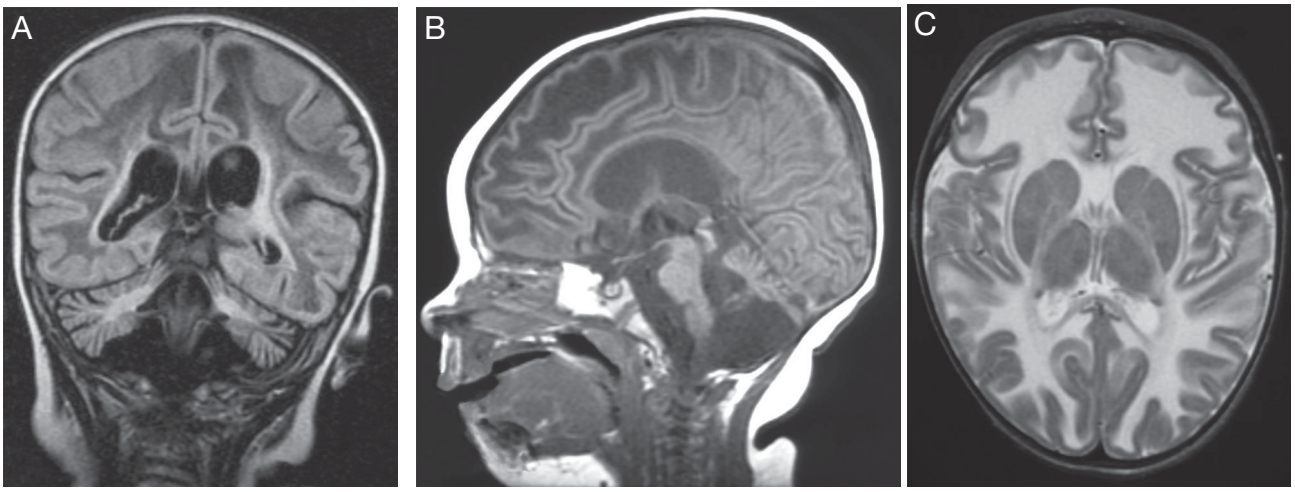

Figure 26.9 *Childhood-Onset Ataxia With Central Nervous System Hypomyelination.*
Conventional magnetic resonance images are shown from a patient with developmental regression, seizures, and spasticity. A and B, T1-weighted images. C, T2-weighted image. Almost the entire subcortical white matter appears homogeneously hyperintense on the T2-weighted image and severely hypointense on the T1-weighted images. There is pronounced atrophy of the posterior fossa structures, including the brainstem and cerebellum. The images also show other results of the atrophy: a septum cavum, ex-vacuo dilatation of all the ventricles, and prominent cisterns.
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

cerebellum, which shows atrophy that mainly involves the vermis. Cerebrospinal fluid has an elevated level of glycine.

Behr Syndrome

Behr syndrome is an autosomal recessive disorder characterized by optic atrophy and cerebellar ataxia with an onset in early childhood. Other features are nystagmus, scotoma, and bilateral retrobulbar neuritis. Spasticity, mental retardation, and posterior column sensory loss also occur. Nerve biopsy findings are consistent with chronic neuropathy with axonal degeneration and regeneration.

Dandy-Walker Malformation

Dandy-Walker malformation may be autosomal recessive or sporadic. A Dandy-Walker variant with hydrocephalus and facial dysmorphism is associated with a deletion on chromosome 3q25.

Dandy-Walker malformation is characterized by cystic dilatation of the fourth ventricle and cerebellar vermis dysplasia. Presentation is usually in the first year of life, secondary to hydrocephalus and posterior fossa symptoms. Features include apnea, cranial neuropathies, nystagmus, papilledema, and anterior fontanelle bulging. Infants may have poor head control, spasticity, poor feeding, and hyperirritability. Older children often have delayed motor and intellectual development; one-third have seizures. Dandy-Walker malformation is associated with corpus callosum agenesis, cortical heterotopias, cerebral gyral abnormalities, occipital encephalocele, syringomyelia, aqueductal stenosis, and hemimegalencephaly.

The differential diagnosis for posterior fossa fluid collection includes familial vermian agenesis (eg, Joubert syndrome), trapped fourth ventricle, enlarged cisterna magna, and arachnoid cyst (Figure 26.10).

- Dandy-Walker malformation is characterized by cystic dilatation of the fourth ventricle and cerebellar vermis dysplasia.
- Dandy-Walker malformation is associated with corpus callosum agenesis, cortical heterotopias, cerebral gyral abnormalities, occipital encephalocele, syringomyelia, aqueductal stenosis, and hemimegalencephaly.

Classic Joubert Syndrome

Classic Joubert syndrome (Joubert syndrome type 1) includes infantile onset of hypotonia, developmental delay, ataxia, abnormal breathing patterns (apnea and tachypnea), mental retardation, oculomotor apraxia, nystagmus, and ptosis. Other features include renal disease, ocular colobomas, liver fibrosis, polydactyly, and pigmentary retinopathy. This autosomal recessive disorder is linked to chromosome 9. It is characterized by a hypoplastic or dysplastic cerebellar vermis with enlargement of the fourth ventricle. The "molar tooth" sign (ie, brainstem abnormalities that resemble a tooth) may be seen: elongated superior cerebellar peduncle, deep interpeduncular fossa, and dysplasia of the superior cerebellar vermis.

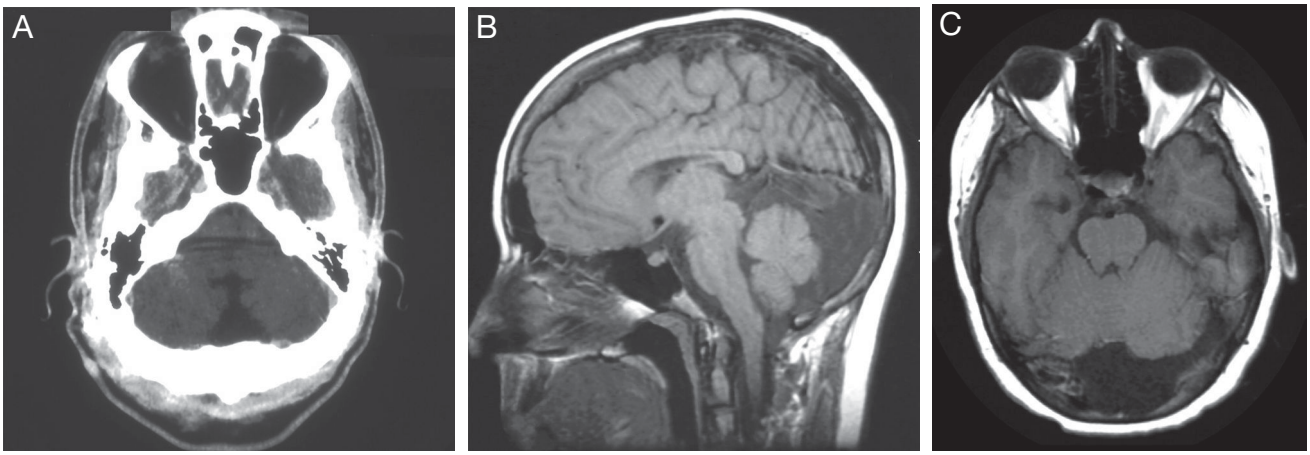

Figure 26.10 *Dandy-Walker Malformation and Arachnoid Cyst.*
A, Nonenhanced computed tomogram shows the characteristic features of vermian hypoplasia and cystic dilatation of the fourth ventricle without enlargement of the posterior fossa. B and C, Magnetic resonance images (T1 weighted) show a true retrocerebellar arachnoid cyst of developmental origin associated with a pronounced mass effect. There is displacement of the transverse sinuses and remodeling of the underlying occipital bone from the arachnoid cyst. The bone remodeling is the result of a chronic mass effect.
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

Other Syndromic Ataxias

Early-onset ataxia with retained reflexes begins in childhood or early adulthood with ataxia; it is similar to Friedreich ataxia but with preserved deep tendon reflexes. Friedreich ataxia genetic testing is positive in some cases. *Ramsay Hunt syndrome* is characterized by ataxia and myoclonus or myoclonic epilepsy. *Unverricht-Lundborg disease* (Baltic myoclonus) is a subtype of Ramsay Hunt syndrome that is caused by a mutation in the gene on chromosome 21q that encodes for cystatin B.

Other Rare Autosomal Recessive Ataxias

Infantile-Onset Olivopontocerebellar Atrophy

Infantile-onset olivopontocerebellar atrophy is a very rare, recessive ataxia that was reported for a single kindred in Finland. Onset is at approximately age 1, shortly after the child learns to walk, with ataxia, peripheral neuropathy, hyporeflexia, extensor plantar response, and athetosis of the hands and feet. By the time the child is schoolaged, the child has ophthalmoplegia, deafness, dysarthria, optic atrophy, and seizures. With the characteristic progressive ataxia and dementia, patients are wheelchair bound by the late teenaged years. The *C10orF2* gene on chromosome 10q24 is a nuclear gene encoding Twinkle, a mitochondrial DNA-specific helicase, and a splice variant called Twinky. Autosomal dominant mutations of the gene cause progressive external ophthalmoplegia.

Cayman Ataxia

A rare, recessive ataxia of early childhood, Cayman ataxia was identified on Grand Cayman Island. The mechanism and clinical phenotype are similar to those of vitamin E deficiency ataxia, with marked psychomotor retardation and nonprogressive cerebellar ataxia. It is linked to mutations in the *ATCAY* gene on chromosome 19, which codes for caytaxin. Caytaxin contains a domain that is homologous to the CRAL-TRIO motif in α-tocopherol transfer protein.

Autosomal Recessive Cerebellar Ataxia Type 1

Autosomal recessive cerebellar ataxia type 1 was identified in a remote French-Canadian population of Quebec. Onset is in early adulthood (age 17–46 years) with slowly progressive ataxia, dysarthria, and disordered eye movements. Hyperreflexia and cerebellar atrophy may occur. The expected life span of affected persons is normal. Mutations in the *SYNE1* gene affect a spectrin cytoskeletal protein that may help actin anchor to plasma membrane and is present in Purkinje cells.

Autosomal Recessive Cerebellar Ataxia Type 2

Autosomal recessive cerebellar ataxia type 2 is due to a deficiency of coenzyme Q_{10}, which is necessary for the electron transport chain, resulting from mutation in the *ADCK3* gene. Affected patients have ataxia, spasticity, cognitive impairment, and hypogonadism. Other phenotypes include infantile multisystem disease, encephalopathy with ragged red fibers, and Leigh syndrome. CoQ_{10} replacement may help clinical features.

Mitochondrial Disease

Ataxia can occur with many mitochondrial disorders, accompanied by external ophthalmoplegia, myopathy, and other features. These include myoclonus epilepsy with ragged red fibers; neuropathy, ataxia, and retinitis pigmentosa; Kearns-Sayre syndrome; progressive external ophthalmoplegia; and mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (see Chapter 76, "Mitochondrial Disease").

Autosomal Dominant Inherited Ataxias

Autosomal dominant inherited ataxias can be subdivided into those with a progressive course (SCAs) and those with episodic findings (episodic ataxias). These are typically numbered in the order of disease description or causative gene. Genetic and clinical features of select disorders are found in Table 26.8.

Spinocerebellar Ataxias

SCAs typically occur in each family generation. Age at onset is usually early to middle adulthood, with a wide range. Most start with gait imbalance followed by limb ataxia, dysarthria, and visual changes. Lack of a family history that indicates affected parents may be due to parental death before symptom onset, reduced penetrance, earlier onset in the child due to anticipation, wrong paternity, or de novo mutations.

SCAs may occur with a pure cerebellar phenotype or with other neurologic or systemic findings. They are grouped by clinical phenotype, based on Harding's original criteria. Autosomal dominant cerebellar ataxia (ADCA) type 1 is a cerebellar syndrome with pyramidal and extrapyramidal features, ophthalmoplegia, and dementia (SCA types 1–4, 8, 12, and 17). ADCA type 2 is a cerebellar syndrome with pigmentary macular degeneration and dystrophy (SCA7). ADCA type 3 is a pure cerebellar syndrome (possibly mild pyramidal signs) (SCA types 5, 6, 10, 11, 14, and 15).

The phenotype can aid in narrowing the differential diagnosis and directing genetic testing (Table 26.4). For example, age at onset (childhood, young adulthood, or older adulthood) can be helpful. Anticipation may occur (SCA types 1 and 7; dentatorubral-pallidoluysian atrophy [DRPLA]). Other useful findings, besides those listed in Table 26.4, include upper motor neuron signs with

Table 26.8 • Clinical Features and Genetics of Select Autosomal Dominant Ataxias

	Genetics		
Disorder	**Chromosome[a]**	**Protein**	**Clinical Features in Addition to Ataxia**
SCA1	6	Ataxin-1	Pyramidal signs Reduced saccadic pursuit progressing to ophthalmoplegia May have peripheral neuropathy and movement disorder Cognitive decline
SCA2	12	Ataxin-2	Similar to SCA1, but peripheral neuropathy and areflexia are prominent early
SCA3 (Machado-Joseph disease)	14	Ataxin-3	Brainstem signs (facial and tongue weakness, atrophy) Parkinsonism or dystonia (or both) May have ophthalmoplegia and ptosis May have neuropathy or amyoatrophy (or both)
SCA6	19	Subunit of a calcium channel[b]	Pure ataxia, but mild pyramidal signs are possible
SCA7	3	Ataxin-7	Visual loss (pigmented retinopathy) Spasticity (pyramidal signs) With or without peripheral neuropathy
DRPLA	12	Atrophin-1	Myoclonic epilepsy, dementia If onset after age 20, psychiatric features may also be present

Abbreviations: DRPLA, dentatorubral-pallidoluysian atrophy; SCA, spinocerebellar ataxia.
[a] The number is the number of the chromosome where the CAG repeat occurs.
[b] The *CACNA1A* gene codes for the α_{1A} subunit of the voltage-dependent P/Q-type calcium channel.

hyperreflexia and possible spasticity (SCA types 1, 3, 7, and 12; less commonly, SCA types 6 and 8) and ophthalmologic findings, including hypermetric saccades (SCA1) and macular dystrophy, pigmentary retinal deterioration, and blindness (SCA7).

Currently, more than 30 SCAs have been identified, and the number continues to increase. Genetic testing has largely divided SCAs into those due to expanded unstable trinucleotide repeats (CAG most commonly, but also CTG and ATTCT) or other point, deletion, or insertion mutations. In patients with SCAs due to unstable nucleotide repeat expansions, anticipation may be expressed, more commonly with paternal transmission. Age at onset and disease severity are inversely related to repeat size. There may be phenotypic variability in a single gene mutation, as the disease progresses in the patient, or between family members.

For patients with SCA, MRI typically shows progressive atrophy of the cerebellum and possibly also of the pons, medulla, middle cerebellar peduncles, and upper cervical cord (Figure 26.11). The T2 hyperintensity "hot cross bun" sign in the pons can be seen with brainstem signs. Pathologic changes typically include cerebellar atrophy, with additional brainstem and spinal cord atrophy in some SCAs. In all SCAs, there is loss of cerebellar Purkinje cells with hypertrophy and hyperplasia of Bergmann glia and possible gliosis of deep cerebellar nuclei (Figures 26.12 and 26.13). Remaining Purkinje cells may be atrophic with torpedoes on proximal axons. Loss of the dendritic tree leads to a thinned molecular layer. Diagnosis by a panel of genetic tests is expensive. However, they are useful for confirming the diagnosis and estimating the risk of transmission to children.

SCA1

The mutation in SCA1 is an unstable CAG repeat expansion in chromosome 6p, coding for the protein ataxin-1. Age at onset is in the 30s, but it can range from childhood to older than 70. Paternal anticipation is seen. Clinical features are cerebellar ataxia with pyramidal signs (spasticity, hyperreflexia, clonus, and extensor plantars). Initial eye signs are decreased blinking and saccadic pursuit. Over time, saccades become slow ophthalmoparesis, sensory polyneuropathy becomes more pronounced than motor axonal polyneuropathy, and dystonia, parkinsonism, chorea, and executive cognitive decline can occur. MRI shows pontocerebellar atrophy.

SCA2

SCA2 is similar to SCA1, but clues are very slow saccades early in the disease course, peripheral neuropathy, and areflexia. Slow saccades progress to supranuclear ophthalmoplegia and complete ophthalmoplegia. An unstable CAG repeat expansion located in chromosome 12q codes for the protein ataxin-2. Longer repeats correlate with earlier onset, myoclonus, rapid progression, dementia, and paternal anticipation. Mean age at onset is the second to fourth decades. Other key features are levodopa-responsive parkinsonism (which may be the initial presentation),

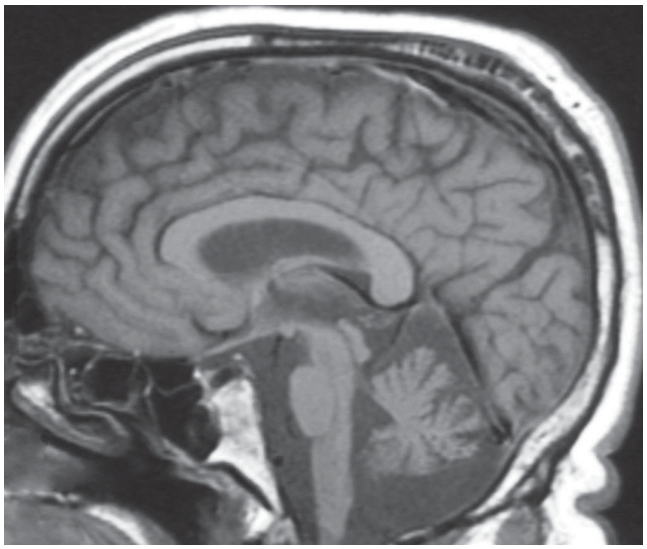

Figure 26.11 *Spinocerebellar Ataxia (SCA).*
T1-weighted magnetic resonance image from a patient with SCA type 2 shows marked pontocerebellar atrophy.
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

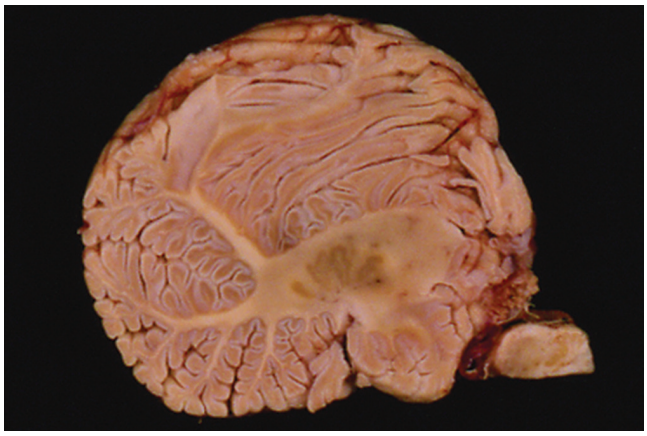

Figure 26.12 *Spinocerebellar Ataxia (SCA) Type 3 (Machado-Joseph Disease).*
The dentate nucleus has undergone atrophy and discoloration. There is relative sparing of the cerebellar folia (location of Purkinje cells) compared with the prominent atrophy seen in SCA type 2 (Figure 26.11).
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

dystonia, myoclonus, kinetic or postural tremor, and early dementia. MRI shows pontocerebellar atrophy.

SCA3

SCA3 (Machado-Joseph disease) is the most common SCA worldwide. The CAG repeat expansion is in chromosome 14q, and the gene product is ataxin-3 (a cytoplasmic protein that accumulates in nuclear inclusions only with disease). SCA3 is similar to SCA1 and SCA2. The age at onset and course resemble those of SCA1, but the phenotype is wider, like that of SCA2. Brainstem signs include facial and tongue fasciculations or myokymia, weak cough, facial atrophy, and dysphagia. Levodopa-responsive parkinsonism may be prominent in SCA3, or dystonia may be the main feature. Multiple eye signs include slow saccades, ophthalmoplegia, ptosis, bulging eyes, and blepharospasm. Patients with later onset may have ataxia, amyotrophy, polyneuropathy, and areflexia.

SCA6

Onset of SCA6 is later (fifth to sixth decades) than for most other SCAs, and it features a relatively pure cerebellar ataxia. The course is benign, with slowly progressive ataxia and commonly vertigo or downbeat nystagmus. Mild pyramidal signs may occur. There is a CAG repeat expansion in the *CACNA1A* gene on chromosome 19p, coding for the α_{1A} subunit of the voltage-dependent P/Q-type calcium channel, which is highly expressed in Purkinje cells. Episodic ataxia type 2 and familial hemiplegic migraine share the same allele, so these features may also occur. Pathology is confined to the cerebellum.

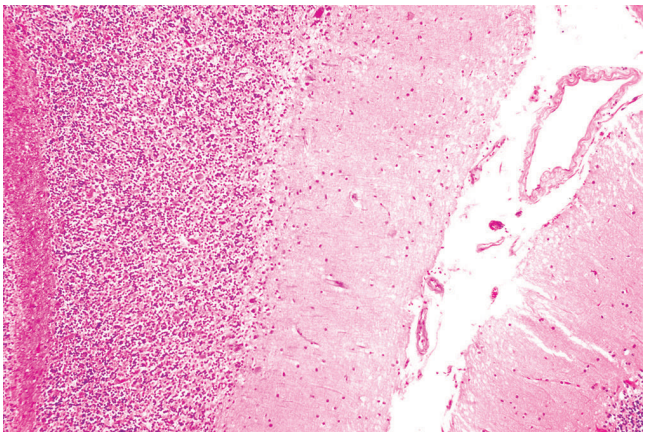

Figure 26.13 *Spinocerebellar Ataxia Type 6.*
There is a severe loss of Purkinje cells and gliosis with relative sparing of the granule cells. (Hematoxylin-eosin.)
(Adapted from Mowzoon N. The cerebellum and cerebellar disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 377–99. Used with permission of Mayo Foundation for Medical Education and Research.)

SCA7

The characteristic feature of SCA7 is severe visual loss due to maculopathy, with often severe ataxia and spasticity. Other features are similar to those of SCA1, SCA2, and SCA3. Dementia, pyramidal signs, and peripheral neuropathy may be present. A CAG repeat expansion in chromosome 3p codes for ataxin-7 and is more unstable than other CAG expansions. With onset in childhood, visual loss often precedes ataxia, and the child can be affected before the parent (because of anticipation) with dementia, seizures, and a more rapidly progressive course.

- For patients with SCA, MRI typically shows progressive atrophy of the cerebellum and possibly also of the pons, medulla, middle cerebellar peduncles, and upper cervical cord. The T2 hyperintensity "hot cross bun" sign in the pons can be seen with brainstem signs.
- SCA3 (Machado-Joseph disease) is the most common SCA worldwide.
- Levodopa-responsive parkinsonism may be prominent in SCA3, or dystonia may be the main feature.

Dentatorubral-Pallidoluysian Atrophy

Most reported cases of DRPLA are from Japan, but cases are also reported in the United States and Europe. The onset of DRPLA before age 20 is typically progressive myoclonic epilepsy with dementia, ataxia, and myoclonus. Onset after age 20 may include ataxia, dementia, choreoathetosis, and psychiatric features. The unstable CAG trinucleotide repeat expansion (usually 49–75) codes for atrophin-1 on chromosome 12p13.31 with high penetrance. MRI may show cerebellar and brainstem atrophy and hyperintense T2 lesions in adults.

- The onset of DRPLA before age 20 is typically progressive myoclonic epilepsy with dementia, ataxia, and myoclonus. Onset after age 20 may include ataxia, dementia, choreoathetosis, and psychiatric features.

X-Linked Inherited Ataxias

Fragile X–Associated Tremor/Ataxia Syndrome

Fragile X–associated tremor/ataxia syndrome is reported in maternal grandfathers of males with fragile X mental retardation. The *FMR1* gene normally has fewer than 54 repeats, but in fragile X mental retardation, more than 200 repeats are present. The maternal grandfathers may carry a premutation range of 55 to 200, and the disease develops in about one-third. Fragile X–associated tremor/ataxia syndrome includes late-onset ataxia, tremor, executive dysfunction, and parkinsonism. Occasionally, females carry premutations, but they have a milder phenotype. This syndrome should be considered in patients with sporadic ataxia, tremor, or MSA. MRI of the brain shows T2 hyperintensity in the middle cerebellar peduncles.

- Fragile X–associated tremor/ataxia syndrome is reported in maternal grandfathers of males with fragile X mental retardation.
- Fragile X–associated tremor/ataxia syndrome includes late-onset ataxia, tremor, executive dysfunction, and parkinsonism.

Table 26.9 • Causes of Episodic Ataxia

Type of Cause	Disorder
Vascular	Transient ischemic attack
Toxins and medications	Alcohol intoxication Antiseizure medication toxicity Benzodiazepine toxicity
Paroxysmal disorders	Migraine Seizure Episodic vertigo
Structural	Intermittent hydrocephalus (third ventricular colloid cyst)
Genetic	Episodic ataxia types 1 and 2 Episodic ataxia with paroxysmal choreoathetosis and spasticity Hyperammonemia (urea cycle defects) Hartnup disease Maple syrup urine disease Pyruvate dehydrogenase deficiency Biotin-dependent carboxylase deficiency

Episodic or Recurrent Cerebellar Ataxias

Several acquired and inherited conditions may result in intermittent, episodic ataxias (Table 26.9). Episodic ataxia types 1 and 2 are autosomal dominant disorders manifesting with short bursts of intermittent ataxia. Patients present in childhood; these disorders are discussed in Chapter 27, "Childhood Movement Disorders."

27 Childhood Movement Disorders[a]

PAUL E. YOUSSEF, DO; KENNETH J. MACK, MD, PHD

Introduction

The phenomenology and classification of movement disorders are similar for adults and children, but the causes and approach are quite distinct. Hyperkinetic disorders are more common than hypokinetic disorders in children. Furthermore, some disorders are exclusively present in infants and children, and others may begin in childhood and persist into adulthood. This chapter focuses primarily on the movement disorders that begin in childhood. Disorders that occur in children or adults without a specific predilection are covered in individual movement disorders sections.

Chorea, Athetosis, and Ballism

Overview

A vast array of genetic and neurodegenerative disorders of childhood can preferentially affect the basal ganglia and result in chorea, athetosis, or ballism. In these conditions when chorea is present, encephalopathy is usually the dominant clinical sign.

Because chorea in childhood may be associated with various chronic, progressive metabolic or neurodegenerative disorders (Table 27.1), the evaluation of the child should include clinical and family histories, neurologic examination, and consideration of diagnostic tests such as determining levels of serum amino acids, urine organic acids, alpha fetoprotein, serum lactate and pyruvate, uric acid, calcium, phosphorus, and thyroid hormone; performing lysosomal enzyme assays; screening for connective tissue disorders; genetic testing; and magnetic resonance imaging (MRI).

Primary (Genetic) Choreas

Benign Hereditary Chorea

Benign hereditary chorea (BHC) is characterized by early childhood onset of a relatively nonprogressive chorea, which is not associated with intellectual deterioration and may diminish during adolescence or persist into adulthood. This is an autosomal dominant disorder with a mutation in the *NKX2.1* gene, which encodes thyroid transcription factor 1.

The abnormal movements usually begin in the first 5 years of life and are often first noted when the child begins to walk. The severity of the choreic movements varies from mild jerking of the extremities to gross sudden jerks that interfere with ambulation and writing. Some children have various degrees of dysarthria, delayed motor development, intention tremor, and athetosis.

Neuroimaging and electroencephalographic results are normal. The lack of progression of chorea and the absence of dementia distinguish BHC from Huntington disease, and the persistence of involuntary movements for many years distinguishes BHC from Sydenham chorea.

No symptomatic treatment has been shown to be consistently effective in these patients; however, dopamine

[a] Portions previously published in Mack KJ. Movement disorders in childhood. In: David RB, Bodensteiner JB, Mandelbaum DE, Olson B, editors. Clinical pediatric neurology. 3rd ed. New York (NY): Demos Medical; c2009. p. 189–209. Used with permission.

Abbreviations: BH4, tetrahydrobiopterin; BHC, benign hereditary chorea; DYT1, early-onset primary torsion dystonia; DYT5, dopa-responsive dystonia; DYT6, adolescent-onset mixed-type dystonia; DYT8, paroxysmal nonkinesigenic dyskinesia; DYT10, paroxysmal kinesigenic dyskinesia; DYT11, myoclonus-dystonia syndrome; EA, episodic ataxia; MRI, magnetic resonance imaging; NBIA, neurodegeneration with brain iron accumulation; OMA, opsoclonus-myoclonus-ataxia; PKAN, pantothenate kinase–associated neurodegeneration; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; SCA, spinocerebellar ataxia

Table 27.1 • Causes of Childhood Chorea and Potentially Relevant Diagnostic Testing

Category	Specific Causes	Diagnostic Testing
Vascular	Stroke	Brain or blood vessel imaging (or both)
	Moyamoya disease	
	Vascular malformation	
Autoimmune	Sydenham chorea	Brain imaging; antistreptolysin O and antideoxyribonuclease B titers
	Systemic lupus erythematosus, antiphospholipid syndrome	Antinuclear antibody Lupus anticoagulant or anticardiolipin antibodies (or both)
Neoplastic or paraneoplastic	Basal ganglia or subthalamic nuclear mass	Brain imaging
Metabolic or endocrine	Hyperthyroidism	Thyrotropin
	Hypernatremia	Electrolyte panel
	Hypocalcemia	Serum calcium
	Hypoparathyroidism	Serum calcium, parathyroid hormone
	Vitamin B_{12} deficiency	Vitamin B_{12} level
	Kernicterus	Clinical history and imaging
Medications or drugs	Antiseizure medications	History of medication use; medication and toxin screening; drug levels
	Psychotropic medications	
	Stimulants	
Genetic disorders	Benign hereditary chorea	
	Wilson disease	Serum copper and ceruloplasmin; slit-lamp examination
	Neurodegeneration with brain iron accumulation	"Eye of the tiger" sign on MRI of the brain
	Huntington disease	CAG repeats in huntingtin gene
	Neuroacanthocytosis	Peripheral blood smear
	Phenylketonuria	Serum amino acids
	Glutaric aciduria	Urine organic acids
	Lesch-Nyhan syndrome	Urine purines and pyrimidines
	Mitochondrial encephalopathies (eg, Leigh disease)	Brain imaging; elevated arterial or cerebrospinal fluid lactate to pyruvate ratio
	Neuronal ceroid lipofuscinosis	Genetic or histologic testing
	Friedreich ataxia	Genetic testing
	Ataxia telangiectasia	Alpha-fetoprotein level; genetic testing
	Spinocerebellar ataxias	Genetic testing
Other	Cardiopulmonary surgery with bypass	Clinical history and imaging
	Burn encephalopathy	Clinical history
	Pregnancy	Clinical history; beta human chorionic gonadotropin
	Dyskinetic (athetotic) cerebral palsy	Clinical history and imaging

Abbreviation: MRI, magnetic resonance imaging.

antagonists, levodopa, and corticosteroids have been reported to improve symptoms in some cases.

Juvenile Huntington Disease

Juvenile Huntington disease is an autosomal dominant neurodegenerative disease resulting from a trinucleotide (CAG) expansion in the huntingtin gene. Individuals with the disease generally have more than 39 CAG repeats (normal <20). In the juvenile form, more than 80 CAG repeats are often present, and the age at onset is younger, with a greater number of repeats. Unlike the adult-onset form, 80% of juvenile-onset Huntington disease is inherited from an affected father. Juvenile-onset Huntington disease accounts for about 5% of reported cases, and the presentation and course differ in children and adults.

Patients with adult-onset Huntington disease may present with cognitive decline, chorea, and psychiatric disturbances, but patients with juvenile-onset Huntington disease most often present with parkinsonism, speech deficits, intellectual abnormalities, and seizures. Adolescents with Huntington disease may initially present with psychiatric illness followed by chorea or dystonia. The juvenile-onset disease progresses about twice as rapidly as the adult-onset version, but typically children survive 10 to 15 years after diagnosis.

MRI shows atrophy of the caudate head and, in later stages, generalized cerebral and cerebellar atrophy. Management consists of symptomatic treatment of chorea (with neuroleptics or tetrabenazine), psychiatric comorbidities (particularly depression), and genetic

counseling. See also Chapter 25, "Hyperkinetic Movement Disorders: Chorea, Tic, and Dystonia."

Secondary (Acquired) Choreas

Sydenham Chorea

Sydenham chorea is the most common *acquired* chorea in children aged 5 to 15 years. It is considered a manifestation of rheumatic fever, a sequela of group A β-hemolytic streptococcal infection. The etiologic streptococcal infection may precede chorea by 1 to 6 months.

The onset of Sydenham chorea is subacute, developing over hours to days, beginning with clumsiness, restlessness, and fatigue. Parents commonly report that their children are having difficulty with activities of daily living and with fine motor tasks such as dressing or writing. The chorea is characterized by quick, uncoordinated motions (often occurring unilaterally), and the athetosis is writhing in nature. Speech is dysarthric, combined with inappropriate adventitial facial movements. Personality changes may occur near the onset of motor dysfunction, with symptoms of inattention, anxiety, emotional lability, and obsessive compulsiveness.

MRI of the brain may be normal or may show increased signal intensity on T2-weighted images in the basal ganglia or cerebral white matter.

Uncomplicated Sydenham chorea is usually a benign, self-limited disorder, and chorea usually disappears by 2 to 6 months and rarely persists past 1 year. Approximately 20% of patients have recurrent episodes, most within the first 2 years after the initial attack. Rheumatic heart disease eventually develops in up to one-third of patients who present with chorea and no other signs of rheumatic fever.

For all children with Sydenham chorea, treatment includes secondary prevention with daily oral penicillin or monthly intramuscular penicillin injections until age 21 years. Suppression of chorea symptoms may not be needed in mild cases. Case series have reported benefit with benzodiazepines, valproate, carbamazepine, haloperidol, and dopamine receptor blocking agents. Treatment with corticosteroids or intravenous immune globulin can also be considered.

Kernicterus

Chronic bilirubin encephalopathy (kernicterus) is caused when brain tissue is exposed to toxic levels of unconjugated bilirubin. Levels of unconjugated bilirubin may be high from physiologic jaundice in healthy newborns or from other factors, such as hemolytic diseases of the newborn.

The severity of neurologic features ranges from mild to severe, depending on the amount and duration of bilirubin exposure, the maturational state of the exposed brain, and factors that favor the net transfer of bilirubin into the brain tissue, such as acidosis and hypoalbuminemia. The 3 classic neurologic sequelae of kernicterus are 1) a hyperkinetic movement disorder consisting mainly of choreoathetosis or dystonia involving all limbs but usually affecting the upper limbs; 2) auditory dysfunction consisting of deafness or hearing loss; and 3) oculomotor impairments, especially impairment of upgaze. Cognitive impairment is variable. MRI of the brain may appear normal in the first year of life, or it may show subtle hyperintensity in the globus pallidus interna or subthalamic nucleus.

Dyskinetic (Athetotic) Cerebral Palsy

Cerebral palsy is a static motor impairment that occurs from insults acquired before, at, or immediately after birth. It can be divided into 4 major types according to the predominant motor disability: spastic (about 50%), dyskinetic (about 20%), ataxic (about 10%), and mixed (about 20%). Movement disorders develop in one-fifth of children with static encephalopathy, and extrapyramidal symptoms are rarely observed before the end of the first year of life, possibly because the pyramidal tracts have not yet been fully myelinated. Dyskinetic forms of cerebral palsy tend to occur in term infants who have severe perinatal asphyxia; however, the cause of dyskinetic cerebral palsy may be heterogeneous and include metabolic or genetic components. This syndrome is characterized by the presence of choreoathetoid and dystonic involuntary movements involving all 4 limbs, typically beginning after the second year of life.

Treatment is individualized and is focused on the dyskinetic symptom causing the greatest difficulty. Benzodiazepines, valproate, carbamazepine, and neuroleptics are often prescribed when choreoathetosis is prominent; anticholinergics (trihexyphenidyl), baclofen, carbidopa-levodopa, and botulinum toxin are prescribed when dystonia is more prominent.

Postpump Chorea

Chorea has been described as a neurologic complication of cardiac surgery in approximately 1% of children. This occurs because of injury to the striatum, which is likely selectively vulnerable at this age. The dyskinetic movements begin 3 to 12 days after surgery, and may be transient or permanent.

- The lack of progression of chorea and the absence of dementia distinguish BHC from Huntington disease, and the persistence of involuntary movements for many years distinguishes BHC from Sydenham chorea.
- In juvenile Huntington disease, >80 CAG repeats are often present, and the age at onset is younger, with a greater number of repeats. Unlike the adult-onset form, 80% of juvenile-onset Huntington disease is inherited from an affected father.
- Adolescents with Huntington disease may initially present with psychiatric illness followed by chorea or dystonia.
- Sydenham chorea is the most common *acquired* chorea in children aged 5–15 years. It is considered a

manifestation of rheumatic fever, a sequela of group A β-hemolytic streptococcal infection.

- Dyskinetic forms of cerebral palsy tend to occur in term infants who have severe perinatal asphyxia; however, the cause of dyskinetic cerebral palsy may be heterogeneous and include metabolic or genetic components.

Dystonia

Overview

Dystonia in childhood may exist as the main symptom or as just 1 neurologic symptom of a genetic, metabolic, or neurodegenerative syndrome (Table 27.2).

Primary Dystonias

Primary dystonias typically begin in childhood or young adulthood as a focal dystonia with later generalization. Significant cognitive impairment may be absent. With advances in genetic testing, specific causes of primary dystonias have been identified with genetic loci, which are designated *DYT* and numbered consecutively; at least 17 different inherited phenotypes have been defined to date. Most primary dystonias do not present in childhood, but a selected group of syndromes that are more common in childhood are described below and summarized in Table 27.3.

Early-Onset Primary (Generalized) Torsion Dystonia

Early-onset primary torsion dystonia (DYT1) is an autosomal dominant condition with incomplete penetrance, caused by a GAG deletion in the *TOR1A* (*DYT1*) gene, which encodes the protein torsin A. DYT1 dystonia is estimated to account for early-onset dystonia in 50% to 60% of non-Jewish populations and in 80% to 90% of Ashkenazi Jewish patients.

The average age at onset is 10 years. The initial main symptom is dystonic posturing of the lower extremity, which may then have variable progression to other limbs, neck muscles, trunk, pelvis, and, rarely, cranial muscles. Symptoms typically generalize within 5 years but may remain multifocal, segmental, or focal.

The diagnosis is based on clinical findings and genetic testing for the disease causing GAG deletion in *TOR1A*. Management is symptomatic, and no medication has provided dramatic relief of symptoms. Trials with carbidopa-levodopa, trihexyphenidyl, benzodiazepines, phenytoin, carbamazepine, and baclofen have resulted in various levels of symptomatic improvement. Deep brain stimulation of the globus pallidus pars interna has shown promising results.

Dopa-Responsive Dystonia

Dopa-responsive dystonia (DYT5) (Segawa syndrome) is an autosomal dominant condition with variable penetrance and is caused by multiple point mutations or deletions in the guanosine triphosphate cyclohydrolase-1 gene (*DYT5*), which encodes the rate-limiting enzymatic step for synthesis of tetrahydrobiopterin (BH4). BH4 is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. Thus, deficiency of BH4 leads to a decreased level of tyrosine hydroxylase and decreased production of dopamine.

Symptoms of DYT5 begin in childhood, usually before the age of 10 years, with progressive dystonia and a sustained dramatic response to low doses of levodopa. Females are preferentially affected (≥2:1). Patients often present with a gait disturbance from dystonia of the

Table 27.2 • Differential Diagnosis of Secondary Generalized Dystonias in Infancy and Childhood

Category	Disorder
Vascular	Ischemic stroke Perinatal cerebral injury
Infectious	Postinfectious
Inflammatory	Autoimmune
Neoplastic or paraneoplastic	Tumor (basal ganglia)
Metabolic or endocrine	Kernicterus
Drugs or toxins	Dopamine receptor blockers (eg, typical antipsychotics)
Genetic—autosomal dominant	Dentatorubral-pallidoluysian atrophy Huntington disease Spinocerebellar ataxias Lesch-Nyhan syndrome Pelizaeus-Merzbacher disease
Genetic—autosomal recessive	Wilson disease Ataxia telangiectasia Neuronal ceroid lipofuscinosis GM_1 and GM_2 gangliosidoses Glutaric aciduria NBIA (most often PKAN) Hartnup disease Juvenile Parkinson disease Metachromatic leukodystrophy Methylmalonic aciduria Niemann-Pick disease type C
Mitochondrial	Leber disease Leigh disease MELAS MERFF
Other	Trauma Cerebral palsy Psychogenic

Abbreviations: MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERFF, myoclonic epilepsy with ragged red fibers; NBIA, neurodegeneration with brain iron accumulation; PKAN, pantothenate kinase–associated neurodegeneration.

Table 27.3 • Comparison of Primary Dystonias That Occur in Childhood

		Clinical Features		
Type	**Genetics**	**Age at Onset**	**Clinical Signs**	**Other**
Early-onset primary torsion dystonia (DYT1)	AD GAG deletion in *TOR1A* gene (torsin A)	Childhood	Lower extremity dystonic posturing progressing to other muscles (over 5 y)	Genetic testing
Dopa-responsive dystonia (Segawa syndrome) (DYT5)	AD Mutation of guanosine triphosphate cyclohydrolase-1 gene	Childhood	Dystonia with dramatic response to levodopa	Marked response to levodopa Parkinsonian features may develop
Adolescent-onset mixed-type dystonia (DYT6)	AD Mutation of *THAP1* gene	Adolescence	Cervical or cranial dystonia	Similar phenotype as DYT1
Myoclonus-dystonia syndrome (DYT11)	AD Mutation of ε-sarcoglycan gene	Childhood or adolescence	Mild dystonia (limb or torticollis)	Obsessive-compulsive features Myoclonus Genetic testing is available

Abbreviation: AD, autosomal dominant.

lower extremity or equinovarus posturing of the foot. As the disorder progresses, dystonia becomes more generalized and features of parkinsonism may appear. Diurnal variation, in which symptoms become more severe during the day and improve after sleeping, is a prominent feature, although some do not experience these fluctuations.

The diagnosis is based on clinical assessment, cerebrospinal fluid examination, and genetic testing. Cerebrospinal fluid catecholamines, catecholamine metabolites, and pterin levels are low (specifically, homovanillic acid, 5-hydroxyindoleacetic acid, and biopterin). A marked response to pharmacologic challenge with low-dose levodopa separates DYT5 from DYT1 and the secondary dystonias. An empirical trial of levodopa should be considered for any child with dystonia.

Adolescent-Onset Mixed-Type Dystonia

Adolescent-onset mixed-type dystonia (DYT6) is an autosomal dominant dystonia caused by mutations in the *THAP1* (*DYT6*) gene. In approximately 50% of affected patients, the onset of dystonia is in the cranial or cervical musculature; the other affected patients have a phenotype typical of DYT1.

Myoclonus-Dystonia Syndrome

Myoclonus-dystonia syndrome (DYT11) is an autosomal dominant condition. The most common genetic cause is a mutation in the ε-sarcoglycan gene.

The onset is typically in childhood or early adolescence, with myoclonus involving the neck and arms being the usual initial symptom in most cases. Dystonia is often mild and usually manifests itself with torticollis or limb dystonia. Obsessive-compulsive features and other psychiatric signs and symptoms may be present. The myoclonus is improved with ingestion of alcohol, and the dystonia is variably alcohol responsive.

The diagnoses are made by clinical features, family history, and sequencing of the ε-sarcoglycan gene, which detects 95% of patients in affected families. Medication management is symptomatic with benzodiazepines, valproate, and levodopa.

Secondary Dystonias

Secondary dystonias have many genetic and acquired causes, and the majority of these conditions include various neurologic manifestations in addition to dystonia (Table 27.2).

Neurodegeneration With Brain Iron Accumulation

Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of disorders differentiated by clinical, radiographic, and molecular features. The autosomal recessive disorder known as pantothenate kinase–associated neurodegeneration (PKAN) accounts for most patients with NBIA and is caused by mutations in the *PANK2* gene encoding pantothenate kinase 2. Pantothenate kinase 2 is a regulatory enzyme in the synthesis of coenzyme A from vitamin B_5 (pantothenate). As a result of the mutation in *PANK2*, abnormal iron deposition and a high concentration of lipofuscin and neuromelanin develop in the substantia nigra pars reticulata and internal segment of the globus pallidus.

PKAN is characterized as having 3 variable presentations: *classic early onset* (<10 years of age), *atypical late onset* (10–18 years of age), and *adult variant*. In the classic

form, the presenting symptoms and signs are usually motor manifestations, including dystonic posturing (cranial and limb musculature), choreoathetoid movements, tremors, spasticity, and gait imbalance. Dysarthria and dysphagia are present in most cases. Personality changes and progressive intellectual deterioration are often present with variable rate of progression. Approximately two-thirds of patients affected with classic PKAN have pigmentary retinal degeneration; optic atrophy occurs less commonly. Seizures are rare. Systemically, acanthocytosis was found in about 8% of patients with classic PKAN. The course of classic PKAN is variable: Progressive neurodegeneration may cause severe disability and death within 1 to 2 years, or the more prevalent and slowly progressive dystonia and spasticity may lead to permanent disability and death by 20 years of age.

In a study of patients who were older at onset (mean age, 14 years), clinical features of atypical late onset PKAN were heterogeneous, extrapyramidal defects were less severe and more slowly progressive, and retinopathy was less common. Speech difficulties, such as palilalia and dysarthria, were often a presenting or early feature in contrast to patients with classic PKAN.

The diagnosis of PKAN is made by the presence of progressive extrapyramidal signs beginning in the first 2 decades and by the nearly pathognomonic MRI abnormality, which shows bilateral areas of hyperintensity within a hypointense medial globus pallidus on T2-weighted images (the "eye of the tiger" sign).

Treatment of PKAN is symptomatic and supportive. Iron chelation has not been effective for lowering iron levels in the central nervous system in NBIA. Baclofen and trihexyphenidyl may help to relieve some of the extrapyramidal symptomatology of disabling dystonia and spasticity, and patients generally do not benefit from levodopa.

Focal Dystonias in Childhood

A child presenting with a focal dystonia may be showing the beginning manifestation of a generalized dystonia. In addition, children may have specific focal dystonias, such as dystonia related to a structural lesion, drug-induced dystonia, torticollis, and writer's cramp.

- Symptoms of DYT5 begin in childhood, usually before the age of 10 years, with progressive dystonia and a sustained dramatic response to low doses of levodopa.
- The autosomal recessive disorder PKAN accounts for most patients with NBIA and is caused by mutations in the *PANK2* gene encoding pantothenate kinase 2.
- The diagnosis of PKAN is made by the presence of progressive extrapyramidal signs beginning in the first 2 decades and by the nearly pathognomonic MRI abnormality, which shows bilateral areas of hyperintensity within a hypointense medial globus pallidus on T2-weighted images (the "eye of the tiger" sign).

Tremor

Overview

When approaching a child with "tremor" or shaking, one must first establish whether the movement is clearly a tremor. Tremor should be distinguished from asterixis, dystonic tremor, clonus, rhythmic myoclonus, epilepsia partialis continua, and spasmus nutans.

When the diagnosis of tremor is secure, the tremor should be categorized as primary or secondary. A tremor can be *primary* (existing as the only manifestation of an underlying condition) or *secondary* (symptomatic of a metabolic state or a more extensive underlying disease). The history, neurologic examination findings, and diagnostic testing can be helpful for distinguishing the cause.

Primary Tremors

Essential Tremor

Benign familial or essential tremor is the most common persistent childhood tremor. This can be inherited in an autosomal dominant pattern, with variable penetrance and severity; children account for approximately 5% to 20% of cases.

The mean age at onset is 7 years. The tremor primarily involves the arms, and it may involve both a postural tremor and an action tremor. Tremor is absent at rest. The characteristic tremor is rapid (5–8 Hz) and exacerbated by stress, anxiety, and antigravity posture. Characteristically the tremor in adults responds dramatically to alcohol. About 70% of patients have a positive family history; however, no unique causative gene has been identified.

Essential tremor is a monosymptomatic disorder that denotes isolated tremor with normal findings on imaging of the brain in the absence of other causes. The condition is not usually debilitating, although slow progression with prolonged plateaus may occur. When activities of daily living are affected, treatment with propranolol (1–3 mg/kg daily) may be therapeutically useful. Other medications such as benzodiazepines, gabapentin, pregabalin, and topiramate may also be helpful in select patients.

Enhanced Physiologic Tremor

Physiologic tremor is present in healthy patients and is usually not visually apparent. The tremor frequency increases through childhood (up to 8–12 Hz) and certain transient stressors, such as increased emotion, fatigue, fever, hunger, or exertion of high levels of force by a muscle, may make the tremor particularly noticeable.

Several medications (Box 27.1) and endocrinologic disorders may worsen physiologic tremor and should be

Box 27.1 • Medications and Other Substances That May Worsen a Physiologic Tremor

- Psychotropic medications
  - Lithium
  - Neuroleptic agents
  - Selective serotonin reuptake inhibitors
  - Tricyclic antidepressants
- Neurologic medications
  - Valproic acid
  - Levodopa
- Endocrine-related medications
  - Corticosteroids
  - Excess thyroid medication
- Other substances
  - Stimulants (eg, amphetamines, cocaine, epinephrine, theophylline)
  - Heavy metals (eg, arsenic, lead, mercury)

sought out in the history and laboratory studies. Endocrine disorders such as thyroid disease and pheochromocytoma can result in enhanced physiologic tremor.

Treatment is not generally needed, nor is medication particularly effective, and progression of enhanced physiologic tremor is probably rare.

Secondary Tremors

Symptomatic or secondary causes of tremor encompass many conditions, including structural lesions (infarctions, tumors, and cysts), metabolic and genetic diseases, medications, toxins, and head trauma. For an otherwise healthy child, assessing for hyperthyroidism and thoroughly reviewing the patient's medications may be an initial approach. If the initial history or examination suggests additional symptoms, signs, or concerns for genetic disorders, additional laboratory testing, brain imaging, and genetic testing may be warranted. If a patient has a new onset of an intention tremor or dystonia (or both), testing for Wilson disease can be important.

Wilson Disease

Overview. Wilson disease (hepatolenticular degeneration) is an autosomal recessive condition caused by mutations in *ATP7B* gene, which encodes the copper-transporting P-type adenosine triphosphatase ATP7B. The mutations result in deposition of copper in the central nervous system, liver, cornea, and other organs. The reduced function of ATP7B leads to decreased liver excretion of copper into the bile, and this in turn leads to increased hepatic accumulation of copper. After the liver has been saturated with copper, the additional copper enters the bloodstream and is deposited in other tissues, including brain tissue.

Clinical Features. In childhood, the manifestation of Wilson disease varies. Initially, it may manifest as hepatic dysfunction (asymptomatic hepatomegaly or hepatitis), with a mean age at onset of about 12 years. Neurologic symptoms of Wilson disease are generally insidious; symptoms include dystonia, dysarthria, drooling, intention tremor, and rigid-akinesia syndrome. Although tremor is common in Wilson disease, it may have variable characteristics, occurring at rest or with action, and it may have multiple position- and task-dependent characteristics. The classic tremor associated with Wilson disease is a wing-beating tremor, characterized by irregular proximal kinetic or postural tremor elicited with arms forward and flexed. Neurologic symptoms develop in half of patients by age 15 years, and patients rarely present before 6 years. Rigidity develops later in the course of the disease. Psychiatric symptoms precede the neurologic abnormalities in approximately 20% of patients and range from subtle changes in personality and school performance to disinhibition and frank psychosis. A Kayser-Fleischer ring, a brown to yellow-green discoloration in Descemet membrane at the limbus of the iris (Figure 27.1), is frequently seen in patients with Wilson disease.

Pathology. Gross examination of the brain shows red-brown discoloration of the putamen with symmetric atrophy and cavitation, and histopathologic specimens often show Alzheimer type II astrocytes in the globus pallidus, thalamus, and brainstem (Figure 27.2). These cells are characterized by enlarged vesicular nucleus and sparse cytoplasm. Opalski cells, round cells with dense

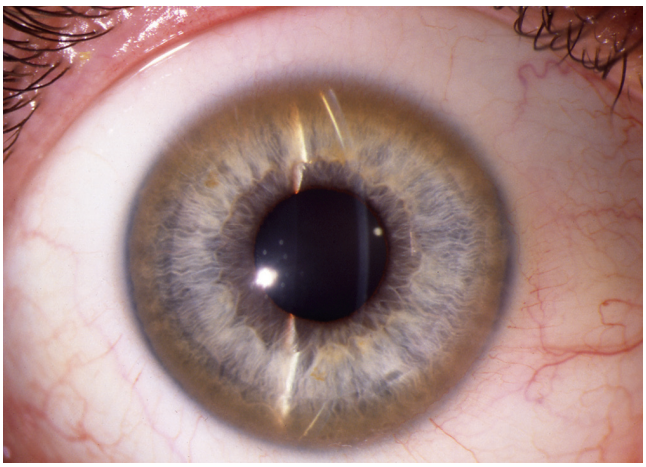

Figure 27.1 *Kayser-Fleischer Ring.*
Slit-lamp examination of a patient with Wilson disease shows a Kayser-Fleischer ring.
(Courtesy of Brian R. Younge, MD, Emeritus Staff, Mayo Clinic, Rochester, Minnesota. Used with permission.)

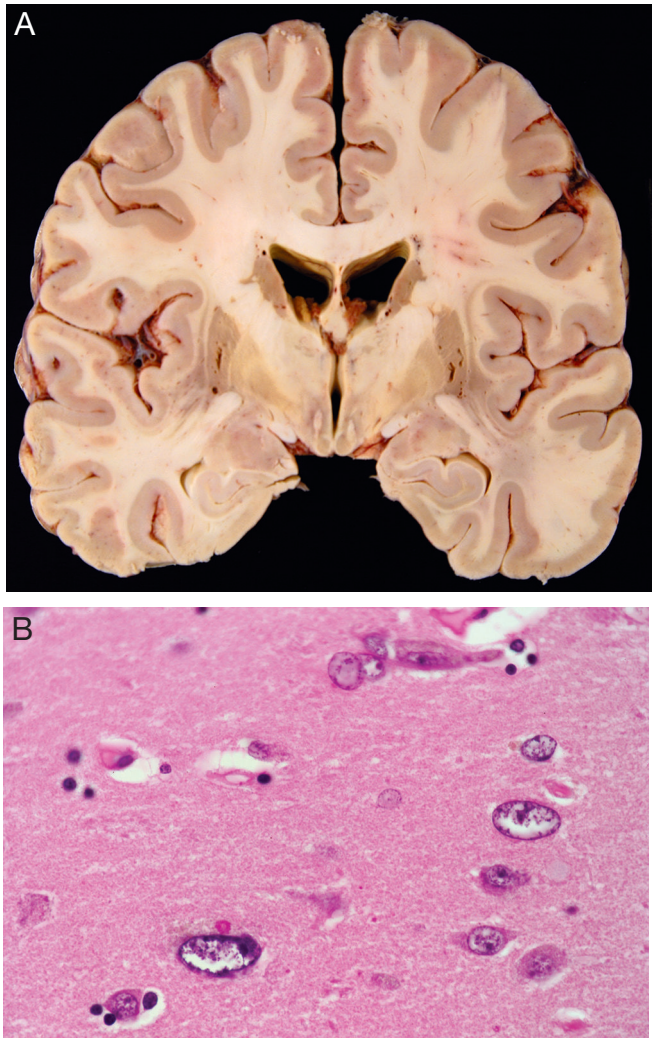

Figure 27.2 *Wilson disease.*
A, There is often atrophy and cavitation of the putamen. B, Alzheimer type II astrocytes are characterized by enlarged vesicular nuclei and sparse cytoplasm.
(Adapted from Mowzoon N. Movement disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 333–76. Used with permission of Mayo Foundation for Medical Education and Research.)

eosinophilic cytoplasm and a small central nucleus, are seen in some cases of Wilson disease.

Diagnosis. Because Wilson disease is treatable, the diagnosis should be considered for all children with a new onset of tremor or dystonia (Box 27.2). A search for low ceruloplasmin levels is a good initial screen for this disease. However, ceruloplasmin levels are subject to false-positive and false-negative results. Increased 24-hour urinary copper excretion (usually >100 mcg/24 h) and slit-lamp examination are helpful to confirm the diagnosis. When the diagnosis is in doubt, genetic testing for *ATP7B* can be performed or the concentration of hepatic parenchymal copper can be determined. MRI abnormalities include T2 hyperintensity signals in the thalami and basal ganglia and, rarely, the "face of the panda" sign in the midbrain.

Box 27.2 • Diagnostic Findings in Wilson Disease

Serum ceruloplasmin level—decreased
Urinary copper excretion (24 h)—increased
Slit-lamp examination—Kayser-Fleischer ring

Treatment. Treatment of Wilson disease with a chelating agent (penicillamine or trientine), with or without zinc, can result in symptomatic improvement. Dietary restriction of copper and addition of pyridoxine are also useful. Orthotopic liver transplant can be considered in select cases of patients with fulminant liver failure.

Psychogenic Tremor

Tremor is a frequent manifestation of psychogenic movement disorders. Psychogenic tremor can usually be distinguished from tremor with an organic basis by its distractibility and variable frequency, amplitude, and axis. Surface electromyographic recordings are often useful to characterize the tremors and show this variability. Frequently, patients who present with psychogenic tremor also have anxiety or a posttraumatic stress disorder.

Treatment of children should be supportive rather than confrontational. A benzodiazepine such as clonazepam can be useful if the symptoms are intermittent, or an antianxiety agent such as fluoxetine can be used if the symptoms are persistent. Working with a psychologist will also be helpful to the patient. Pain may be present from chronic headaches or reflex sympathetic dystrophy and may exacerbate the symptoms, so pain needs to be addressed in many patients.

- Several medications (Box 27.1) and endocrinologic disorders may worsen physiologic tremor and should be sought out in the history and laboratory studies.
- Wilson disease (hepatolenticular degeneration) is an autosomal recessive condition caused by mutations in *ATP7B* gene, which encodes the copper-transporting P-type adenosine triphosphatase ATP7B. The mutations result in deposition of copper in the central nervous system, liver, cornea, and other organs.
- Neurologic symptoms of Wilson disease are generally insidious; symptoms include dystonia, dysarthria, drooling, intention tremor, and rigid-akinesia syndrome.
- A Kayser-Fleischer ring, a brown to yellow-green discoloration in Descemet membrane at the limbus of

the iris, is frequently seen in patients with Wilson disease.
- Because Wilson disease is treatable, the diagnosis should be considered for all children with a new onset of tremor or dystonia (Box 27.2).
- Treatment of Wilson disease with a chelating agent (penicillamine or trientine), with or without zinc, can result in symptomatic improvement.

Tic Disorders

Overview

Tics are the most common movement disorder in children. The definition of *tic* is reviewed in Chapter 21, "Classification and Approach to Movement Disorders." Tics have several common distinguishing features, including a waxing and waning course and presence in typical locations. Exacerbations are provoked by stress, fear, anxiety, excitement, or illness. Tics are characteristically suppressible, with reduction occurring during intense focus, or when engaged in an activity. Tics can occur during sleep. Most patients report a premonitory "urge" or sensory phenomenon that resolves after the motor or phonic tic is permitted to occur.

Tic disorders are diagnosed solely on the clinical history and examination. *Transient tic disorder* is defined by tics that last for at least 4 weeks and resolve before 1 year. A motor or vocal tic that persists for more than 1 year is a *chronic tic disorder*.

Tourette Syndrome

Tourette syndrome is probably inherited through an autosomal dominant pattern with incomplete penetrance and variable expressivity; however, identification of specific genes remains elusive for most patients. Although there is evidence to suggest a strong genetic contribution, nongenetic factors (eg, history of prematurity, anxiety, head injury, infections, and medications) may also have a role.

Patients with Tourette syndrome have multiple motor and vocal tics that occur daily without a tic-free interval of more than 3 months and with an onset before age 18 years. Tics may appear in the preschool or early grade-school years, with an average age at onset of 6 years. Often tics seem to increase in severity during childhood, reaching a peak period of tic severity at age 10 to 12 years.

Although Tourette syndrome was thought to be a lifelong disorder, its course can be highly variable, and many patients show fewer tics or complete disappearance of tics by late adolescence or early adulthood.

Comorbid Symptoms in Tic Disorders

Over half of children with Tourette syndrome may have symptoms of attention-deficit/hyperactivity disorder, obsessive-compulsive symptoms, depression, or other behavioral disorders. Typically, the attentional problems are evident before the onset of tics. The use of stimulant medications for attention-deficit/hyperactivity disorder may coincide with the first appearance of tics, but this does not mean that the stimulants caused the tics. Controlled studies have shown a positive benefit of stimulants on both attention and tics. Anxiety or obsessive-compulsive symptoms can be quite troubling and may respond to selective serotonin reuptake inhibitors or to cognitive behavioral therapy.

Treatment of Tourette Syndrome and Tic Disorders

A therapeutic plan for Tourette syndrome and tic disorders includes education of the patient and family, behavioral approaches, and medications. The goal of pharmacotherapy for tics is not to completely suppress them but rather to reduce their frequency or severity to a level at which physical or psychosocial disturbances are minimized. Several types of medication groups have been used. For milder tics, often patients are prescribed an α_2-adrenergic agonist, such as clonidine. Other agents, including guanfacine, baclofen, topiramate, levetiracetam, and clonazepam, have been tried with variable response rates. For more severe tics, typical neuroleptics (haloperidol, pimozide, and fluphenazine) and atypical neuroleptics (risperidone, olanzapine, and ziprasidone) may be the most efficacious; however, side effects frequently limit their usefulness.

- Patients with Tourette syndrome have multiple motor and vocal tics that occur daily without a tic-free interval >3 months and with an onset before age 18 years.
- Over half of children with Tourette syndrome may have symptoms of attention-deficit/hyperactivity disorder, obsessive-compulsive symptoms, depression, or other behavioral disorders.

Myoclonus

Overview

Myoclonus can be *primary*, existing as the only manifestation of a disorder, or *secondary*, from a more extensive underlying disease. It can result from disease of the cerebral cortex, subcortical regions, spinal cord, and, occasionally the peripheral nerves. It can also be present in some normal situations (sleep, exercise, and anxiety).

Primary Myoclonic Disorders

Essential Myoclonus

Essential myoclonus is a relatively mild, multifocal myoclonic syndrome with symptom onset in the first or second

decade of life. It is thought to be inherited as an autosomal dominant trait with incomplete penetrance, and many patients have mutations in the *SGCE* gene, which is also associated with myoclonus-dystonia syndrome (DYT11). Essential myoclonus may be slowly progressive for a few years after onset and then stabilize; its long-term course is benign. Additional neuropsychiatric symptoms and signs can be seen, such as anxiety, inattention, and dystonia. The myoclonic movements are usually prominent in the upper body and may be induced with action or dampened by alcohol.

Treatment is symptomatic, and essential myoclonus may respond to benzodiazepines, anticonvulsants, or levodopa.

Primary Epileptic Myoclonic Disorders

Myoclonic seizures are cortically generated movements that can occur in various pediatric epilepsy syndromes, including Lennox-Gastaut syndrome, childhood absence epilepsy, benign myoclonic epilepsy of infancy, Dravet syndrome, myoclonic-astatic epilepsy (Doose syndrome), juvenile myoclonic epilepsy, and epilepsia partialis continua.

Secondary Myoclonic Disorders

Myoclonus can be symptomatic of many genetic and acquired conditions, including infectious encephalitides, toxic or metabolic conditions, hypoxic or anoxic insults, and neurodegenerative conditions (Table 27.4). This section highlights opsoclonus-myoclonus-ataxia (OMA) syndrome, a main secondary cause of myoclonus in children. Other secondary causes of myoclonus are discussed in Chapter 24, "Hyperkinetic Movement Disorders: Tremor and Myoclonus."

Table 27.4 • Differential Diagnosis of Myoclonus in Infants and Children

Category	Disorder
Vascular	Stroke Hypoxic or anoxic injury
Infectious	Viral encephalitis
Inflammatory	Rasmussen encephalitis
Neoplastic or paraneoplastic	Opsoclonus-myoclonus-ataxia syndrome Neuroblastoma Spinal cord tumors
Metabolic or endocrine	Electrolyte imbalances Hepatic failure Renal failure and dialysis syndrome
Drugs or toxins	Antiseizure medications Levodopa Tricyclic antidepressants Selective serotonin reuptake inhibitors
Genetic	Essential myoclonus Myoclonus-dystonia syndrome (DYT11) Hereditary hyperekplexia NBIA (mostly PKAN) Lysosomal storage diseases Neuronal ceroid lipofuscinosis Huntington disease Wilson disease Epileptic myoclonus
Other	Physiologic (ie, hypnic jerks) Developmental (ie, benign neonatal myoclonus and benign myoclonus of early infancy) Trauma Psychogenic

Abbreviations: NBIA, neurodegeneration with brain iron accumulation; PKAN, pantothenate kinase–associated neurodegeneration.

OMA Syndrome

OMA syndrome is an uncommon acquired disorder of late infancy or early childhood and is characterized by the acute or subacute onset of rapid, "dancing" eye movements (*opsoclonus*) and myoclonic jerking movements of the limbs or trunk. OMA syndrome has several potential causes and may be idiopathic, associated with viral infections, or associated with neuroblastoma. When OMA syndrome is associated with a neuroblastoma, neurologic symptoms may occur before a tumor is found.

The onset of myoclonus is acute, often occurring after a nonspecific respiratory or gastrointestinal tract illness, and reaches maximal intensity in 2 to 7 days. The myoclonic movements are intense and brief, with continual shocklike muscular contractions that are irregularly timed and of variable amplitude. They are widely distributed across muscle groups, asymmetric, increased by startle, present at rest, and abolished only by deep sleep. Abnormal eye movements (opsoclonus) temporally unrelated to myoclonus consist of rapid (up to 8 displacements or rotations per second), irregular, conjugate ocular movements, mainly horizontal but also vertical and diagonal. The eye movements are exacerbated by the same stimuli as the myoclonus. Patients may also exhibit cognitive and mood changes as well, which persist past the myoclonic stages of this illness.

Useful imaging may include gadolinium-enhanced MRI of the neck, chest, abdomen, and pelvis. Urinary catecholamine levels are rarely diagnostic. Results from MRI of the brain, electroencephalography, and cerebrospinal fluid analysis are usually unremarkable. The use of commercially available paraneoplastic autoantibody panels has not been informative. Approximately 50% of patients with OMA syndrome do not have an identifiable neuroblastoma; in these instances, infectious or postinfectious causes are more likely.

Results of treatment range from complete recovery in 3 months to persistence over several years, which is noted

more frequently. Incomplete recovery may be followed by relapse related to infection or discontinuation of effective therapy. Most cases show a remarkable response to corticotropin or other immunosuppressive therapy. Treatment of neuroblastoma may involve surgery or chemotherapy or both. Most patients have sequelae, including mental retardation, dysarthria, learning disabilities, or attention-deficit/hyperactivity disorder. Physical, occupational, and speech therapy may be beneficial, along with symptomatic treatment of behavioral problems and insomnia.

Startle Syndromes

Startle syndromes are characterized by an exaggerated motor response to unexpected auditory, visual, or somatosensory stimuli. An exaggerated startle response may be of cortical or brainstem origin and can be a component of epilepsy (startle epilepsy) or hereditary hyperekplexia, or it may be sporadic.

Hereditary Hyperekplexia

Hereditary hyperekplexia, also known as familial startle disease, is a nonepileptic paroxysmal movement disorder characterized by exaggerated stimulus-induced myoclonus. Hereditary hyperekplexia is usually inherited in an autosomal dominant pattern, with mutations in the α subunit of the inhibitory glycine receptor (*GLRA1*) gene, which acts at the inhibitory chloride receptor.

Patients with the major form of hereditary hyperekplexia present in the neonatal period with persistent hypertonia during wakefulness and failure to thrive due to constant startle and stiffening (also referred to as stiff baby syndrome). Shoulder girdle muscles are particularly stiff, and the phenomenology of the startle involves flexion and extension of the neck and abduction of the arms. The neonatal form improves spontaneously in the first year of life; however, exaggerated startle may interfere with walking and cause falls. Symptoms may be exacerbated during adolescence and may be variably alleviated in adulthood. The minor form of hyperekplexia features only an abnormal startle response without generalized stiffness or tonic spasms.

The condition is diagnosed clinically, according to the history and examination without other neurologic signs, but genetic testing can be considered in some cases. Clonazepam or other benzodiazepines are the initial treatment of choice; however, anticonvulsants such as sodium valproate may also be effective.

- OMA syndrome is an uncommon acquired disorder of late infancy or early childhood and is characterized by the acute or subacute onset of rapid, "dancing" eye movements (*opsoclonus*) and myoclonic jerking movements of the limbs or trunk. OMA syndrome has several potential causes and may be idiopathic, associated with viral infections, or associated with neuroblastoma.
- Hereditary hyperekplexia is usually inherited in an autosomal dominant pattern, with mutations in the α subunit of the inhibitory glycine receptor (*GLRA1*) gene, which acts at the inhibitory chloride receptor.
- In the major form of hereditary hyperekplexia, shoulder girdle muscles are particularly stiff, and the phenomenology of the startle involves flexion and extension of the neck and abduction of the arms.

Paroxysmal Dyskinesias

Overview

Paroxysmal dyskinesias often begin in childhood and are characterized by episodic attacks of involuntary, hyperkinetic (dystonic, choreoathetoid, or ballistic) movements with preserved consciousness. The clinical characteristics of paroxysmal dyskinesias can be complex because the various hyperkinetic movements may occur individually or in combination. They need to be distinguished from other paroxysmal symptoms of infancy and childhood (Box 27.3).

The etiology of paroxysmal dyskinesias is beginning to be understood, with many cases being primary (familial or sporadic). Rarely, the cause is secondary to other known causes, such as trauma, stroke, demyelinating disease, toxins, or infection. The paroxysmal dyskinesias are classified into 3 types: paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD), and paroxysmal exertion-induced dyskinesia.

Paroxysmal Kinesigenic Dyskinesia

PKD (DYT10) is the most common form of all the paroxysmal dyskinesias. PKD is often inherited in an autosomal dominant pattern. Mutations in the proline-rich transmembrane protein 2 (*PRRT2)* gene have been identified in affected patients. Approximately one-fourth of the cases are sporadic or secondary to cerebral palsy, metabolic or endocrine disorders, or demyelinating disease. The age at onset is usually 5 to 15 years in familial cases but may be variable in sporadic cases. Males are more often affected than females (4:1).

The disorder is characterized by episodic attacks of unilateral or bilateral dystonia or choreoathetosis, precipitated by sudden movement. PKD attacks are of short duration (usually <1 minute). They can occur frequently—up to 100 times daily—but are typically more sporadic. Patients with these episodes may have an aura of tightness or other vague sensation before the episode, and some patients can abort some of the attacks by various maneuvers. The attacks may diminish during adulthood, and

Box 27.3 • Differential Diagnosis of Ataxia in Infants and Children by Type of Presentation

- Acute
  - Ischemic stroke
  - Vertebrobasilar dissection
  - Brain hemorrhage
  - Acute cerebellar ataxia
  - Intoxications (anticonvulsant, antihistamines, alcohol, benzodiazepines)
- Subacute
  - Infectious or parainfectious cerebellitis
  - Opsoclonus-myoclonus-ataxia syndrome
  - Acute disseminated encephalomyelitis
  - Cerebellar abscess or cyst
  - Posterior fossa neoplasms
- Chronic
  - Congenital cerebellar malformations (eg, Dandy-Walker malformation, Joubert syndrome)
  - Friedreich ataxia
  - Ataxia telangiectasia
  - Spinocerebellar ataxias
  - Refsum disease
  - Cerebrotendinous xanthomatosis
  - Abetalipoproteinemia
  - Leukoencephalopathy with vanishing white matter disease (ie, childhood ataxia with central hypomyelination)
- Episodic or recurring
  - Transient ischemic attack
  - Migraine
  - Episodic ataxia types 1 and 2
  - Metabolic ataxias (eg, pyruvate dehydrogenase deficiency, maple syrup urine disease, mitochondrial disorders)
  - Psychogenic

patients do not typically have progressive neurologic deficits. Electroencephalograms during episodes are normal.

The response to anticonvulsant medication is dramatic in most instances. Carbamazepine or oxcarbazepine are the medications prescribed most commonly. The serum concentration for controlling the attacks is usually much lower than that for treating epilepsy. Other anticonvulsants used include valproic acid, levetiracetam, lamotrigine, and clonazepam. Some patients have responded to levodopa.

Paroxysmal Nonkinesigenic Dyskinesia

PNKD (DYT8) occurs less frequently than the kinesigenic form. PNKD is transmitted through an autosomal dominant mode of inheritance, and an association with mutations in the myofibrillogenesis regulator 1 (*MR1*) gene on chromosome 2 has been found in multiple families. The age at onset is usually in early childhood, but a smaller number of patients do not exhibit attacks until adulthood. As in the kinesigenic form, males are more often affected than females (1.5:1). Results from routine laboratory studies, including electroencephalograms during the attacks, have been normal. No pathologic findings have been identified in the central nervous system.

PNKD is characterized by episodic attacks of unilateral or bilateral dystonia or choreoathetosis, typically lasting 10 minutes to 1 hour. The frequency is highly variable. The hyperkinetic movements may involve the face, trunk, or extremities and often involve the laryngeal muscles, causing dysarthria and dysphasia. Episodes may start in 1 limb and spread to involve the face or other extremities. The hyperkinetic movements are not precipitated by movement but usually by fatigue, alcohol, caffeine, stress, and emotional excitement. Attacks may be remitted by sleep, and the neurologic examination is normal between attacks.

Unlike in the kinesigenic form, the frequency of attacks in PNKD has not been reduced by many different anticonvulsants. Benzodiazepines and avoidance of precipitating factors can significantly reduce the frequency of the episodes. Prognosis is variable, and while attacks tend to remit with age, complete remission is uncommon.

Paroxysmal Exertion-Induced Dyskinesia

Paroxysmal exertion-induced dyskinesia is less common than PKD and PNKD and is characterized by paroxysmal episodes of spasticity or choreoathetosis triggered by prolonged, continuous exercise, unlike the sudden movement that triggers PKD. Stress and cold may also be precipitating factors. The duration of episodes is typically 5 to 30 minutes, often involving the lower limbs, although it may spread to other body parts. The frequency varies from 1 daily to 2 monthly.

Paroxysmal exertion-induced dyskinesia has been reported with glucose transporter deficiency, although other genetic mechanisms may be involved as well. The age at onset is usually in the first or second decade. Management involves avoidance of prolonged exercise, and although drug therapy is often ineffective, symptomatic improvement with acetazolamide and levodopa has been reported in isolated cases.

- Paroxysmal dyskinesias often begin in childhood and are characterized by episodic attacks of involuntary, hyperkinetic (dystonic, choreoathetoid, or ballistic) movements with preserved consciousness.
- PKD attacks are of short duration (usually <1 minute). They can occur frequently—up to 100 times daily—but are typically more sporadic.

- Unlike in the kinesigenic form, the frequency of attacks in PNKD has not been reduced by many different anticonvulsants.

Ataxia

Overview

Ataxia may be caused by a heterogeneous group of disorders that can adversely affect cerebellar function in children (Box 27.3). Most commonly, these problems are static and nonspecific, and the children are clumsier than their peers or are ataxic because of associated congenital cerebellar malformations (eg, Dandy-Walker malformations, cerebellar hypoplasia). Acute ataxias are second most common and result from infectious or postinfectious cerebellar conditions, intoxications, and vascular or traumatic insults. Acute ataxias may also be recurrent, such as in patients with recessively inherited inborn errors of metabolism, episodic ataxias, migraine, and functional movement disorders. Subacute ataxias may be caused by posterior fossa neoplasms, OMA syndrome, and acute disseminated encephalomyelitis. In addition, various genetic and degenerative conditions can cause chronic progressive ataxia in childhood. This section highlights selected disorders resulting in ataxia in childhood. More detailed information on childhood and adult causes of ataxia are reviewed in Chapter 26, "Cerebellar Disorders and Ataxias."

Acute Cerebellar Ataxia

Pathophysiology

The pathophysiology of acute cerebellar ataxia is not entirely understood, but it may be similar to that of paraneoplastic ataxia in adults.

Clinical Features

Acute cerebellar ataxia usually occurs in children aged 2 to 5 years and usually develops days to weeks after a clinical or subclinical infection or vaccination. Patients with acute cerebellar ataxia most often present with a sudden disturbance of gait and balance. Although gait ataxia is the most prominent sign, appendicular ataxia and nystagmus also occur. Finger dysmetria is seen in two-thirds of these children, but it is strikingly mild compared with that in gait ataxia. Transient behavioral alterations and school difficulties are seen in at least one-third of children with acute cerebellar ataxia.

Diagnosis and Treatment

Laboratory studies show a mild cerebrospinal fluid pleocytosis, and neuroimaging study findings are typically normal, although occasionally abnormal signals are seen in the cerebellum.

Treatment is supportive, and approximately 90% of children completely recover from the ataxia, typically within the first few months after the onset of disease. One-fifth of children may retain behavioral problems or speech impairment.

Episodic Ataxias

Episodic ataxias (EAs) are autosomal dominant channelopathies characterized by recurrent episodes of cerebellar ataxia, vertigo, dysarthria, and nystagmus, starting in childhood and lasting for minutes or hours, with otherwise normal brain functions. Two main forms are recognized: EA type 1 (EA1) and EA type 2 (EA2). The cause of EA1 is a mutation in the *KCNA1* gene encoding a voltage-gated potassium channel. The cause of EA2 is a mutation in the calcium channel subunit gene, *CACNA1A*, on chromosome 19. Rarer forms are beyond the scope of this text.

Episodic Ataxia Type 1

In children with EA1, episodes begin in infancy or childhood and are characterized by brief paroxysmal bouts of ataxia, dysarthria, and nystagmus lasting several minutes. The frequency is variable, and episodes may occur daily or may be separated by weeks or months. Ataxia of the trunk and extremities is frequently so severe during the episodes that the patient cannot stand without assistance. Speech becomes dysarthric and difficult to understand, although receptive language function remains intact.

Between attacks, a diagnostic clinical feature is the nearly constant presence of continuous muscle activity (*interictal myokymia*) of the hand, tongue, or eyelids.

Triggers are abrupt postural change, emotional stress, and caloric stimulation of vestibular apparatus.

Findings from MRI studies are usually unremarkable for young children; however, for patients whose symptoms persist over a prolonged period, neuroimaging frequently shows cerebellar atrophy, especially of the vermis.

Treatment with acetazolamide may symptomatically reduce the frequency or severity of ataxic episodes but may not always be effective long term. The prognosis is good, with attacks becoming milder in adulthood.

Episodic Ataxia Type 2

EA2 is the most common of all episodic ataxias. Like the episodes in EA1, ataxic episodes in EA2 begin in early childhood; however, the duration of each attack is more prolonged, lasting hours to days, and the attacks are more commonly associated with nausea, vomiting, and vertigo. The frequency is also variable, from daily to yearly. More than 50% of patients have migrainous symptoms during the attack, and familial hemiplegic migraine is an allelic disorder with EA2.

Interictally, most patients have downbeating nystagmus. Myokymia is not a feature of EA2. Triggers for the

episodes include exertion, alcohol, caffeine, stress, and intercurrent illness.

Acetazolamide can be dramatically effective in reducing the frequency and severity of ataxic episodes in approximately 50% to 75% of patients with EA2. Over time, chronic progressive gait ataxia may develop. Cerebellar atrophy may occur.

Inherited Ataxias

Autosomal dominant ataxias include the spinocerebellar ataxias (SCAs), which are a heterogeneous group of conditions characterized by premature cerebellar neuronal loss and involvement of the optic nerve, basal ganglia, brainstem, and spinal cord in some types. Clinical features of SCA include various progressive ataxia, extrapyramidal symptoms, retinal degeneration, deafness, ophthalmoplegia, dorsal column dysfunction, and peripheral neuropathy. Most patients with SCAs do not present in childhood; however, some SCAs do arise in childhood (Table 27.5). SCAs are discussed in more detail in Chapter 26, "Cerebellar Disorders and Ataxias."

Several autosomal recessive disorders occur with ataxia in childhood; the 2 most notable are Friedreich ataxia and ataxia-telangiectasia. These disorders are compared in Table 27.6 but are covered in more detail in Chapter 26, "Cerebellar Disorders and Ataxias."

- EAs are autosomal dominant channelopathies characterized by recurrent episodes of cerebellar ataxia, vertigo, dysarthria, and nystagmus, starting in childhood and lasting for minutes or hours, with otherwise normal brain functions.
- Like the episodes in EA1, ataxic episodes in EA2 begin in early childhood; however, the duration of each attack is more prolonged, lasting hours to days, and the attacks are more commonly associated with nausea, vomiting, and vertigo.

Transient and Developmental Movement Disorders in Childhood

Clinical Characteristics and Phenomenology

The immature nervous system may produce many motor movements that are benign. Recognition of these transient and developmental movement disorders is critical to distinguish them from a more serious underlying condition.

Benign Myoclonus of Early Infancy

Benign myoclonus of early infancy is characterized by clusters of myoclonic spasms, resembling infantile spasms, that involve flexion or extension of the neck, trunk, and extremities. The onset of episodes is usually between 3 and 9 months of age and occurs only during wakefulness. The normal ictal and interictal electroencephalograms distinguish this disorder from infantile spasms. The cause is unknown, but the prognosis is good, and spells typically resolve completely by 15 months of age. Neurodevelopment is usually normal, and only reassurance is required.

Jitteriness

Jitteriness is commonly seen within the first week of life and is present in up to 50% of normal term infants. However, jitteriness can accompany hypoxic-ischemic injury or electrolyte derangements in the neonate. The affected infant has generalized, symmetric, rhythmic oscillatory movements that resemble tremor or clonus. The movement is sensitive to stimuli and is triggered by startle

Table 27.5 • Autosomal Dominant Ataxias in Childhood

	Genetics		Age at Onset		
Disease	**Chromosome**	**Mutation**	**Earliest**	**Mean**	**Clinical Features**
SCA1	6p23	CAG expansion in ataxin-1 gene	15 y	35 y	Progressive ataxia, slow saccades, pyramidal tract signs, mild cognitive impairment
SCA2	12q24	CAG expansion in ataxin-2 gene	6 mo	30 y	Progressive ataxia, dysarthria, parkinsonism, very slow saccades, hyporeflexia
SCA3 (Machado-Joseph disease)	14q24	CAG expansion in ataxin-3 gene	10 y	. . .	Progressive ataxia, dystonia, pyramidal tract signs, parkinsonism, rapid progression
SCA7	3p21	CAG expansion in ataxin-7 gene	1 y	29 y	Progressive ataxia, macular degeneration, pyramidal tract signs, slow saccades, seizures
SCA13	19q	Mutation in *KCNC3* gene	Childhood	. . .	Progressive ataxia, nystagmus, dysarthria, mild mental retardation

Abbreviation: SCA, spinocerebellar ataxia.

Table 27.6 • Comparison of the 2 Most Common Autosomal Recessive Ataxias in Childhood

Feature	Friedreich Ataxia	Ataxia-Telangiectasia
Prevalence	1–2 per 100,000	. . .
Genetics	Autosomal recessive Unstable GAA repeat in the first intron of the gene encoding the mitochondrial protein frataxin	Autosomal recessive Point mutation or deletion in ataxia-telangiectasia mutated gene
Age at onset of symptoms	Childhood (range, 2 y to teens)	Toddlerhood
Clinical features	Progressive gait ataxia Facial weakness Dysarthria, dysphagia Decreased DTRs Sensorineural hearing loss Skeletal abnormalities Hypertrophic cardiomyopathy Diabetes mellitus (occasionally)	Progressive ataxia Choreoathetotic movements Oculomotor apraxia Loss of DTRs Telangiectasias of conjunctiva and skin At risk for recurrent infection (usually sinopulmonary) At risk for lymphoreticular neoplasms
Diagnosis	Clinical Genetic testing	Decreased IgA and IgE levels Elevated AFP and CEA
Prognosis	Lose ambulation by 15–20 y Death commonly due to cardiomyopathy	Lose ambulation in second decade Short-term memory deficits can develop in third to fourth decade Hypersensitive to radiography Death often due to infection or malignancy

Abbreviations: AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; DTR, deep tendon reflex; Ig, immunoglobulin.

or crying and suppressed by passive flexion of the limb. There are no abnormal movements of the head or eyes to suggest an epileptiform phenomenon. Most jitteriness usually resolves shortly after birth, but it may persist up to 6 months of age.

Shuddering

Shuddering episodes usually occur in infancy or early childhood and are characterized by periods of rapid tremor of the head, shoulders, and arms that resemble shivering. Consciousness is preserved during the episodes. The duration of events typically lasts several seconds, the events may occur up to 100 times daily, and they are often triggered by excitement or surprise. Shuddering is often confused with epileptic seizures; however, the ictal and interictal electroencephalograms are normal. Shuddering episodes typically resolve as the child grows older. Neurodevelopment is normal, and only reassurance is required.

Spasmus Nutans

Spasmus nutans is a benign syndrome of late infancy (3–12 months) that consists of a triad of vertical ("yes-yes") or horizontal ("no-no") head tremor, pendular nystagmus, and a head tilt. Spontaneous remissions of the head nodding typically occur by 2 years of age, although some cases persist up to 6 years of age. Subclinical nystagmus may persist until 5 to 12 years of age. Case reports of spasmus nutans have described an association with a glioma of the optic chiasm or the third ventricle; however, the prevalence of tumors in spasmus nutans is estimated to be less than 2%.

Stereotypies

Stereotypies occur in normal children as well as in children who are delayed in their development or who have some degree of autism. The movements are repetitive, nonpurposeful, and rhythmic, and the child can exert some degree of volitional control over them. Common examples include head banging, rocking, jumping, or flapping of the hands and arms. Often the movements occur more frequently when the child is excited or bored. In the nonautistic child with normal intelligence, the stereotypies may also be associated with anxiety, obsessive-compulsive symptoms, and perfectionism. The movements can be transient or they may persist for years. Medical treatment of stereotypies is not necessary, and pharmacotherapy is generally ineffective.

- Spasmus nutans is a benign syndrome of late infancy (3–12 months) that consists of a triad of vertical ("yes-yes") or horizontal ("no-no") head tremor, pendular nystagmus, and a head tilt.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

IV.1. A 64-year-old woman presents for evaluation of increasingly frequent episodes of syncope and, more recently, some dream reenactment behavior. On examination, her blood pressure decreases from 170/85 mm Hg supine to 90/60 mm Hg standing without a corresponding increase in heart rate. Her cognitive function is normal. She has moderate diffuse bradykinesia and rigidity, postural instability, and mild appendicular ataxia. Which of the following is the most appropriate next step in her management?

a. Refer her for polysomnography to assess for nocturnal laryngeal stridor
b. Initiate high-dose parenteral corticosteroids
c. Initiate donepezil
d. Recommend that she avoid sleeping with the head of the bed elevated
e. Initiate a low-dose β-blocker for orthostatic intolerance

IV.2. A 69-year-old man is referred for increasingly frequent falls. On examination, he has very slow saccadic velocities, occasional ocular square wave jerks, and severe axial rigidity with impaired postural reflexes. Which of the following imaging findings would you most likely encounter in the evaluation of this patient?

a. Cruciform pontine T2-signal hyperintensity on magnetic resonance imaging (MRI) ("hot cross bun" sign)
b. Asymmetric frontoparietal cortical atrophy on MRI
c. Normal fluorodopa F 18 positron emission tomographic imaging
d. Midbrain atrophy on MRI, resulting in the "hummingbird" sign
e. Symmetric, extensive calcification of the putamen, pallidum, and dentate nuclei

IV.3. A 17-year-old adolescent boy presents for evaluation of social withdrawal and new upper limb tremor. On examination, he has a high-amplitude, irregular, postural tremor of the upper limbs most prominent in proximal muscles. On ocular examination, a brownish limbic corneal discoloration is noted. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are significantly elevated. Which of the following genes is most likely involved in the diagnostic abnormality in this patient?

a. *PANK2*
b. *THAP1*
c. *NKX2.1*
d. *TOR1A*
e. *ATP7B*

IV.4. A 16-year-old adolescent girl presents for evaluation of abnormal movements. For several years, she has had a fluctuating problem with briefly suppressible urges to shake her head. These are worse when she is "stressed out," and they are socially embarrassing. During the interview she makes subtle, intermittent grunting noises. Which of the following is the most appropriate next step?

a. Urgent referral to a psychiatrist for treatment of a psychogenic movement disorder
b. Lumbar puncture for measurement of cerebrospinal fluid catecholamines
c. Initiation of low-dose oral clonidine
d. Referral to a medical geneticist for assessment of trinucleotide repeats in the huntingtin gene
e. Urgent electroencephalography to exclude nonconvulsive status epilepticus

IV.5. A 23-year-old man is evaluated for imbalance. On examination, he has severe axial and appendicular ataxia. He also has nearly complete loss of proprioception and vibration sensation, absent muscle stretch reflexes throughout, and extensor plantar responses. Which of the following is most likely to apply?

a. Significant GAA expansion in both *FRDA* alleles
b. Elevated serum alpha-fetoprotein level
c. Acanthocytes on blood smear
d. Extensive subcortical T2-signal hyperintensity on MRI
e. Elevated serum lactate level

IV.6. A 59-year-old man is referred by his primary care physician for evaluation of falls. On examination he has an ataxic, wide-based gait and mild appendicular ataxia. Imaging of his brain demonstrates significant atrophy of the cerebellum vermis. Use of which of the following medications would be important for you to assess in your history?

a. Fluoxetine
b. Lovastatin
c. Azithromycin
d. Hydroxychloroquine
e. Phenytoin

IV.7. A 72-year-old woman comes to your clinic for evaluation of right hand tremor. In addition to the tremor, she has had several years of intermittent dream reenactment behavior and almost complete anosmia. On examination, you note diffuse bradykinesia and hypokinesia. She has a slow resting tremor of the right hand and moderate cogwheeling rigidity in all limbs, which is also worse on the right. Which of the following statements regarding her treatment is most accurate?

a. She should be referred for consideration of early subthalamic nucleus deep brain stimulation
b. She should be started on high-dose pramipexole
c. Midodrine should be prescribed to prevent inevitable orthostatic hypotension
d. Carbidopa-levodopa should be taken only well before or after meals
e. Regular exercise should be avoided to reduce the risk of falls

IV.8. You have diagnosed slowly progressive idiopathic Parkinson disease in a 78-year-old man. His bradykinesia and rigidity are well controlled on a regimen of carbidopa-levodopa. Which of the following potential adverse effects should you make the patient aware of?
a. Livedo reticularis
b. Impulsive behaviors such as inappropriate gambling
c. Hypertension
d. Dry mouth
e. Hepatotoxicity

IV.9. A 48-year-old surgeon is referred to you for evaluation of several years of upper limb tremor (right worse than left). On examination, she has a low-amplitude 8-Hz postural tremor that abolishes at rest. She has normal muscle tone and postural reflexes and no evidence of bradykinesia. Her father had a similar tremor. Which of the following statements regarding this diagnosis is most accurate?
a. Excellent response to low-dose domaminergic agents is diagnostic of this disorder
b. Failure to improve with ethanol excludes this diagnosis
c. The diagnosis can be confirmed only at autopsy
d. The tremor may eventually involve the voice
e. Selegiline has been shown to slow the progression of the tremor

IV.10. A 59-year-old man is referred to your clinic for evaluation of lower limb discomfort. On questioning, he describes an unpleasant sensation in both lower limbs that improves with walking or after sitting. He has had no falls. Neurologic examination findings are normal, although when asked to stand after surface electromyography electrodes are applied over his lower limb muscles, he remarks that the transduced waveforms on the speaker "sound like a helicopter." Which of the following is the most likely diagnosis?
a. Orthostatic tremor
b. Holmes tremor
c. Idiopathic Parkinson disease
d. Dentatorubral-pallidoluysian atrophy
e. Psychogenic movement disorder

IV.11. A 52-year-old man comes to your clinic for evaluation of uncontrollable movements. He has a history of severe depression. On examination, diffuse choreic movements most prominently affect the upper limbs. On further questioning, he reports that his father had a similar movement disorder before committing suicide at the age of 61. Which of the following statements regarding his diagnosis is correct?
a. Genetic counseling should not be performed until the mutation is confirmed
b. Structural brain imaging with MRI is normal even in advanced disease
c. Reserpine would have to be used with caution given his history of depression
d. The presence of psychosis would effectively exclude the most likely diagnosis in this case
e. Striatal stem cell implantation provides significant benefit in slowing disease progression

IV.12. A 32-year-old woman reports a 2-year history of painful, uncontrollable head movements. Initially, she described intermittent forced head turning to the left. More recently, she has had difficulty with involuntary simultaneous bilateral eye closure. On examination, she has intermittent leftward torticollic head turns and marked hypertrophy of the right sternocleidomastoid muscle. Which of the following statements regarding her treatment is most accurate?
a. Treatment with carbamazepine or its derivatives eliminates symptoms in a majority of patients
b. Surgical denervation of affected cervical muscles is the most appropriate first-line therapy
c. Given the high suspicion for a psychogenic cause for the movements, paroxetine should be administered
d. Chemodenervation with botulinum toxin injection is an appropriate first-line therapy but may result in dysphagia
e. Close observation is appropriate since most cases will spontaneously remit

Answers

IV.1. Answer a.
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IV.2. Answer d.
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IV.3. Answer e.
Singer HS, Mink JW, Gilbert DL, Jankovic J. Movement disorders in childhood. Philadelphia (PA): Saunders/Elsevier; c2010. 279 p.

IV.4. Answer c.
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IV.5. Answer a.
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IV.6. Answer e.
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IV.10. Answer a.
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IV.11. Answer c.
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Section
V

Behavioral Neurology

Bryan K. Woodruff, MD, *editor*

28 Syndromes of Cognitive Dysfunction[a]

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Introduction

Cognitive function refers to the mental process of knowing things. It includes high-level cortical functions such as memory, language, perception, and executive function (planning, initiating, and reasoning). This function generally depends on the alert state and focused attention. Dysfunction of cognition without a change in consciousness may result in various disorders, including aphasia, apraxia, agnosia, executive dysfunction, and memory disorders such as dementia and amnesia. Transient dysfunction of cognition associated with a change in level of consciousness or attention may be due to delirium or confusional states. This chapter broadly introduces the specific definitions of cognitive dysfunction and the overall differential diagnoses. Individual diseases and clinical problems are presented in the next several chapters.

Delirium

Definition and Criteria

Delirium refers to a fluctuating level of consciousness with impairment in behavior and mental function caused by a physical disease. *The Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*) defines criteria for delirium due to a general medical condition (see below), delirium related to substance intoxication, delirium due to substance withdrawal, delirium due to multiple causes, and delirium not otherwise specified. The criteria for all are similar except for criterion D, which reflects the underlying cause.

The *DSM-5* criteria for delirium include the following:

A. A disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
C. An additional disturbance in cognition (eg, memory deficit, disorientation, language, visuospatial ability, or perception)
D. The disturbances in criteria A and C are not better explained by another preexisting established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (ie, due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies

Additional clinical features of delirium may include emotional disturbance (eg, depression, euphoria, fear, and

[a] Portions previously published in American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text Revision. Washington (DC): The Association; c2000. p. 157; and American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Chapter: Neurocognitive disorders, delirium. Section II: diagnostic criteria and codes. Arlington (VA): American Psychiatric Association; c2013. 947 p. Used with permission.

Abbreviations: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); *DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision)

agitation), psychomotor impairment, hallucinations, tremor, or impairment in sleep features. Terms such as *acute confusional state* and *encephalopathy* are often interchanged with the term *delirium*, but there is no agreement on whether these are distinct entities and no specific criteria exist to define them.

Epidemiology

Delirium is common in the hospitalized elderly patient. Rates of delirium in elderly patients have been estimated to be between 10% and 50%. Delirium in the hospital setting has multiple contributing factors including preexisting patient factors, environmental factors, the medical condition, and medications or drugs a patient is taking (Box 28.1). Patients with an increased likelihood for development of delirium include those with structural brain disorders such as stroke, dementia, and Parkinson disease. In addition, older patients, those with sensory impairments (hearing loss, reduced vision), and those with advanced cancers are at increased risk. Conditions that can precipitate and contribute to delirium and confusion are multiple (Box 28.2). Medications may be associated with delirium in susceptible patients (Box 28.3).

Box 28.1 • Multifactorial Causes of Delirium

- Preexisting factors
  - Age
  - Parkinson disease
  - Stroke
  - Dementia
  - Advanced cancer
  - Sensory impairment at baseline
- Environmental factors
  - Intensive care unit
  - Recent surgery
  - Sleep deprivation
  - Restraints
- Medical condition (see Box 28.2 for details)
  - Severity of illness
  - Medical comorbidities
  - Association of pain
- Medications (see Box 28.3 for details)
  - Anticholinergics
  - Cardiovascular medications
  - Pain medications
  - Neurologic and psychiatric medications
  - Antibiotics
  - Anesthetics

Box 28.2 • Conditions That Precipitate and Contribute to Delirium

- Vascular
  - Posterior reversible encephalopathy syndrome
  - Hypertensive encephalopathy
  - Subdural hematoma
- Infectious
  - Systemic infection/fever
  - Sepsis
  - Meningitis
  - Encephalitis
  - Brain abscess
- Inflammatory
  - Sepsis/SIRS
  - Steroid-responsive encephalopathy
- Neoplastic
  - Brain tumor
  - Paraneoplastic encephalopathy
- Metabolic
  - Electrolyte imbalance (sodium, magnesium, phosphate, calcium)
  - Hypoxia
  - Hypercarbia
  - Glucose (hyperglycemia or hypoglycemia)
  - Increased ammonia value (related to liver or isolated hyperammonemia)
  - Wernicke encephalopathy
  - Vitamin deficiencies (B_{12}, folate, niacin)
  - Endocrine imbalance (thyroid, parathyroid, pituitary, adrenal, pancreas)
  - Renal failure
  - Liver failure
  - Cardiac failure
  - Anemia
- Drugs/toxins (see also Box 28.3)
  - Prescription and over-the-counter medications: adverse effects, withdrawals, or toxicities
  - Illicit drug toxicities or withdrawals
  - Toxins
- Trauma/injury
  - Considerable trauma (especially head injury)
  - Burns
- Other
  - Seizures
  - Hypothermia or hyperthermia
  - Pain

Abbreviation: SIRS, systemic inflammatory response syndrome.

Box 28.3 • Common Medications That May Result in Delirium

- Anticholinergics
  - Atropine, benztropine, diphenhydramine, scopolamine, trihexyphenidyl
- Medications used for pain control
  - Opioids
- Antihypertensives and cardiac medications
  - Antiarrhythmic medications, β-blockers, clonidine, digoxin, diruetics
- Other neurologic medications
  - Dopamine agonists (amantadine, bromocriptine, levodopa, pergolide, pramipexole, ropinirole)
  - Antiseizure medications (carbamazepine, levetiracetam, phenytoin, valproate, vigabatrin)
  - Cholinesterase inhibitors (donepezil)
- Psychiatric medications
  - Lithium, mirtazapine, selective serotonin reuptake inhibitors, tricyclic antidepressants
- Gastrointestinal medications
  - Antiemetics, histamine$_2$ blockers, loperamide
- Sedative-hypnotics/muscle relaxants
  - Benzodiazepines, barbiturates, baclofen, cyclobenzaprine
- Medications used to treat cancer
- Antibiotics
  - Acyclovir, aminoglycosides, amphotericin B, antimalarials, cephalosporins, cycloserine, fluoroquinolones, isoniazid, interferon, linezolid, macrolides, metronidazole, nalidixic acid, penicillins, rifampin, sulfonamides
- Other
  - Hypoglycemic agents
  - Corticosteroids
  - Anesthetics

Table 28.1 • Clinical Features That Distinguish Delirium From Dementia

Clinical Feature	Delirium	Dementia
Onset	Acute to subacute	Subacute to chronic
Course	Fluctuating, resolves	Continuously progressive
Duration	Days to weeks	Indefinite
Level of consciousness	Impaired	Not impaired
Level of attention	Impaired	Not impaired (exceptions: diffuse Lewy-body disease, vascular dementia, and frontotemporal dementia)
Agitation	Frequent	Infrequent
Hallucinations	Frequent	Infrequent (exception: diffuse Lewy-body disease)
Motor activity	Agitation, hypoactive or hyperactive	No specific features

Adapted from Cerejeira J, Mukaetova-Ladinska EB. A clinical update on delirium: from early recognition to effective management. Nurs Res Pract. 2011;2011:875196. Epub 2011 Jun 16. Open access article distributed under the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0/legalcode) modified 2014 Oct 29.

Evaluation and Diagnosis

The evaluation of a "confused" patient involves a careful history and neurologic examination, including mental status. Be careful to distinguish delirium from dementia (Table 28.1), psychiatric illness (depression), focal cortical syndromes (bifrontal lesion, bioccipital lesion, bitemporal lobe lesion, dominant temporal lobe with Wernicke aphasia, and nondominant parietal lobe with neglect), and nonconvulsive status epilepticus.

If the diagnosis fits the criteria for delirium (*DSM-IV-Text Revision* [TR] or Confusion Assessment Method [Box 28.4]), a diagnostic evaluation is performed to rule out potential causes. Given the most common causes of delirium, the first round of testing often includes 1) assessing fluid and electrolyte balance (dehydration, sodium, kidney function); 2) ruling out common infections (urinary, respiratory, related to intravenous or other intravascular lines); 3) assessing medications and potential toxins (toxicities, withdrawals, interactions); 4) assessing metabolic status (glucose and calcium levels, liver, kidney, and thyroid functions); and 5) assessing oxygenation and perfusion (blood pressure). In certain instances, based on history and examination, additional studies may be recommended, including head imaging, lumbar puncture, and determining levels of ammonia, blood gas, vitamins, cortisol levels, and others.

Treatment

Treatment of delirium is aimed at identifying and treating contributing medical factors, avoiding precipitating medications when possible, normalizing the environment (improvement of sleep, avoidance of restraints when possible, use of hearing and visual aids), and preventing harm to the patient or staff. Intravenous thiamine should be considered in patients with delirium who are at risk for nutritional deficiency. If treating the underlying condition and conservative measures are not helping, or the patient presents a risk to self or others, medications can be cautiously used. Neuroleptics are commonly used, including haloperidol and newer atypical antipsychotics. Benzodiazepines

Box 28.4 • The Confusion Assessment Method (CAM) Diagnostic Algorithm

Feature 1: Acute onset or fluctuating course

This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?

Feature 2: Inattention

This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

Feature 3: Disorganized thinking

This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4: Altered level of consciousness

This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

Adapted from Inouye SK, van Dyck CA, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. Ann Int Med. 1990 Dec 15;113(12):941–8. Used with permission.

can worsen delirium and are generally not recommended unless antipsychotic medications are contraindicated or the patient is being treated for alcohol or benzodiazepine withdrawal.

There are no medications known to prevent delirium; however, prevention of delirium is aimed at avoiding triggers and normalizing the environment.

- Delirium refers to a fluctuating level of consciousness with impairment in behavior and mental function caused by a physical disease.
- Delirium in the hospital setting has multiple contributing factors including preexisting patient factors, environmental factors, the medical condition, and medications or drugs a patient is taking (Box 28.1).
- Intravenous thiamine should be considered in patients with delirium who are at risk for nutritional deficiency.

Dementia

Definition and Criteria

Dementia is loss of memory in addition to at least 1 other cognitive domain (language, praxis, perception, executive function). The impairment affects one's ability for independent daily function. Dementia may be due to many causes, with Alzheimer disease being most prevalent.

The *DSM-IV-TR* criteria for dementia of Alzheimer type are as follows:

A. The development of multiple cognitive deficits manifested by both
   1. memory impairment (inability to learn new information or recall previously learned information)
   2. one (or more) of the following cognitive disturbances:
      a. Aphasia (language disturbance)
      b. Apraxia (impaired ability to carry out motor activities despite intact motor function)
      c. Agnosia (failure to recognize or identify objects despite intact sensory sensation)
      d. Executive dysfunction (ie, planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning

C. The course is characterized by a gradual onset and continuing cognitive decline

D. The cognitive deficits in criteria A1 and A2 are not due to any of the following:
   1. other central nervous system conditions that cause deficits in memory and cognition (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   2. systemic conditions that are known to cause dementia (eg, hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   3. substance-induced conditions

E. The deficits do not occur exclusively during the course of delirium

F. The disturbance is not better accounted for by another Axis I disorder (eg, major depressive disorder, schizophrenia)

The differential diagnosis of dementia is broad (Box 28.5). Alzheimer disease accounts for 60% to 80% of dementia; however, there are important and treatable diseases to assess for in select patients.

Box 28.5 • Differential Diagnosis of Dementia

- Vascular
  - Vascular dementia
  - Multi-infarct dementia
  - Binswanger disease
  - CNS vasculitis
  - Subdural hematoma
- Infectious
  - Prion: Creutzfeld-Jakob disease
  - Bacterial: syphilis, Lyme disease, Whipple disease
  - Viral: HIV
  - Fungal: chronic meningitis
- Inflammatory/autoimmune
  - Steroid-responsive encephalopathy
  - Multiple sclerosis
  - Autoimmune: Sjögren syndrome and lupus
- Neoplastic
  - Bifrontal or bithalamic tumor
  - Carcinomatous meningitis
  - Paraneoplastic (limbic encephalitis)
- Toxic/metabolic
  - Vitamin deficiency: B_{12}, folate, B_3-niacin, thiamine (Wernicke-Korsakoff syndrome), Marchiafava-Bignami disease, chronic alcoholism
  - Hypothyroidism
  - Heavy metals: arsenic, lead, mercury, manganese
  - Superficial siderosis
  - Hepatic failure
  - Renal failure/dialysis related
- Genetic
  - CADASIL
  - Familial Alzheimer disease
  - Huntington disease
  - Frontotemporal dementia with motor neuron disease
- Degenerative
  - Alzheimer disease
  - Diffuse Lewy-body disease
  - Corticobasal ganglionic degeneration
  - Frontotemporal dementia
  - Primary progressive aphasia
  - PSP
- Trauma
  - Pugilistic dementia
- Other
  - Normal-pressure hydrocephalus
  - Pseudodementia (depression)

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system; HIV, human immunodeficiency virus; PSP, progressive supranuclear palsy.

Evaluation

Patients with cognitive concern should undergo an initial history and physical examination, including a mental status examination. The onset and course of the disease, medications the patient is taking, and comorbidities (depression, vascular disease, risk factors) are important to elucidating an underlying cause. Changes in behavior, mood, and memory should be discussed with family members familiar with the patient to obtain collateral information. The Mini-Mental State Examination is commonly used to screen patients for dementia. A score of less than 24 of 30 may suggest delirium or dementia (87% specificity; 82% sensitivity). The neurologic examination should focus on whether there are any focal neurologic signs, abnormal gait, or signs suggestive of a specific cause (eg, associated parkinsonism, tremor, myoclonus). A screen for depression (pseudodementia) should also be considered.

Some guidelines suggest that initial testing include vitamin B_{12} and thyroid laboratory testing and head imaging. However, select patients may require more in-depth testing. Patients at risk for particular conditions or those who are young (<60 years) or in whom the onset is acute to subacute may require additional testing (Box 28.6).

Box 28.6 • Select Testing in Patients With Dementia

Test	When to Consider
Formal neuropsychometric testing	When brief, in-office cognitive testing is equivocal or patient tests well in office, but historically not functioning well
HIV, Lyme disease, syphilis	In patients at risk for these individual diseases
Electroencephalography	If Creutzfeld-Jakob disease is a consideration or frequent, nonconvulsive seizures are considered
Spinal fluid examination	If chronic meningitis or CNS vasculitis is suggested by subacute course, associated headaches, or enhancement on MRI; if Creutzfeld-Jakob disease is considered, spinal fluid testing may be useful
Positron emission tomography	Investigational; considered in some patients to attempt to distinguish type of dementia

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging.

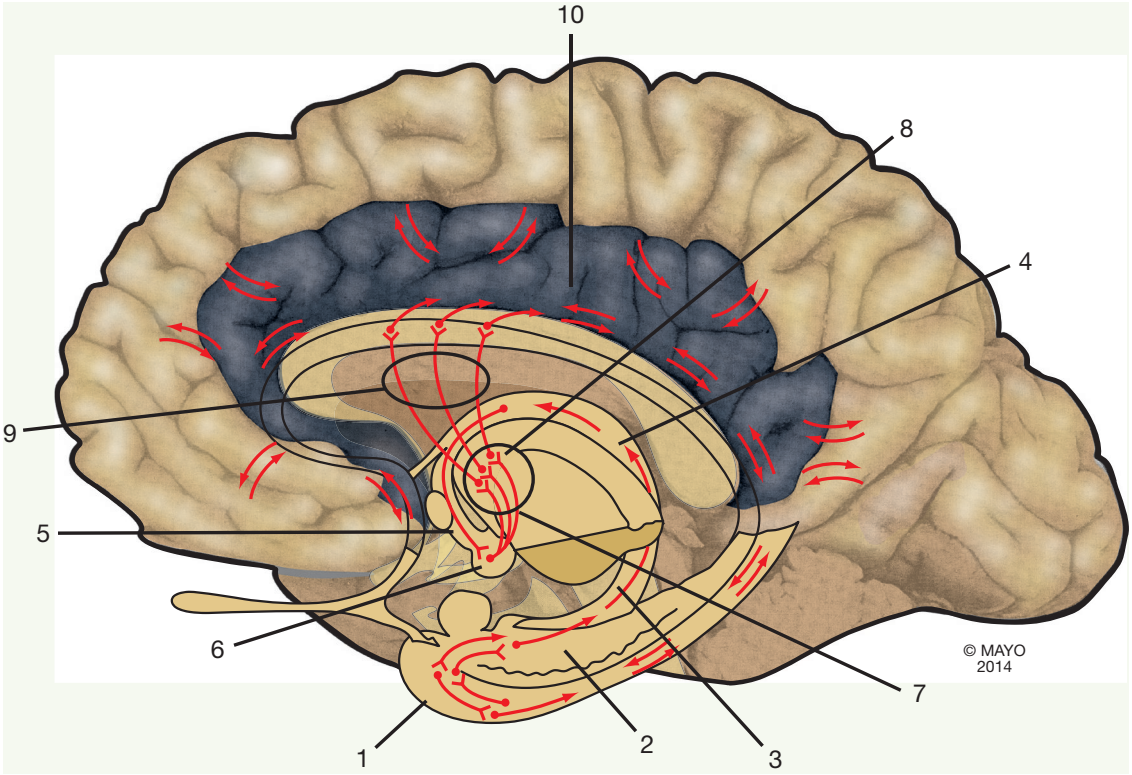

Figure 28.1 *Circuit of Papez.*
1, Entorhinal cortex; 2, hippocampus proper; 3, fimbria of fornix; 4, body of fornix; 5, column of fornix; 6, mamillary body; 7, mamillothalamic tract; 8, anterior nucleus of thalamus; 9, thalamocingulate radiation; 10, cingulate gyrus.
(Adapted from Mowzoon N. Behavioral Neurology. Part A: Neurobiology of cognitive function. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 279–96. Used with permission of Mayo Foundation for Medical Education and Research.)

Treatment

Treatment of dementia is aimed at the identified cause. See other chapters in this section of behavioral neurology for individual treatments.

- Dementia is loss of memory in addition to at least 1 other cognitive domain (language, praxis, perception, executive function).
- A score of less than 24 of 30 on the mental status test may suggest delirium or dementia (87% specificity; 82% sensitivity).
- Some guidelines suggest that initial testing for dementia include vitamin B_{12} and thyroid laboratory testing and head imaging.

Amnesia

Definition and Criteria

Amnesia refers to the inability to learn new information and may also impair retrieval of previously learned information. More specifically, it is impairment of declarative memory (learning of facts, material, new events).

Amnesia may result from damage of the Papez circuit, usually bilaterally (Figure 28.1). There are many causes of amnesia, both transient and persistent (Box 28.7).

Evaluation

The evaluation of amnesia involves a careful history detailing the onset and course of the disease and any provoking factors (stress, head trauma, substantial alcohol use, nutritional deficiency, sleep deprivation). Concurrent headache, fever, or other neurologic symptoms may raise concern of an underlying infection, venous stroke, or mass lesion. Neurologic examination should include a mental status examination to determine whether the amnesia is isolated or other cognitive deficits have occurred. Typically, registration, digit span, facts, calculation, and attention are normal. Only short-term recall of new information is impaired. Amnesia should be distinguished from delirium or acute confusional state. If amnesia is confirmed, testing often includes head imaging.

Treatment

Treatment of amnesia depends on the underlying cause. In general, thiamine 100 mg intravenously is given at onset,

Box 28.7 • Differential Diagnosis of Amnesia

- Vascular
  - Anoxic injury (bitemporal injury)
  - Bithalamic cerebral ischemia (bilateral internal cerebral vein infarction or artery of Percheron cerebral infarction)
- Infectious/inflammatory
  - Herpes encephalitis (bitemporal involvement)
- Neoplastic
  - Neoplastic lesion along the circuit of Papez (butterfly glioma of the thalamus)
- Toxic/metabolic/drugs
  - B_1 (thiamine) deficiency (Wernicke-Korsakoff syndrome)
  - Carbon monoxide exposure
  - Sulfur compound toxicities
  - Heavy metal: lead, mercury
  - Ilicit drug use
  - Medications (rare): benzodiazepine, zopiclone, scopalamine, dicyclomine, statin
- Degenerative
  - Dementias
- Trauma/iatrogenic
  - Neurosurgery
  - Head trauma
- Psychiatric
- Other
  - Frequent seizures
  - Mesial temporal sclerosis
  - Transient global amnesia

as Wernicke encephalopathy may have some reversibility. Oxygen status, electrolyte values, glucose value, and a toxicology screen should be obtained. Head imaging is often performed unless a more obvious cause is identified. Cognitive rehabilitation may be considered in certain instances.

Specific Disorders

Transient Global Amnesia

Transient global amnesia is a rare condition in which patients have reversible anterograde amnesia. Patients are often between the ages of 50 and 80 years and have the abrupt onset of amnesia. In some cases, physical or emotional stress or Valsalva maneuvers have preceded the event. Patients often ask repetitive questions about where they are, what is happening, and what time it is. Other cognitive domains are generally intact, and patients are able to carry out usual motor tasks. Symptoms often last between 1 and 12 hours and then improve spontaneously.

The underlying cause of transient global amnesia is not clear, but hypotheses include vascular, migrainous, venous congestion, or epilepsy. Evaluation often involves ruling out other potential causes of amnesia. There is no specific treatment because the condition resolves spontaneously. Recurrence rates are generally considered to be low, although the literature has suggested recurrence rates to be between 3% and 25%.

Wernicke-Korsakoff Syndrome

Wernicke encephalopathy due to thiamine deficiency presents as a triad of encephalopathy, ataxia, and oculomotor abnormalities. More than 80% of patients go on to have development of a Korsakoff amnestic syndrome. For additional details, see Chapter 78, "Neurologic Complications of Nutritional Disorders."

- Amnesia refers to the inability to learn new information and may also impair retrieval of previously learned information.
- Amnesia may result from damage of the Papez circuit, usually bilaterally (Figure 28.1). There are many causes of amnesia, both transient and persistent (Box 28.7).

29 A Review of Focal Cortical Syndromes

KELLY D. FLEMMING, MD; RICHARD J. CASELLI, MD

Introduction

Recognizing classic focal cortical syndromes is useful in clinical practice to aid in localization and, in some cases, to provide clues to a diagnosis. Classic focal cortical syndromes are reviewed in the neuroscience section in Volume 1 in full detail. Because some of the related neuroanatomy is clinically relevant and may be included in a recertification examination, parts of that section are concisely reviewed in this chapter.

Sensory Processing and Recognizing Objects

Networks

The primary visual cortex predominantly analyzes central vision. The macula is represented posteriorly in the calcarine cortex, and the peripheral retina is represented anteriorly. From the primary visual cortex, information is processed in secondary visual cortices and surrounding heteromodal areas. The dorsal stream (occipitoparietal) aids in determining object position and motion. This information aids in visually guided exploration of an object. The ventral stream (occipitotemporal) provides information about the color of an object.

Semantic memory refers to the ability to recognize objects and their meaning or concept. Specific sensory input from visual, somatosensory, and auditory areas of the brain provides information regarding shape, color, texture, sound, and other attributes. This information from primary cortices and association cortices is transmitted to heteromodal areas, where it is integrated to allow recognition of an object (or face) and its meaning. The anterior middle temporal gyrus and temporal pole are important in this regard.

Dysfunction

An agnosia is an inability to identify an object despite one being able to perceive it (see, hear, and touch it). Lesions in unimodal sensory association areas may result in agnosias. Table 29.1 summarizes common agnosias and their localization.

- The dorsal stream (occipitoparietal) aids in determining object position and motion.
- The ventral stream (occipitotemporal) provides information about the color of an object.
- Semantic memory refers to the ability to recognize objects and their meaning or concept.
- An agnosia is an inability to identify an object despite one being able to perceive it (see, hear, and touch it).
- Lesions in unimodal sensory association areas may result in agnosias.

Spatial Attention

Networks

The posterior parietal lobe, in addition to the pulvinar nucleus of the thalamus, receives integrated sensory information (auditory, visual, somatosensory). This heteromodal area of the parietal lobe projects to the prefrontal eye fields and dorsolateral prefrontal cortex. This network is involved in attention to one's extrapersonal space (Figure 29.1A).

Dysfunction

Lesions of this parietal heteromodal region result in several clinical syndromes (Figure 29.1B and 29.1C, Table 29.2).

Table 29.1 • Select Agnosias

Focal Cortical Syndrome	Description	Localization
Akinetopsia	Inability to perceive motion of objects	Occipitoparietal
Hemiachromatopsia	Loss of color perception	Occipitotemporal
Proposagnosia	Inability to recognize a familiar face	Occipitotemporal (bilateral; fusiform and lingual gyri)
Tactile agnosia (astereognosia)	Inability to identify an object by palpating it	Parietal (somatosensory association areas)
Agraphesthesia	Inability to recognize letters written on palmar surface of hand	Parietal (somatosensory association areas)
Atopognosia	Inability to localize touch	Parietal (somatosensory association areas)
Pure word deafness	Inability to recognize spoken language, but can recognize environmental sounds	Temporal (auditory association areas)
Anton syndrome	Cortical blindness, visual anosognosia (deny blindness), confabulation	Bilateral medial occipital lobes

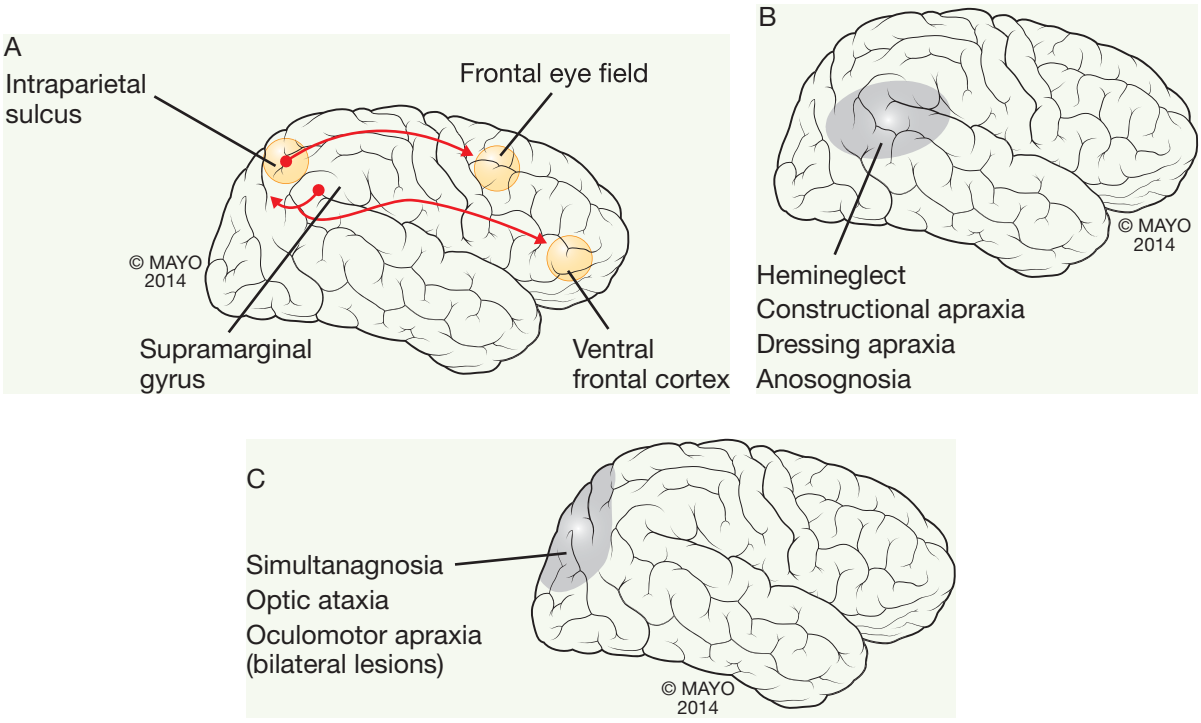

Figure 29.1 *Networks of Spatial Attention.*
A, Cortical areas involved in spatial attention. They include the intraparietal sulcus that integrates multiple information about position and movement of an object in space and projects to the frontal eye fields, which direct gaze toward the object of interest. These areas are interconnected and form a bilateral network that includes the pulvinar of the thalamus and cingulate cortex and is critical for attention and guidance of movement toward contralateral space. A second group of areas in the right hemisphere, including the inferior parietal lobule (supramarginal gyrus) and ventral frontal cortex, are activated in response to novel, unexpected stimuli. B, Lesions of the right inferior parietal lobule (and adjacent superior temporal cortex) produce sensory neglect of the contralateral body, constructional apraxia, dressing apraxia, and anosognosia. C, Bilateral lesions of superior parietal cortex and adjacent occipital cortex produce Balint syndrome, characterized by simultanagnosia, oculomotor apraxia, and optic ataxia.
(Adapted from Benarroch EE, Daube JR, Flemming KD, Westmoreland BF. Mayo Clinic medical neurosciences: organized by neurologic systems and levels. 5th ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. Chapter 16B, The supratentorial level: telencephalon; p. 701–63. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 29.2 • Disorders Involving the Parietal Heteromodal Regions

Focal Cortical Syndrome	Description	Localization
Spatial neglect	Inability to orient to items on the contralateral side	Nondominant parietal
Constructional apraxia	Inability to draw a particular figure (eg, neglecting the left side of a clock drawing)	Nondominant parietal
Dressing apraxia	Failure to dress the contralateral side of body	Nondominant parietal
Anosognosia	Inability to recognize a deficit	Nondominant parietal
Balint syndrome	Asimulantanagnosia (unable to see more than 1 object simultaneously), oculomotor apraxia (difficulty in voluntarily moving fixation), optic ataxia (reaches past the correct location of an object)	Bilateral superior parietal lobule

Motor Programs and Execution

Networks

Executing a motor program requires multiple areas of the brain. A person must first be aware of surroundings and space (posterior parietal heteromodal region) in order to direct attention to where to move and avoid obstacles. Areas of the prefrontal cortex and anterior cingulate gyrus aid in goal-directed movement. For example, if I am hungry and, through visual scanning, recognize food, I am going to direct my attention toward the food and then select a motor program for walking to the object. The frontal eye fields and the temporoparietal–occipital cortex are involved in directing eyes. The supplementary motor region aids in learning and preparing for movement and generating motor sequences. This information is then transmitted to the primary motor cortices.

Dysfunction

Apraxia is the inability to perform a skilled movement in the absence of weakness, sensory loss, or incoordination. Apraxia may result from a lesion of the posterior parietal cortex or the premotor or supplementary areas of the cortex.

Ideomotor apraxia is the inability to perform a skilled movement. For example, a patient is asked to perform a sequence of movements but is unable. Lesions resulting in ideomotor apraxia may include the motor association cortex or parietal lobe.

Ideational apraxia is generally a substitution of 1 movement for another. Patients lose the ability to perceive the typical use of an object. For example, a patient is asked to pantomime the use of a toothbrush but pantomimes the use of a hammer instead.

- Apraxia is the inability to perform a skilled movement in the absence of weakness, sensory loss, or incoordination.
- Apraxia may result from a lesion of the posterior parietal cortex or the premotor or supplementary areas of the cortex.

Language

Networks

The left hemisphere is dominant for language (recognizing, understanding, and retrieving words for spoken and written language) in most right-handed persons. In left-handed persons, the left hemisphere is dominant for language in most (about two-thirds). Areas involved in language on the dominant hemisphere include the Broca area and Wernicke area, which are connected by the arcuate fasciculus (Figure 29.2). The right hemisphere, or nondominant hemisphere, interprets prosody of speech and metaphoric language.

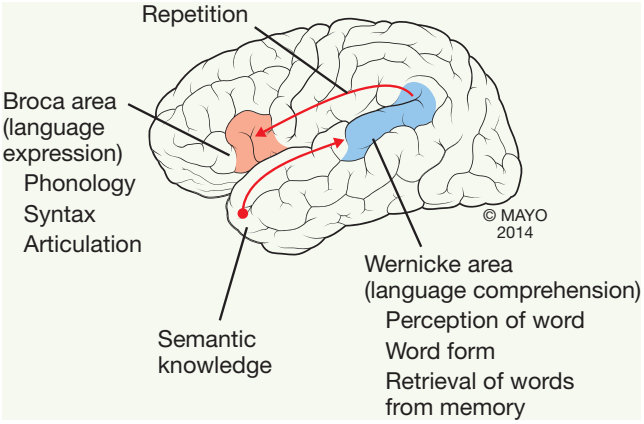

Figure 29.2 *The Perisylvian Language Network. This network is located in the left hemisphere of most right-handed and most left-handed persons.*
(Adapted from Benarroch EE, Daube JR, Flemming KD, Westmoreland BF. Mayo Clinic medical neurosciences: organized by neurologic systems and levels. 5th ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. Chapter 16B, The supratentorial level: telencephalon; p. 701–63. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 29.3 • Types of Aphasia

Type	Naming	Fluency	Comprehension	Repetition	Localization
Anomia	–	+	+	+	Left lateral and anterior temporal
Conduction	±	+	+	–	Left arcuate fasciculus
Transcortical sensory	–	+	–	+	Left temporo-occipital
Wernicke	–	+	–	–	Left superior temporal and inferior parietal
Transcortical motor	–	–	+	+	Left frontal
Broca	–	–	+	–	Left frontal operculum
Transcortical mixed	–	–	–	+	Watershed area
Global	–	–	–	–	Perisylvian (frontal and temporal)

Abbreviations: +, intact; –, impaired; ±, may or may not be impaired.

Dysfunction

Disturbance of language function is referred to as aphasia. Aphasia is typically assessed by naming objects, repeating statements, determining whether the language is fluent or nonfluent, and assessing comprehension. The types of aphasia are listed in Table 29.3.

Alexia refers to the inability to read despite normal vision. Alexia with agraphia (inability to write) can occur with a lesion of the left angular gyrus. Alexia without agraphia occurs when a lesion is in the left occipital lobe and affecting the splenium of the corpus callosum. Information in the right visual cortex cannot be transferred to the Wernicke area for interpretation.

Gerstmann syndrome is characterized by acalculia (inability to perform calculations), finger agnosia (inability to recognize fingers), agraphia (inability to write), and left-right disorientation. The lesion is generally in the left inferior parietal lobe or near the angular gyrus (Figure 29.3).

- Aphasia is typically assessed by naming objects, repeating statements, determining whether the language is fluent or nonfluent, and assessing comprehension.
- Gerstmann syndrome is characterized by acalculia, finger agnosia, agraphia, and left-right disorientation and usually localizes to the dominant angular gyrus.

Complex Behavior and Executive Functions

Networks and Dysfunction

The prefrontal cortex, along with its connections to multiple subcortical structures, is an important area involved in complex behavior. The dorsolateral prefrontal cortex is involved in executive function and attention, including working memory. Patients with dysfunction of the dorsolateral prefrontal cortex often have poor decision making, inability to complete tasks, and difficulty sustaining attention. The orbitofrontal prefrontal cortex interconnects with the limbic system and modulates emotional responses to prior experience or decision making. Dysfunction of this region can result from trauma, and patients are often disinhibited socially. The anterior cingulate cortex interconnects with the orbitofrontal region and is important for behavioral drive. Dysfunction of this area may result in apathy, acquired

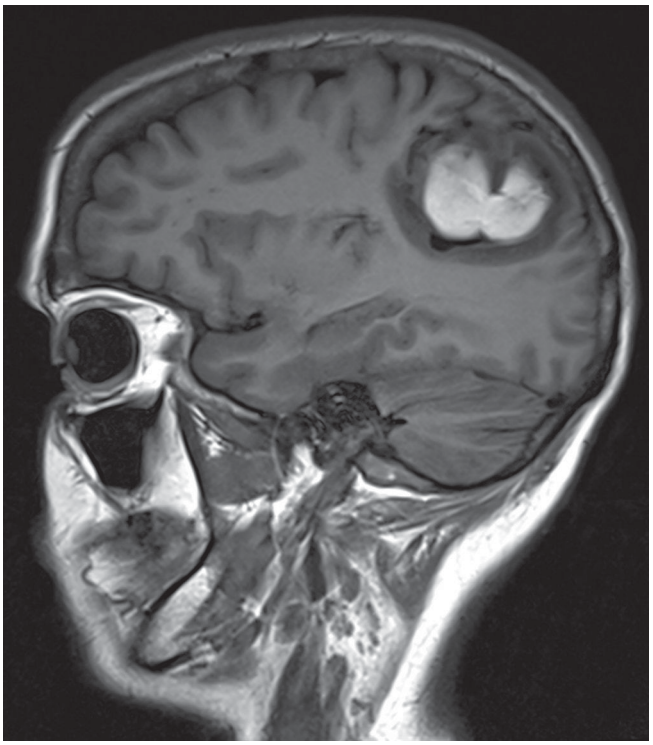

Figure 29.3 *Magnetic Resonance Imaging in a Patient With Gerstmann Syndrome.*
This patient presented with difficulty calculating, did not know her left hand from right, could not identify her thumb from her ring finger, and had difficulty writing. Scan of the brain shows a hemorrhage in the dominant parietal lobe.

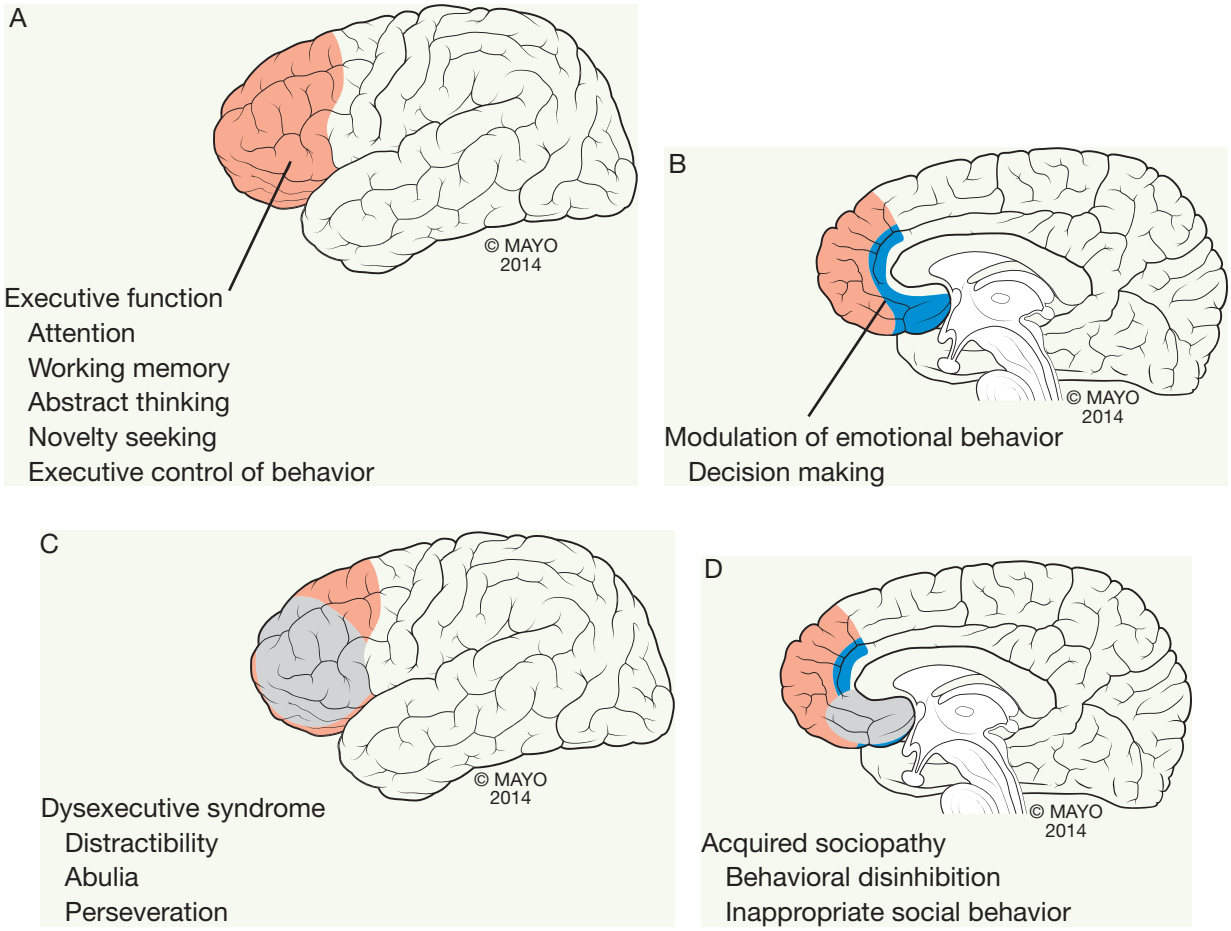

Figure 29.4 *Function and Dysfunction of Prefrontal Cortex.*
Functions of the heteromodal dorsolateral prefrontal cortex (salmon area) (A) and paralimbic orbitomedial prefrontal cortex (blue area) (B). Lesions (gray area) of the dorsolateral prefrontal cortex produce a dysexecutive syndrome (C), and those of the orbitomedial prefrontal cortex impair decision making and social behavior (D).
(Adapted from Benarroch EE, Daube JR, Flemming KD, Westmoreland BF. Mayo Clinic medical neurosciences: organized by neurologic systems and levels. 5th ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. Chapter 16B, The supratentorial level: telencephalon; p. 701–63. Used with permission of Mayo Foundation for Medical Education and Research.)

sociopathy, and diminished self-awareness. Figure 29.4 illustrates the location and function, as well as dysfunction, of the prefrontal cortex.

- The dorsolateral prefrontal cortex is involved in executive function and attention, including working memory.
- The orbitofrontal prefrontal cortex interconnects with the limbic system and modulates emotional responses to prior experience or decision making.
- The anterior cingulate cortex interconnects with the orbitofrontal region and is important for behavioral drive.

30 Mild Cognitive Impairment and Alzheimer Disease

QURAT UL AIN KHAN, MD; NILÜFER TANER, MD, PHD

Introduction

Alzheimer disease (AD) is the most common cause of dementia in the United States and worldwide. Many patients present initially with mild cognitive impairment (MCI). This chapter reviews the clinical features of MCI and AD, the clinical evaluation of these entities, and approaches to management.

Mild Cognitive Impairment

Definition

MCI is a condition defined by cognitive decline that is greater than expected by aging alone but does not meet criteria for dementia because of intact abilities of daily living. MCI is considered to be a prodrome to dementia, especially AD, given its increased risk of progression to this condition. MCI, which likely represents the earliest stages of dementia in many cases, requires clinical follow-up and is expected to become an important intervention point in future clinical trials of novel preventive therapies.

Epidemiology

The incidence and prevalence estimates of MCI vary among studies on the basis of the definition of MCI used and the study design. The incidence of MCI is 21.5 to 71.3 cases per 1,000 person-years; incidence rates are higher in association with older age, lower education, and male sex in different studies. The incidence also varies on the basis of subtypes of MCI (discussed below). Amnestic MCI (aMCI) has a higher incidence than nonamnestic MCI (naMCI); the ratio for incidence of aMCI to naMCI is 2.5:1. The population-based estimate of prevalence for MCI is 10% to 20% in subjects older than 65 years; the ratio for prevalence of aMCI to naMCI is 2:1.

The annual conversion rate from MCI to dementia is 5% to 10% in population-based studies and 10% to 15% in specialty clinics; in comparison, the rate is 1% to 2% per year in the general US population. MCI can revert to normal cognition at a rate of 25% to 30% per year, although reversion rates as low as 12.3% per year are reported from population-based studies. Long-term follow-up studies are required to determine the extent of second conversion from normal to MCI. Suggested predictive factors for progression from MCI to dementia or AD include greater disease severity at baseline, presence of apolipoprotein ε4 (*APOE4*) allele, hippocampal atrophy on magnetic resonance imaging (MRI) of the brain, temporal and parietal hypometabolism on fluorodeoxyglucose FDG 18 positron emission tomography (^{18}FDG-PET), low amyloid-β 42 (Aβ42) and high tau levels in cerebrospinal fluid, and presence of brain Aβ on carbon 11–labeled Pittsburgh compound B PET (11C-PiB-PET). Many of these potential predictive factors are currently used only in the research setting, and their clinical utility remains to be established.

Abbreviations: Aβ, amyloid-beta; AD, Alzheimer disease; aMCI, amnestic MCI; *APOE4*, apolipoprotein ε4 gene; *APP*, amyloid protein precursor gene; 11C-PiB-PET, carbon 11-labeled Pittsburgh compound B positron emission tomography; ^{18}FDG-PET, fluorodeoxyglucose FDG 18 positron emission tomography; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; naMCI, nonamnestic MCI; NINCDS-ADRDA, National Institute of Neurological, Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; *PSEN1*, presenilin 1 gene; *PSEN2*, presenilin 2 gene

Pathophysiology

The available clinicopathologic studies of MCI at autopsy suggest that most patients (60%) have evidence of the pathologic features of AD with a considerable presence of vascular disease. In a population-based study of subjects with MCI who were followed to dementia and underwent autopsy, the majority with aMCI had AD neuropathologic findings (75%-83%), and other pathologic findings were present in 25% to 50% of cases, including vascular lesions, Lewy bodies, hippocampal sclerosis, argyrophilic grain disease, or frontotemporal lobar degeneration. These studies highlight the underlying heterogeneity of this condition.

Clinical Features

MCI is classified into aMCI and naMCI subtypes based on the presence or absence of memory complaints, respectively, and further into single-domain and multiple-domain subtypes based on the presence of only a single impaired cognitive domain or multiple impaired cognitive domains, respectively. In one study, clinical AD developed in more than 90% of the aMCI patients who progressed to dementia. naMCI is characterized by cognitive impairment in nonmemory domains, such as attention, language, and visuospatial skills and may represent a prodrome for non-Alzheimer dementias, such as frontotemporal lobar degeneration or dementia with Lewy bodies (Figure 30.1).

Diagnosis

History from the patient and informant is important for making a diagnosis of MCI. By definition, cognitive impairment should be a change from the usual state for the patient, and, despite this impairment, the patient with MCI should function independently in his or her daily routine. Patients with aMCI may complain of forgetting important and recent information, such as conversations, appointments, or news. Patients with naMCI may have impairment in word finding (language domain), driving directions (visuospatial domain), or planning (executive domain). Slow onset of symptoms with gradual progression is typical of a neurodegenerative cause, such as AD, whereas abrupt onset, stepwise course, or concomitant focal motor or sensory deficits may herald a vascular cause.

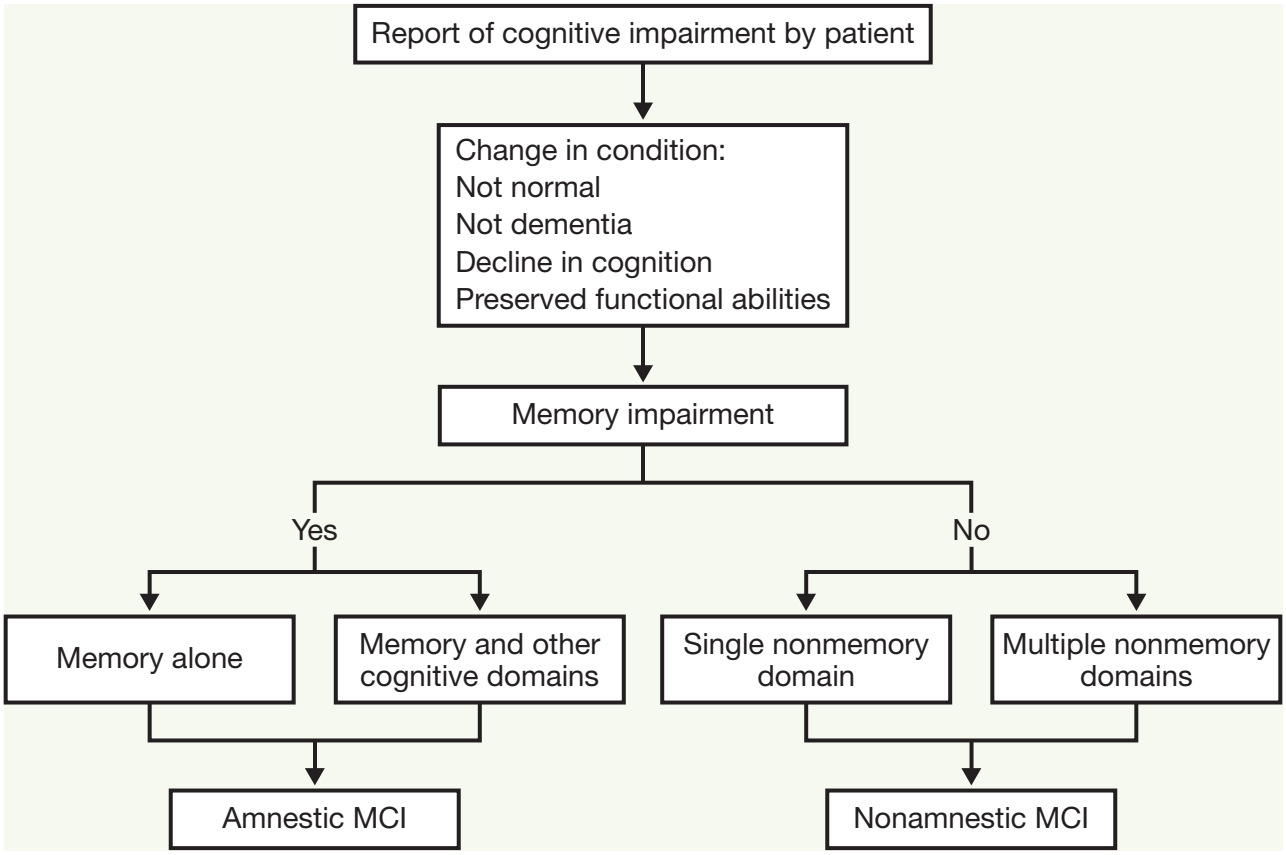

Figure 30.1 *Diagnostic Algorithm for Amnestic and Nonamnestic Mild Cognitive Impairment. MCI indicates mild cognitive impairment.*

(Adapted from Petersen RC. Mild cognitive impairment. CONTINUUM: Lifelong Learn Neurol. 2004 Feb;10[1, Dementia]:9–28. Used with permission.)

Thorough review of mood, medications, and sleep may uncover depression, use of certain drugs (anticholinergics, narcotic analgesics, benzodiazepines), or symptoms of sleep apnea, which could impair cognition and lead to MCI. Presence of hallucinations, dream enactment, fluctuations of symptoms, parkinsonism, or autonomic dysfunction is suggestive of dementia with Lewy bodies, and behavioral changes may be due to frontotemporal lobar degeneration.

Bedside cognitive tests such as the Mini-Mental State Examination, Short Test of Mental Status, or Montreal Cognitive Assessment may be useful but can be insensitive. Formal neuropsychologic testing is often useful to differentiate the degree of cognitive decline from that of normal aging. Brain imaging is necessary to rule out potentially treatable or alternative causes such as subdural hematoma, tumor, or hydrocephalus and to evaluate the extent of vascular disease. Although structural MRI is also helpful to detect the presence of hippocampal and cortical atrophy, which may be a risk factor for progression to AD, its use in the clinical setting is not established for this purpose. Laboratory studies, including complete blood count, electrolytes, liver and renal function, vitamin B_{12}, and thyroid-stimulating hormone, are recommended to rule out metabolic abnormalities. Advanced imaging and cerebrospinal fluid biomarkers are not yet in use for diagnosis of MCI in the clinical setting.

Management

Currently, there are no medications for MCI approved by the US Food and Drug Administration. Patients should be counseled about the potential heterogeneity of the underlying cause and the uncertainty about progression or reversion. In general, all patients with MCI should undergo repeat neuropsychologic and neurologic evaluation in 6 to 12 months after diagnosis to evaluate for progressive cognitive decline and development of dementia. Anticholinesterases used in AD management (donepezil, galantamine, rivastigmine) are not effective for reducing the rate of progression from MCI to dementia in clinical trials, with the exception of donepezil, which in 1 study reduced progression to AD for the first 12 months but not for the complete 36 months of the study.

Cognitive exercises and aerobic physical activities, which are associated with reduced cognitive decline or improved cognition in intervention studies, should be recommended in MCI. Given the association between cardiovascular risk factors, including obesity, hyperlipidemia, hypertension, and diabetes mellitus with dementia, AD, or cognitive impairment, optimization of these factors in MCI is recommended, although there is no evidence that this would reduce progression of cognitive decline.

- MCI is considered to be a prodrome to dementia, especially Alzheimer disease (AD), given its increased risk of progression to this condition.
- Incidence rates of MCI are higher in association with older age, lower education, and male sex in different studies.
- The annual conversion rate from MCI to dementia is 5% to 10% in population-based studies and 10% to 15% in specialty clinics; in comparison, the rate is 1% to 2% per year in the general US population.
- Patients with aMCI may complain of forgetting important and recent information, such as conversations, appointments, or news. Patients with naMCI may have impairment in word finding (language domain), driving directions (visuospatial domain), or planning (executive domain).
- Anticholinesterases used in AD management (donepezil, galantamine, rivastigmine) are not effective for reducing the rate of progression from MCI to dementia in clinical trials, with the exception of donepezil, which in 1 study reduced progression to AD for the first 12 months but not for the complete 36 months of the study.

Alzheimer Disease

Epidemiology

AD is a neurodegenerative condition that is the most common cause of dementia in the United States and worldwide, most often presenting as a gradually progressive memory decline that leads to functional impairment. AD currently affects about 5.4 million people in the United States, and this number is expected to increase to up to 16 million by 2050. One in 8 people 65 years or older and nearly half of people 85 years or older have AD, which is the fifth leading cause of death for people 65 years or older. Age, female sex, African-American and Hispanic ethnicities, hypertension, hyperlipidemia, diabetes mellitus, smoking, head trauma, poor socioeconomic status, low education, and environmental and occupational exposures (eg, pesticides or other environmental pollutants) are risk factors for AD. In addition to cognitive and physical exercise, a diet rich in antioxidants, fish oil, B-complex and C vitamins, and alcohol in moderation have been proposed as protective factors. Mendelian mutations in the amyloid precursor protein gene (*APP*) on chromosome 21, presenilin 1 (*PSEN1*) on chromosome 14, and presenilin 2 (*PSEN2*) on chromosome 1, cause autosomal-dominant early-onset forms of AD, which account for less than 1% of this condition.

Additionally, AD develops at an earlier age in patients with trisomy 21 or *APP* triplication. Late-onset AD, broadly defined as occurring after 65 years of age, also has a substantial genetic component, accounting for up to 80% of disease risk. *APOE* on chromosome 19 has 3 major isoforms (ε2, ε3, ε4), of which *APOE* ε4 associates with risk of late-onset AD, but it is neither necessary nor sufficient for

its development, unlike the deterministic, early-onset AD mutations. A single copy of the *APOE* ε4 allele increases the risk of AD by 3 to 4 times, and persons with both copies have a 10 to 13 times greater risk than those who lack this risk allele. *APOE* is estimated to account for about 20% of the risk of AD based on population studies. Recently, large genome-wide scans identified 9 additional genetic loci (near the following genes: *ABCA7, BIN1, CD2AP, CD33, CLU, CR1, EPHA1, MS4A4A, PICALM*) that are associated with risk of AD, although the actual disease genes and their functional variants underlying this risk remain to be established.

The risk for AD is likely due to a combination of different genetic and environmental factors and their interaction. Discovery of these factors is essential for understanding the pathophysiology of this condition and effective drug development.

Pathophysiology and Pathology

AD has 2 pathologic hallmarks, namely, senile plaques, composed mainly of extracellular deposits of Aβ, and neurofibrillary tangles, which consist of intraneuronal accumulation of the microtubule-associated protein tau (Figure 30.2). Aβ is a neurotoxic peptide generated by processing of the amyloid precursor protein, a transmembrane protein, via 2 enzymatic activities, β- and γ-secretase. Presenilins are integral components of the γ-secretase enzyme complex. Thus, all 3 genes that have causative mutations leading to early-onset forms of AD play key roles in Aβ metabolism, which led to the generation of the "amyloid cascade hypothesis" as the proposed central pathogenic event in AD. According to this hypothesis, increased Aβ (due to greater production or lesser degradation) results in a cascade of events, including inflammation, abnormal phosphorylation and accumulation of tau, and synaptic loss with eventual cell loss, resulting in dementia. *APOE* and other novel genes implicated in AD suggest additional pathophysiologic mechanisms for this complex disease, including lipid metabolism, cell signaling, and trafficking pathways.

The distribution and density of amyloid plaques and neurofibrillary tangles are associated with increasing disease severity. Although there are different morphologic types of senile plaques (eg, diffuse, cotton-wool), neuritic plaques, which are characterized by Aβ centers surrounded by dystrophic neurites that often stain for phosphorylated tau, correlate most closely with neuronal injury. Neurofibrillary tangles are proposed to propagate from the entorhinal cortex in the earliest neuropathologic stage of AD to the neocortex in the latest stages, with ultimate involvement of the primary motor and sensory cortices. In atypical forms of AD presenting with nonmemory symptoms, neuropathologic evidence of AD is often more pronounced in the relevant brain region (eg, early involvement of the occipital cortex in visual variant of AD).

Other neuropathologic findings in AD include neuronal or synaptic loss, gliosis, granulovacuolar degeneration, cerebral amyloid angiopathy, argyrophilic grain disease, and transactive response DNA-binding protein (TDP-43)–immunoreactive inclusions. AD neuropathologic changes can coexist with other comorbidities, including Lewy body disease, vascular disease, and hippocampal sclerosis.

On gross pathologic examination, the typical AD brain shows atrophy of the medial temporal and parietal lobes with ventricular dilatation (Figure 30.3). Focal atrophy of other brain regions may occur in atypical presentations of AD.

Clinical Features

AD is typically characterized by an insidious onset of memory problems that impair daily function and gradually progress to also involve nonmemory domains. In 1984, the National Institute of Neurological, Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) proposed criteria for definite, probable, and possible AD (Box 30.1).

In 2011, the National Institute on Aging-Alzheimer's Association workgroups suggested new criteria for AD based on clinical and research evidence. The proposed core criteria are for dementia, probable AD, and possible AD. The new criteria do not require memory impairment for AD diagnosis and accept that AD can present as nonamnestic variants, including the visual variant (ie, posterior cortical atrophy syndrome), with deficits in visuospatial functioning (eg, difficulty recognizing faces or objects, simultanagnosia, alexia), language variant with prominent word-finding difficulties (ie, logopenic primary progressive aphasia syndrome), and executive dysfunction with impairment in reasoning, judgment, and decision-making abilities. All cases of probable AD by the proposed 2011 criteria would also fit the 1984 criteria for probable AD. Patients with possible AD according to the new criteria, have an atypical course, concomitant cerebrovascular disease, features of dementia with Lewy bodies, or "evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition." Not all patients with possible AD by the 2011 proposed criteria would meet the 1984 NINCDS-ADRDA criteria of possible AD. A new diagnostic category, "probable AD with increased level of certainty," incorporates information from subsequent evaluations or causative genetic mutations.

There are new proposed criteria for "probable or possible AD with evidence of the AD pathophysiologic process" based on biomarker data. However, these criteria are for research purposes and are not yet intended for clinical use. Clinical presentation of AD can also include multiple neuropsychiatric symptoms, such as apathy, anxiety,

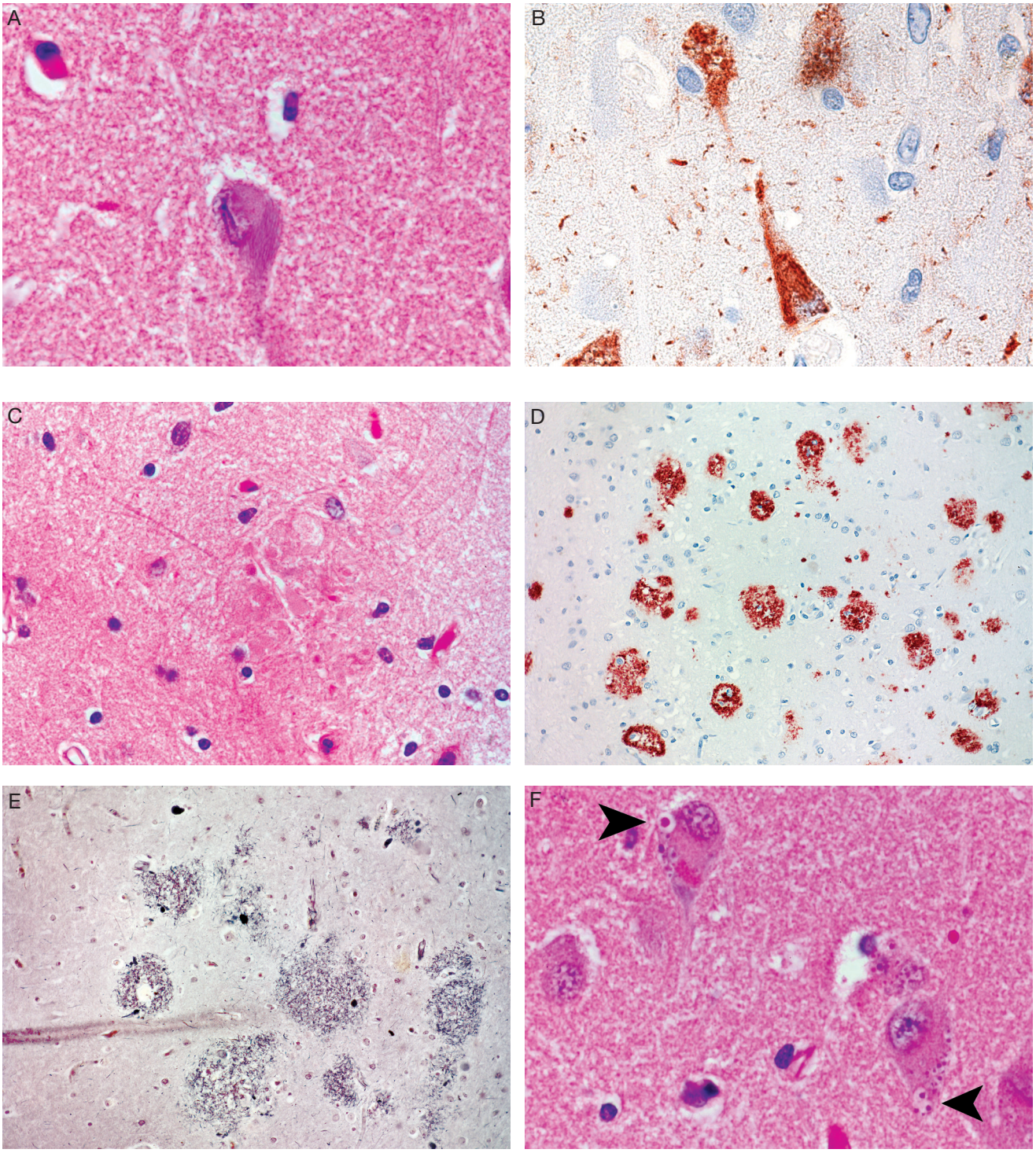

Figure 30.2 *Histologic Findings in Alzheimer Disease.*
Neurofibrillary tangles are faintly basophilic and may be flame-shaped (A and B) or globular filamentous structures. They are neuronal inclusions composed of aggregates of hyperphosphorylated tau protein as paired helical filaments and are usually best demonstrated with tau immunohistochemistry (B). C, Diffuse plaques: extracellular, poorly defined depositions of amyloid protein. They may be detected better with use of β-amyloid immunohistochemistry (D) or Bielschowsky silver stain (E). Granulovacuolar degeneration may be seen in some neurons (F, arrowheads).
(Adapted from Mowzoon N. Behavioral Neurology. Part B: Syndromes of cognitive dysfunction. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 297–332. Used with permission of Mayo Foundation for Medical Education and Research.)

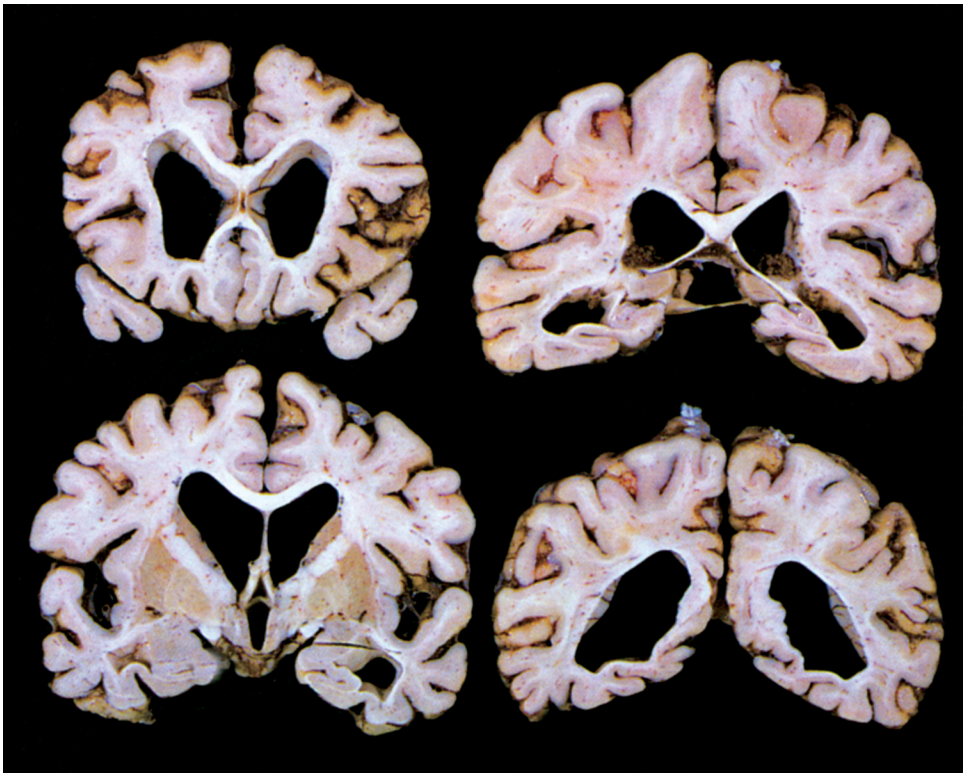

Figure 30.3 *Gross Specimen of a Brain With Alzheimer disease.*
Note profound bilateral hippocampal atrophy disproportionate to diffuse cortical atrophy.
(Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York (NY): Gower Medical Publishing; c1988. p. 220. Used with permission of Mayo Foundation for Medical Education and Research.)

depression, delusions, hallucinations, agitation, irritability, dysphoria, disinhibition, and euphoria.

Diagnosis

The clinical approaches and tests routinely used in the diagnosis of AD are the same as those used in the diagnosis of MCI discussed above. A Mini-Mental State Examination score of less than 24 of 30 may suggest dementia (87% specificity; 82% sensitivity).

Brain computed tomography or structural MRI often shows atrophy of medial and lateral temporal lobe structures (eg, hippocampi), inferior parietal lobe, and insula (Figure 30.4). MRI with contrast is indicated in patients with a history of cancer. Formal neuropsychologic testing should be pursued in all subjects to evaluate severity and pattern of cognitive impairment and to obtain a baseline, although this should not be done in patients in more severe stages of AD (Mini-Mental State Examination score ≤15 can be used as an approximate threshold) as it is unlikely to be beneficial because of decline in cognition globally at this stage.

Other biomarkers that can increase the certainty of diagnosis of an underlying AD pathophysiologic process are ^{18}FDG-PET, low cerebrospinal fluid levels of Aβ42, high

Box 30.1 • Criteria for Diagnosis of Alzheimer Disease

I. Criteria for clinical diagnosis of *probable* Alzheimer disease
   a. Dementia established by clinical examination, documented by mental status examination, and confirmed by neuropsychologic tests
   b. Deficits in 2 or more areas of cognition
   c. Progressive worsening of memory and other cognitive functions
   d. No disturbance of consciousness
   e. Onset between ages 40–90 years, most often after age 65 *and*
   f. Absence of systemic disorders or other brain diseases that in and of themselves could account for progressive deficits in memory and cognition

II. Diagnosis of *probable* Alzheimer disease is supported by
   a. Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)
   b. Impaired activities of daily living and altered patterns of behavior
   c. Family history of similar disorders, particularly if confirmed with pathologic examination *and*
   d. Laboratory results of

(Continued on next page)

i. Normal CSF examination with lumbar puncture
ii. Normal pattern or nonspecific changes on EEG (an example of the latter may be increased diffuse slow-wave activity or bitemporal slowing)
iii. Neurodiagnostic evidence of cerebral atrophy with progression documented by serial observation

III. Other clinical features consistent with the diagnosis of *probable* Alzheimer disease, after *exclusion* of causes of dementia other than Alzheimer disease, include
   a. Plateau in the course of progression of the illness
   b. Associated symptoms of depression; insomnia; incontinence; delusions; illusions; hallucinations; catastrophic verbal, emotional, or physical outbursts; sexual disorders; and weight loss
   c. Other neurologic signs and symptoms such as increased muscle tone, gait disorder, and myoclonus
   d. Seizures in advanced age
   e. Normal neuroimaging features for age
IV. Features that make the diagnosis of *probable* Alzheimer disease *uncertain* or *unlikely* include
   a. Sudden, apoplectic onset
   b. Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness
   c. Seizures or gait disturbances at the onset or very early in the course of the illness
V. Clinical diagnosis of *possible* Alzheimer disease
   a. May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course
   b. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia
   c. Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause
VI. Criteria for diagnosis of *definite* Alzheimer disease are
   a. Clinical criteria for probable Alzheimer disease
   b. Histopathologic evidence obtained from biopsy or autopsy
VII. Classification of Alzheimer disease for research purposes should specify features that may differentiate subtypes of the disorder, such as
   a. Familial occurrence
   b. Onset before age 65 years
   c. Presence of trisomy 21
   d. Coexistence of other relevant conditions such as Parkinson disease

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram.

Adapted from McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939–44. Used with permission.

phosphorylated and total tau, presence of amyloid by 11C-PiB-PET, or other amyloid PET imaging methods. As in MCI, currently these biomarkers are not recommended for routine diagnostic purposes in AD. ^{18}FDG-PET or single-photon emission computed tomography can sometimes be used to differentiate AD (involvement of temporal, parietal, frontal regions) from frontotemporal dementia (involvement of frontal and temporal regions), but these studies are not definitive.

Additional tests such as electroencephalography and other laboratory studies, including inflammatory marker tests, paraneoplastic panel, human immunodeficiency virus testing, Lyme disease serologic tests, or spinal tap should be reserved for atypical presentations, including early or abrupt onset, fluctuations, rapid decline, and systemic signs and symptoms (eg, fever, weight loss). In patients with early-onset disease who have a strong family history, genetic testing for causative mutations in *APP, PSEN1*, and *PSEN2* may be considered and requires medical-genetics counseling both before and after testing. No other genetic testing is recommended in AD, including *APOE*.

Management

Two classes of medications used to treat AD are acetylcholinesterase inhibitors and an *N*-methyl-D-aspartate antagonist (Table 30.1). Acetylcholinesterase inhibitors are approved by the US Food and Drug Administration for mild to moderate AD and include donepezil, rivastigmine, galantamine, and tacrine, although tacrine is not used in the clinical setting because of its hepatotoxicity. Other acetylcholinesterase inhibitors may cause adverse effects such as nausea, vomiting, diarrhea, muscle cramps, anorexia, and vivid dreams. They should be used with caution in people who have underlying cardiovascular disease because of their potential to cause bradycardia or arrhythmias. A baseline electrocardiogram is generally recommended to rule out atrial fibrillation or heart block, which can be worsened by these medications. Additional caution should be exercised in patients with chronic obstructive pulmonary disease or asthma. Dose adjustments may be necessary based on adverse effects.

All of these medications *may* improve cognitive and noncognitive symptoms of AD but *do not* alter the pathophysiologic process or course of the disease. They have been shown to slow cognitive decline, although this result is not sustained. Proposed protective factors for reducing cognitive decline in AD include physical and mental activity, moderate amount of alcohol, Mediterranean diet, foods rich in curcumin and antioxidants, and low intake of saturated fatty acids. Disease-modifying agents such as β- and γ-secretase inhibitors and active and passive immunization strategies targeting Aβ are currently in clinical trials.

For management of neuropsychiatric symptoms in AD, including agitation, psychosis, apathy, and depression,

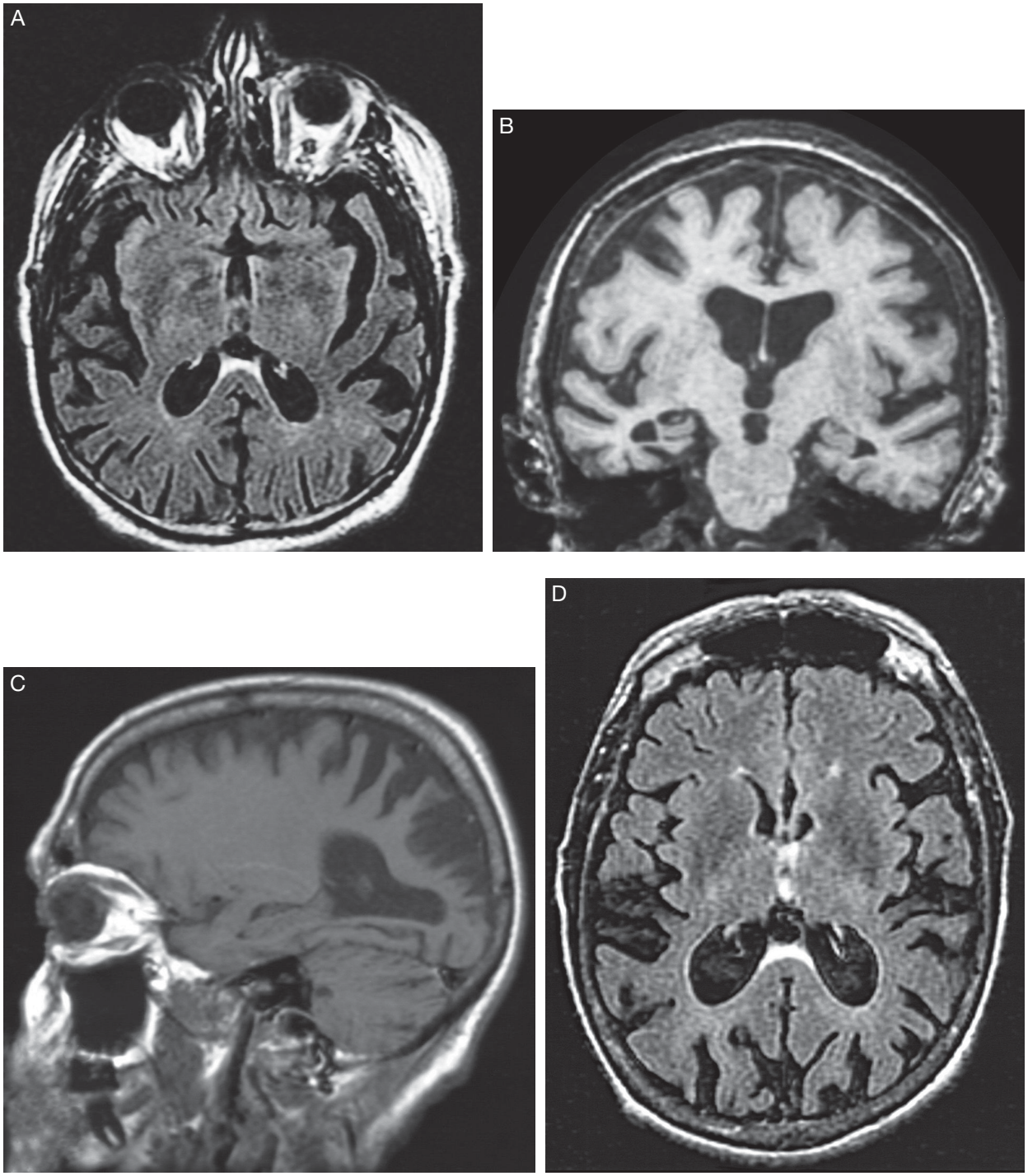

Figure 30.4 *Neuroimaging in Alzheimer Disease.*
A, Axial fluid-attenuated inversion recovery sequence demonstrating bitemporal atrophy. Mesial temporal structures and hippocampi are better seen in coronal sequences (B). B, Coronal T1-weighted image shows asymmetric, bilateral hippocampal atrophy, which seems more prominent on the right. There is also diffuse cortical atrophy, but the degree of hippocampal atrophy is more pronounced. C, Sagittal T1-weighted and, D, axial FLAIR images from another patient with Alzheimer disease who presented with Balint syndrome. Note the prominent occipitoparietal atrophy in both C and D.
(Adapted from Mowzoon N. Behavioral Neurology. Part B: Syndromes of cognitive dysfunction. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 297–332. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 30.1 • Medications Commonly Used for Alzheimer Dementia

Drug	Mechanism	Available	Common Dose	Adverse Effects
Donepezil	Acetylcholinesterase inhibitor	5-mg tablet 10-mg tablet 23-mg tablet (also disintegrating oral tablets)	5 mg daily for 4–8 weeks, then increase to 10 mg daily	Nausea, anorexia, bradycardia, muscle cramps, diarrhea, vivid dreams Use with caution in patients with cardiovascular disease (potential for arrhythmia or bradycardia)
Galantamine	Acetylcholinesterase inhibitor	4-mg tablet 8-mg tablet 12-mg tablet (also extended-release formulation and oral solution)	4 mg twice daily for 30 days, then 8 mg twice daily for 30 days, then 12 mg twice daily	Similar to effects listed above
Rivastigmine	Acetylcholinesterase and butyrylcholinesterase inhibitor	Oral 1.5-mg tablet 3-mg tablet 6-mg tablet Transdermal patch 4.6-mg/24-h patch 9.5-mg/24-h patch 13.3-mg/24-h patch	1.5 mg twice daily for 30 days, then 3 mg twice daily, then increase to 6 mg twice daily if tolerated	Similar to effects listed above Patch may have fewer gastrointestinal effects, but it can result in skin irritation; useful for patients with swallowing problems
Memantine	NMDA receptor antagonist	5-mg tablet 10-mg tablet (also available in oral solution and extended release)	5 mg orally daily and increase at a minimum of 1-week intervals by 5 mg to a goal dose of 10 mg twice daily Dose adjustment for renal disease	Confusion, dizziness, headaches

Abbreviation: NMDA, *N*-methyl-D-aspartate.

underlying medical problems should first be ruled out (eg, urinary tract infection, cardiac disease, pneumonia). Medications should be reviewed, and use of those with anticholinergic (antihistamines, oxybutynin, tricyclic antidepressants) or sedative properties (benzodiazepines, anticonvulsants), opioids, and other pain medications should be discontinued or replaced with alternatives without cognitive adverse effects when possible. Nonpharmacologic management of behavioral symptoms should be pursued initially by interventions such as assessing the environment for disruptions or discomfort, reassurance, distraction, or exercise. Sleep problems, including insomnia, sleep apnea, and rapid-eye-movement sleep behavior disorder, should be identified and treated.

Pharmacologic management may be necessary if behavioral management techniques are not sufficient or if there is risk of harm to the patient or others. Selective serotonin reuptake inhibitors are commonly used for depression. Acetylcholinesterase inhibitors or stimulants may be helpful for the management of apathy. Trazodone may be useful for agitation. Antipsychotic agents carry a black-box warning for use in elderly patients with dementia because of an increased risk of death, but they can be helpful for treating psychotic and agitated behaviors if used with caution for a limited time. Atypical agents such as quetiapine, risperidone, or olanzapine are preferred over typical agents because of their better adverse effect profile. A baseline electrocardiogram and another one after achieving maintenance dosing is recommended with these agents given their effects on QT prolongation. Anticonvulsants such as valproic acid may also be prescribed for controlling agitation and disruptive behavior.

Other, nonpharmacologic aspects of managing AD include counseling about safety issues (eg, supervision of medications) and finances, establishing appropriate caregiver support in later stages of the disease, and obtaining a driver's evaluation or recommending driving cessation. Patients and caregivers may benefit from educational seminars at memory disorder clinics and support group meetings. Families should be directed to the local chapter of the Alzheimer's Association for additional resources.

- AD is the most common cause of dementia in the United States and worldwide.
- A single copy of the *APOE* ε4 allele increases the risk of AD by 3 to 4 times, and persons with both copies have a 10 to 13 times greater risk than those who lack this risk allele.
- AD has 2 pathologic hallmarks, namely, senile plaques, composed mainly of extracellular deposits of Aβ, and neurofibrillary tangles, which consist of intraneuronal accumulation of the microtubule-associated protein tau (Figure 30.2).
- Neurofibrillary tangles are proposed to propagate from the entorhinal cortex in the earliest neuropathologic stage of AD to the neocortex in the latest stages, with ultimate involvement of the primary motor and sensory cortices.
- A Mini-Mental State Examination score of less than 24 of 30 may suggest dementia (87% specificity; 82% sensitivity).
- Before treatment of AD with acetylcholinesterase inhibitors, a baseline electrocardiogram is generally recommended to rule out atrial fibrillation or heart block, which can be worsened by these medications.
- Additional caution should be exercised when using acetylcholinesterase inhibitors in patients with chronic obstructive pulmonary disease or asthma.
  Dose adjustments may be necessary based on adverse effects.

31 Frontotemporal Dementias

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Introduction

Frontotemporal dementia **(FTD)** is a broad clinical term that includes disorders caused by the progressive degeneration of the frontal and temporal lobes. Frontal lobe functions include personality control, executive function, and verbal expression. The temporal lobe is associated with behavior and language perception. FTD is clinically characterized by progressive personality and behavioral changes and deficits in executive and language functions. Memory problems are not prominent during the early stage of illness.

The clinical spectrum of FTD encompasses 2 distinct clinical variants, depending on which brain regions are primarily damaged (Figure 31.1): the behavioral variant FTD (bvFTD) and the language variant (primary progressive aphasia [PPA]). The language variant is further divided into 3 clinical variants: nonfluent or agrammatic variant PPA (NFAV-PPA), semantic variant PPA (SV-PPA), and logopenic variant PPA (LV-PPA). FTD can also be accompanied by motor neuron disease (MND) and by atypical parkinsonian disorders, such as corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). Some investigators believe that CBS and PSP should be considered an FTD given the shared abnormality (accumulated tau protein); however, this nomenclature continues to evolve.

- FTD is clinically characterized by progressive personality and behavioral changes and deficits in executive and language functions.
- The clinical spectrum of FTD encompasses 2 distinct clinical variants, depending on which brain regions are primarily damaged (Figure 31.1): the behavioral variant FTD (bvFTD) and the language variant (primary progressive aphasia [PPA]).

Epidemiology

FTD is the second most common early-onset dementia; however, its exact incidence and prevalence remain unclear. The incidence rate for FTD is between 2.7 and 15 cases per 100,000 in the age group 45 to 64 years. The average age at symptomatic disease onset for FTD is 50 to 60 years. Disease duration is between 6 and 11 years, whereas disease duration of FTD accompanied by MND is approximately 3 years. There are no sex differences in FTD; however, men tend to be more frequently affected by both bvFTD and SV-PPA than women. Additionally, women may be affected by NFAV-PPA more than men.

- The average age at symptomatic disease onset for FTD is 50 to 60 years.

Abbreviations: AD, Alzheimer disease; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; ECD-SPECT, ethyl cysteinate dimer single-photon emission computed tomography; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; FTD, frontotemporal dementia; FTLD, frontotemporal lobe degeneration; FTLD-tau, frontotemporal lobe degeneration with tau inclusions; FTLD-TDP, frontotemporal lobe degeneration with ubiquitin and transactive response DNA-binding protein-43–positive inclusions but tau-negative inclusions; HMPAO-SPECT, hexamethylpropyleneamine oxime single-photon emission computed tomography; LV-PPA, logopenic variant primary progressive aphasia; MND, motor neuron disease; MRI, magnetic resonance imaging; NFAV-PPA, nonfluent/agrammatic variant primary progressive aphasia; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; SV-PPA, semantic variant primary progressive aphasia

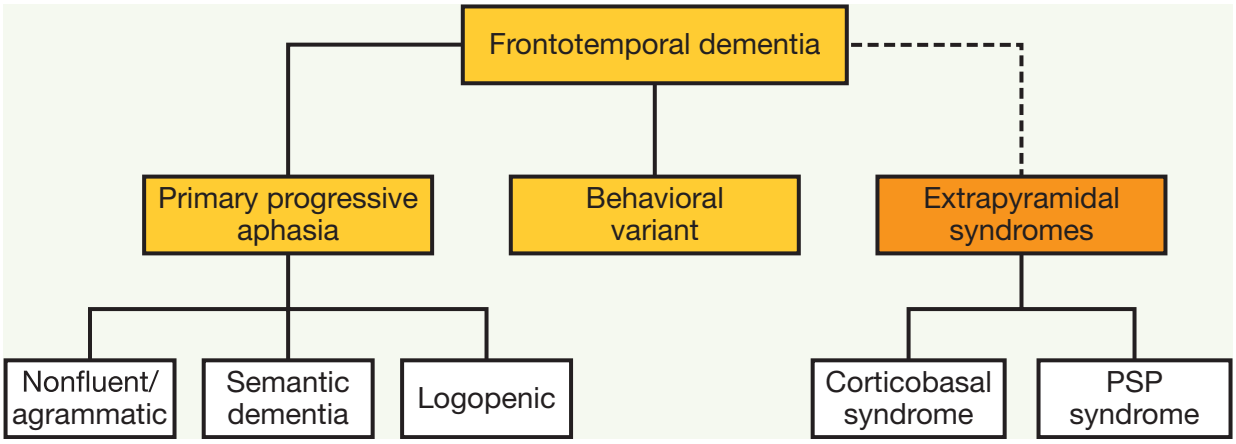

Figure 31.1 *Variants of Frontotemporal Dementia. PSP indicates progressive supranuclear palsy.*

- Disease duration is between 6 and 11 years, whereas disease duration of FTD accompanied by MND is approximately 3 years.

Genetics

Approximately 20% to 25% of patients with FTD have a positive family history for this disease, which is usually suggestive of an autosomal dominant inheritance pattern. Up to 50% of patients with bvFTD have a positive family history. This percentage is much lower in patients with SV-PPA and NFAV-PPA.

Recently, pathogenic gene mutations have been identified (Table 31.1). The 3 most frequent mutations are in *MAPT, C9orf72*, and *PGRN* genes (Table 31.2), followed by the *VCP* gene. Mutations in the *CHMP2B, TARDBP, SQSTM1, UBQLN2*, and *FUS* genes are rare. Mutations in the *VCP* gene result in FTD with myopathy and Paget disease.

- Approximately 20% to 25% of patients with FTD have a positive family history for this disease, which is usually suggestive of an autosomal dominant inheritance pattern.
- Up to 50% of patients with bvFTD have a positive family history.

Histopathology

Frontotemporal lobe degeneration (FTLD) is the common underlying abnormality of FTD. Macroscopically, there is

Table 31.1 • Comparison of the Gene Proteins and Functions of Genetic Forms of Frontotemporal Dementia

Gene	Chromosome	Gene Protein	Function
MAPT	17q21.1	Tau	Stabilizes microtubles in neurons; important for cell shape, cell division, and axonal transport
PGRN	17q21.31	Progranulin	Progranulin is a secreted growth factor that functions in multiple cellular processes such as development, wound repair, and inflammation
C9orf72	9p21.2	C9orf72	Present in the neuronal cytoplasm and in the presynaptic terminals; unknown function
VCP	9p13.3	Valosin-containing protein	Cell division, fusing membranes within cells, reassembling cell structures after cell division, preventing apoptosis of cells, repairing DNA damage
CHMP2B	3p11.2	Charged multivesicular body protein 2B	Important for neuronal survival
TARDBP	1p36.2	Transactive response DNA-binding protein (TDP-43)	Binds DNA to regulate transcription
SQSTM1	5q35	p-62	Proteasome-dependent proteolysis
UBQLN2	Xp11.21	Ubiquilin 2	Regulates degradation of ubiquinated proteins through a ubiquitin proteasome system
FUS	16p.11.2	Fused in sarcoma gene	Bind DNA to regulate transcription

Table 31.2 • Comparison of the Most Common Inherited Frontotemporal Dementias

Gene	Chromosome Inheritance	Protein	Mean Age at Onset (Range) and Duration, y	Clinical Features
MAPT	17q21.1 AD	Tau	50 (25–76) Duration: 7	Early: personality and behavioral changes; ± parkinsonism Asymmetric rigidity Eye movement abnormalities Late: executive dysfunction, visuospatial dysfunction, pyramidal symptoms
C9orf72	9p21.2	C9orf72	58 (30–76) Duration: 6	Behavioral variant FTD Parkinsonism (35%) Motor neuron disease
PGRN	17q21.31 AD	Progranulin	60 (48–83) Duration: 7	Early: behavioral or personality changes, language impairment, and psychiatric disease; ± parkinsonism Late: dysphagia, mutism, pyramidal signs, myoclonus

Abbreviations: AD, autosomal dominant; FTD, frontotemporal dementia; ±, with or without.

selective atrophy of the frontal and temporal cortex (Figure 31.2). Microscopically neuronal loss, gliosis, and spongiosis of the superficial layers are seen.

FTLD can be divided into 2 major subgroups: with tau-positive inclusions (FTLD-tau) and with ubiquitin and transactive response DNA-binding-43–positive inclusions but tau-negative inclusions (FTLD-TDP). These pathologic subtypes are associated with genetic mutations. FTLD-tau is frequently caused by mutations in the *MAPT* gene. FTLD-TDP is frequently caused by genetic mutations in the *PGRN* gene, *C9orf72* gene, and *VCP* gene. A minority of FTLD cases have yet another type of abnormality—ubiquitin-positive, TDP-43 negative, and *FUS*-positive (FTLD-*FUS*)—that is not necessarily associated with genetic defects in the *FUS* gene.

bvFTD could be pathologically characterized either by FTLD-tau and FTLD-TDP or even occasionally by FTLD-*FUS*. NFAV-PPA is characterized by FTLD-tau abnormality, albeit in some cases FTLD-TDP, Alzheimer disease (AD), or Pick body abnormality can be present. SV-PPA is usually characterized by FTLD-TDP abnormality and only rarely by FTLD-tau or AD abnormality. FTLD-MND is characterized by FTLD-TDP abnormality. LV-PPA is characterized by AD abnormality, and rarely by FTLD-tau and FTLD-TDP.

- FTLD can be divided into 2 major subgroups: with tau-positive inclusions (FTLD-tau) and with ubiquitin and TDP-43-positive inclusions but tau-negative inclusions (FTLD-TDP).

Clinical Features

There are 2 major FTD variants: bvFTD and PPA. bvFTD is the most common variant of FTD and accounts for approximately half of all cases. PPA is divided into 3 variants: NFAV-PPA, SV-PPA, and LV-PPA. All of the variants of FTD can occur simultaneously with MND (FTD-MND); simultaneous occurrence is most frequent in bvFTD, occasional in NFAV-PPA, and very rare in SV-PPA and LV-PPA. Additionally, there is clinical overlap with other degenerative disorders such as PSP and corticobasal degeneration.

Behavioral Type

Criteria for bvFTD are listed in Box 31.1. The symptoms are related to the location of anatomical damage. bvFTD is topographically associated with symmetrical frontal and anterior temporal dysfunction.

bvFTD is a syndrome characterized by progressive personality and behavioral deterioration. In the early stage of the illness, patients may exhibit disinhibition, apathy, inertia, loss of empathy, perseveration, stereotyped or compulsive behavior, and lack of initiation. During the course of the illness, hyperorality, dietary changes, and executive deficits can also develop. Some patients have language difficulties, including problems with naming, motor speech production, and grammar. MND develops in less than 20% of patients, and approximately 10% present with parkinsonism resembling the akinetic-rigid type. Patients only rarely present with memory impairment. However, in patients with late onset of disease (>65 years), memory impairments are more common but behavioral and personality changes are less common, findings that could lead to misdiagnosis.

MND can be associated with this variant, more commonly than with the other variants.

Structural brain magnetic resonance imaging (MRI) shows the frontal or anterior temporal lobe atrophy (Figure 31.2A and 31.2B). ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and technetium Tc 99m-hexamethylpropyleneamine oxime single-photon

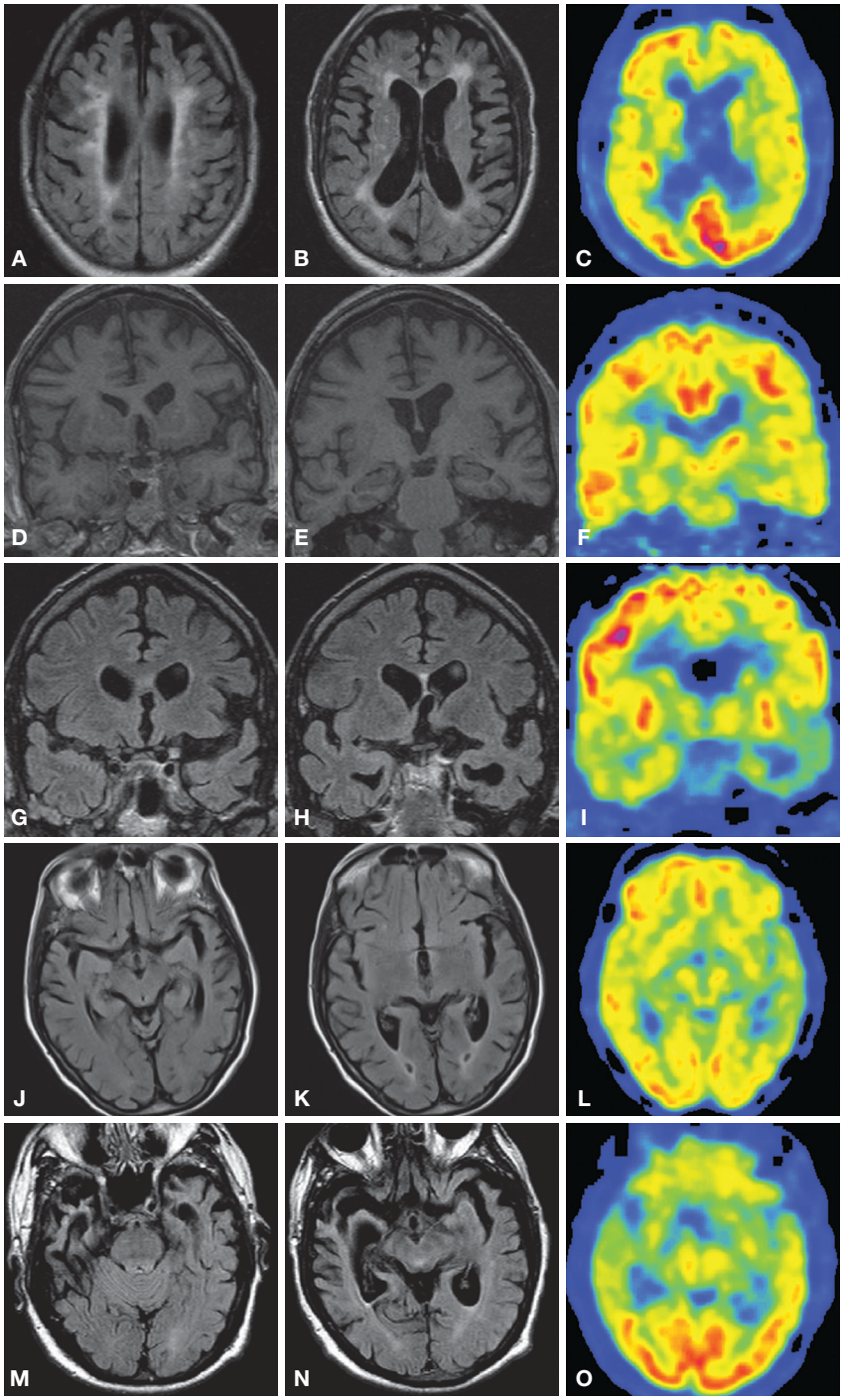

Figure 31.2 *Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) of Each Variant of Frontotemporal Dementia.*

Bilateral frontal and anterior temporal lobe atrophy on axial fluid-attenuated inversion recovery (FLAIR) MRI (A and B) and hypometabolism in bilateral frontotemporal lobes on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) (C) in a patient with behavior variant of frontotemporal dementia. Left anterior perisylvian atrophy on coronal T1-weighted MRI images (D and E) and hypometabolism in the posterior frontal, parietal, and temporal lobes on FDG-PET (F) in a patient with nonfluent or agrammatic variant primary progressive aphasia (PPA). Left-side predominant anterior temporal lobe atrophy on coronal FLAIR MRI images (G and H) and hypometabolism in the left-side predominant temporal lobes on FDG-PET (I) in a patient with semantic variant PPA. Left posterior perisylvian atrophy on axial T1-weighted MRI images (J and K) and hypometabolism in the left temporal lobe on FDG-PET (L) of a patient with logopenic variant PPA. Right-side predominant temporal lobe atrophy on FLAIR MRI images (M and N) and hypometabolism in the left-side predominant temporal lobe on FDG-PET (O) in a patient with right temporal variant frontotemporal dementia clinically presenting with semantic dementia.

Box 31.1 • International Consensus Criteria for Behavioral Variant FTD (FTDC)

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD:

A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant)

II. Possible bvFTD

Three of the following behavioral/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events

A. Early[a] behavioral disinhibition (one of the following symptoms [A.1–A.3] must be present):
  A.1. Socially inappropriate behavior
  A.2. Loss of manners or decorum
  A.3. Impulsive, rash, or careless actions

B. Early apathy or inertia (one of the following symptoms [B.1–B.2] must be present):
  B.1. Apathy
  B.2. Inertia

C. Early loss of sympathy or empathy (one of the following symptoms [C.1–C.2] must be present):
  C.1. Diminished response to other people's needs and feelings
  C.2. Diminished social interest, interrelatedness, or personal warmth

D. Early perseverative, stereotyped, or compulsive/ritualistic behavior (one of the following symptoms [D.1–D.3] must be present):
  D.1. Simple repetitive movements
  D.2. Complex, compulsive, or ritualistic behaviors
  D.3. Stereotypy of speech

E. Hyperorality and dietary changes (one of the following symptoms [E.1–E.3] must be present):
  E.1. Altered food preferences
  E.2. Binge eating, increased consumption of alcohol or cigarettes
  E.3. Oral exploration or consumption of inedible objects

F. Neuropsychologic profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following symptoms [F.1–F.3] must be present):
  F.1. Deficits in executive tasks
  F.2. Relative sparing of episodic memory
  F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria:

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

C. Imaging results consistent with bvFTD (one of the following [C.1–C.2] must be present):
  C.1. Frontal and/or anterior temporal atrophy on MRI or CT
  C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioral variant FTD with definite FTLD pathology

Criterion A and either criterion B or C must be present to meet criteria

A. Meets criteria for possible or probable bvFTD

B. Histopathologic evidence of FTLD on biopsy or at postmortem

C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD

A. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders

B. Behavioral disturbance is better accounted for by a psychiatric diagnosis

C. Biomarkers strongly indicative of Alzheimer disease or other neurodegenerative process

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; CT, computed tomography; FTDC, International Behavioural Variant Frontotemporal Dementia Criteria Consortium; FTLD, frontotemporal lobe degeneration; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

[a] As a general guideline, *early* refers to symptom presentation within the first 3 years.

Adapted from Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011 Sep;134(Pt 9):2456–77. Epub 2011 Aug 2. Used with permission.

emission computed tomography (HMPAO-SPECT) or technetium Tc 99m-ethyl cysteinate dimer single-photon emission computed tomography (ECD-SPECT) show hypometabolism or hypoperfusion in the frontal or anterior temporal lobes (Figure 31.2C).

Primary Progressive Aphasia

Nonfluent or Agrammatic Variant

NFAV-PPA is topographically associated with damage in the left frontal and insular cortex. It is a syndrome that is characterized by progressive deterioration in speech production. Patients have agrammatism, sound distortions and deletions, and inappropriate substitutions. Patients may also have impaired motor speech functions such as effortful language output, nonfluent speech, and reduced rate of speech. Single-word comprehension and naming are initially spared; however, they are impaired in the later stage of the illness. Sentence repetition may also be impaired, but object knowledge is relatively spared. Behavioral changes, such as apathy and poor motivation, are less common.

Patients may also have development of akinetic-rigid parkinsonism, myoclonus, and apraxia, which are all suggestive of a diagnosis of CBS. In other patients, parkinsonian rigidity is symmetrical with the presence of vertical gaze palsy, which is suggestive of a diagnosis of PSP.

Brain MRI shows left anterior perisylvian atrophy (Figure 31.2D and 31.2E). FDG-PET and HMPAO-SPECT show predominant hypometabolism or hypoperfusion in the same region (Figure 31.2F).

Semantic Variant

SV-PPA is associated with degeneration in the ventral and lateral portions of the anterior temporal cortex, and this usually involves the left side more than right, given the language disturbance. If the right side is more involved than the left, then the patient may have prosopagnosia. SV-PPA is a syndrome characterized by progressive loss of vocabulary. Deficits in confrontation naming and single-word comprehension are the prominent features. Grammar, motor speech, and sentence repetition are spared, although some patients have semantic paraphasias. Sentence comprehensions and object knowledge are impaired. In the later stages of the illness, patients may have behavioral changes, such as obsessive behavior and disinhibition. Parkinsonism is uncommon.

Structural brain MRI shows left anterior temporal lobe atrophy (Figure 31.2G and 31.2H). FDG-PET and HMPAO-SPECT show predominant hypometabolism or hypoperfusion in the same region (Figure 31.2I).

Logopenic Variant

LV-PPA is associated with damage in the left posterior temporal and inferior parietal cortex. It is characterized by difficulty in word finding. Impaired single-word retrieval and sentence repetition are common. Patients have a slow rate of speech; however, prosody and articulation are preserved. Single-word comprehension is relatively spared, whereas sentence comprehension is markedly impaired. Patients do not commonly have behavioral abnormalities or personality changes until the late stage of illness. Dysphagia may also occur as a late manifestation. Most patients are able to take care of their daily needs until late in the disease course.

Structural brain MRI detects atrophy in the predominant left posterior perisylvian or parietal lobe (Figure 31.2J and 31.2K). FDG-PET and ECD-SPECT show predominant hypometabolism or hypoperfusion in the left temporal-parietal junction (Figure 31.2L).

Clinical characteristics of the 3 variants of PPA are summarized in Table 31.3.

Table 31.3 • Clinical Characteristics of Each Variant of Primary Progressive Aphasia

Characteristic	NFAV-PPA	SV-PPA	LV-PPA
Grammar	Impaired (short, simple phrases and omissions of grammatical morphemes)	Spared	Spared
Motor speech	Slow and effortful speech Disrupted prosody Disrupted articulation	Spared	Slow speech Preserved prosody Preserved articulation
Sound errors	Distortions, deletions, substitutions, insertions, transpositions of speech sounds	Spared	Substitutions
Confrontation naming	Impaired	Impaired	Impaired
Word finding	Impaired in the later stage	Impaired	Impaired
Sentence and phrase repetition	May be impaired	Spared	Impaired
Single-word comprehension	Spared	Impaired	Spared
Sentence comprehension	Impaired	Impaired	Impaired
Object knowledge	Spared	Impaired	Spared
Behavioral and personality changes	Rare	May occur	Rare
Episodic memory	Relatively spared	Relatively spared	Impaired
Extrapyramidal signs	May occur in the later stage	Rare	Rare
MRI/localization	Left anterior perisylvian atrophy	Atrophy of left anterior temporal lobe	Atrophy of the left posterior perisylvian or parietal lobe

Abbreviations: LV-PPA, logopenic variant primary progressive aphasia; MRI, magnetic resonance imaging; NFAV-PPA, nonfluent/agrammatic variant primary progressive aphasia; SV-PPA, semantic variant primary progressive aphasia.

Right Temporal Variant

The right temporal variant of FTD is a rare form that predominantly affects the right side of the brain. It can be clinically divided into to 2 subtypes: bvFTD and semantic dementia. The bvFTD type of the right temporal variant of FTD is clinically characterized by personality and behavioral changes, executive dysfunction, and parkinsonism. The semantic dementia form of right temporal variant FTD is clinically characterized by word-finding and comprehension difficulties, prosopagnosia, topographagnosia, personality changes, and behavior changes. Structural brain MRI shows right-side predominant temporal lobe atrophy (Figure 31.2M and 31.2N). FDG-PET shows predominant hypometabolism in the same region (Figure 31.2O). The bvFTD type of right temporal variant FTD is related to tau abnormality, and most patients have the *MAPT* mutations. The semantic dementia form of the right temporal variant of FTD is related to TDP-43 abnormality without the *MAPT* or *PGRN* mutations.

Overlap Syndrome

FTD has an overlap of clinical features with other degenerative disorders including MND, PSP, CBS, and other tauopathies. MND is clinically characterized by upper and lower motor neuron signs and bulbar signs. MND is predominantly associated with FTD because of the mutations that are found in the *C9orf72* and *TARDBP* genes. PSP is clinically characterized by axial rigidity, postural instability, and supranuclear palsy. CBS is clinically characterized by asymmetrical rigidity, apraxia, cortical sensory loss, and alien-limb phenomenon. PSP can occur with FTD when there are mutations in the *MAPT* gene. CBS can occur with FTD when it is caused by mutations in the *PGRN, MAPT*, and *C9orf72* genes.

- bvFTD is the most common variant of FTD and accounts for approximately half of all cases. Criteria for bvFTD are listed in Box 31.1.
- All of the variants of FTD can occur simultaneously with MND (FTD-MND); simultaneous occurrence is most frequent in bvFTD, occasional in NFAV-PPA, and very rare in SV-PPA and LV-PPA.
- In the early stage of bvFTD, patients may exhibit disinhibition, apathy, inertia, loss of empathy, perseveration, stereotyped or compulsive behavior, and lack of initiation.
- NFAV-PPA is a syndrome that is characterized by progressive deterioration in speech production.
- SV-PPA is a syndrome characterized by progressive loss of vocabulary.
- LV-PPA is characterized by difficulty in word finding.
- The right temporal variant of FTD is a rare form that predominantly affects the right side of the brain.
- FTD has an overlap of clinical features with other degenerative disorders including MND, PSP, CBS, and other tauopathies.

Diagnosis

A detailed history from the patient and family members or caregivers, formal neurologic examination, psychiatric assessment, neuropsychologic evaluation, and routine blood and urine tests are important for confirming the diagnosis of FTD and for excluding alternative diagnoses, as with any dementia syndrome.

Structural neuroimaging such as brain MRI is essential, and FDG-PET, HMPAO-SPECT, and ECD-SPECT are appropriate in some cases. Cerebrospinal fluid amyloid/tau ratio can assist in distinguishing between FTD and AD, albeit its value is still limited. Therefore, currently, it is not recommended for routine diagnostic purposes. Results of clinical molecular genetic testing, if positive, can provide a precise diagnosis, but this testing is costly and should include appropriate genetic counseling, as for other incurable hereditary neurodegenerative disorders.

- For the diagnosis of FTD, structural neuroimaging such as brain MRI is essential, and FDG-PET, HMPAO-SPECT, and ECD-SPECT are appropriate in some cases.

Treatment and Management

No curative therapy is available currently, and there are also no US Food and Drug Administration–approved symptomatic medications for the management of FTD. The current strategies include pharmacologic and nonpharmacologic treatments.

Pharmacologic Therapy

Selective serotonin reuptake inhibitors are commonly used to reduce the behavioral and psychiatric symptoms. However, they need to be used judiciously because they can potentially impair cognition. Antipsychotic drugs, such as risperidone, olanzapine, or quetiapine, are used to manage severe behavioral problems, including disinhibition and aggressive behavior. Parkinsonism is usually not responsive to any dopaminergic therapy, albeit L-dopa could be tried because some patients can have a beneficial response. Unfortunately, this beneficial response is frequently partial or transient. Parkinsonism in FTD cases caused by *TARDBP* gene mutations may respond well to L-dopa. Cholinesterase inhibitors are not typically helpful.

Nonpharmacologic Therapy

Physical, occupational, and speech therapies are important. Patients with NFAV-PPA benefit from communication devices. Home safety evaluations and education for family members and caregivers are essential. Patients with FTD should not drive.

32 Parkinsonism-Related Dementias[a]

BRADLEY F. BOEVE, MD

Introduction

The differential diagnosis for dementia is very wide (see Chapter 28, "Syndromes of Cognitive Dysfunction"), and the coexistence of parkinsonism with a slowly progressive course suggesting a degenerative cause narrows the differential diagnosis considerably. In patients with the combination of dementia and parkinsonism (often collectively termed the parkinsonism-related dementias), the 4 most common neurodegenerative entities are 1) the Lewy body dementias (which include dementia with Lewy bodies [DLB] and Parkinson disease with dementia [PDD]), 2) corticobasal syndrome (CBS) or corticobasal degeneration (CBD), 3) Richardson syndrome or progressive supranuclear palsy (PSP), and 4) frontotemporal dementia with parkinsonism (FTDP).

This review compares and contrasts the demographic, genetic, clinical, neuropsychologic, neuroimaging, and neuropathologic features differentiating these disorders to aid in diagnosis (Tables 32.1 and 32.2). This chapter reviews DLB in detail. Salient features related to the dementia aspects of PSP and corticobasal ganglionic degeneration are also reviewed, but these diseases are presented in more detail in Chapter 23, "Atypical Parkinsonian Syndromes." Similarly, FTDP is reviewed in further detail in Chapter 31, "Frontotemporal Dementias."

Dementia With Lewy Bodies

Overview

The antemortem and postmortem features of DLB and PDD have considerable overlap. The primary differentiating feature is the temporal sequence between the onset of dementia and the onset of parkinsonism. In PDD, dementia develops at least 1 year after the onset of parkinsonism, whereas in DLB (with the other core features, see below), parkinsonism develops at any point after the onset of dementia or within 1 year after the onset of dementia.

Neuropathologic Features

Both DLB and PDD are associated with Lewy body disease (LBD), characterized by nigral pallor, Lewy bodies in neurons (Figure 32.1), and Lewy neurites in neuronal processes. Pathologically, Lewy-related disease is caused by abnormal accumulations of the protein α-synuclein, and LBD is considered 1 of the synucleinopathies. In contrast to Alzheimer disease, the primary tauopathies of CBD, PSP, and FTDP due to *MAPT* mutations, the TDPopathies of FTDP due to *PGRN* mutations, and the hexanucleotide expansion mutation in *C9orf72*—in which neuronal loss in the neocortex, limbic structures, and sometimes striatal structures is usually profound—the degree of neuronal loss in LBD in similar structures is much milder. However, almost every neurochemical system that has been studied

[a] Portions previously published in Boeve BF. Progressive supranuclear palsy. Parkinsonism Relat Disord. 2012 Jan;18 Suppl 1:S192–4 and Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol. 2003;54 Suppl 5:S15–9. Used with permission.

Abbreviations: CBD, corticobasal degeneration; CBS, corticobasal syndrome; CT, computed tomography; DaTscanning, dopamine transporter imaging using ioflupane SPECT; DLB, dementia with Lewy bodies; FDG-PET, fluorodeoxyglucose positron emission tomography; FTDP, frontotemporal dementia with parkinsonism; LBD, Lewy body disease; MRI, magnetic resonance imaging; PDD, Parkinson disease with dementia; PSP, progressive supranuclear palsy; SPECT, single-photon emission computed tomography

Table 32.1 • Demographic, Genetic, and Clinical Features Differentiating Dementias Associated With Parkinsonism

Feature	DLB	CBS/CBD	PSP	FTDP
Demographic				
Age at onset, y	50–90	50–80	50–80	30–70
Sex	M>F	M = F	M = F	M = F
Clinical course, y	7–8 (range, 2–15)	3–6 (range, 3–10)	3–6 (range, 2–8)	5–10 (range, 2–25)
Family history of neurodegenerative disease	~50%	Uncommon	Uncommon	>95%
Genetic				
Mutations	Rare	Considered sporadic	Considered sporadic	*MAPT, PGRN, C9orf72*
Associations	*APOE*	Tau haplotype	Tau haplotype	Depends on mutation
Clinical				
Core features	Cognitive impairment Parkinsonism Visual hallucinations Fluctuations RBD very common	Cognitive impairment Parkinsonism Limb apraxia, alien limb Cortical sensory loss Tremor, myoclonus, dystonia RBD very rare	Cognitive impairment Parkinsonism Supranuclear gaze palsy Postural instability with frequent falls RBD rare	Cognitive impairment Parkinsonism RBD very rare
Qualitative features of parkinsonism	Usually symmetric Postural tremor Bradykinesia > rigidity Levodopa-responsive, sometimes	Usually asymmetric Tremor, variable Limb rigidity/bradykinesia, marked Levodopa-responsive, rarely	Usually symmetric Tremor, often absent Axial > limb rigidity Generalized bradykinesia Levodopa-responsive, rarely	*MAPT* and *C9orf72*, symmetric *PGRN*, often asymmetric Tremor, rare Akinetic-rigid syndrome Levodopa-responsive, rarely

Abbreviations: CBD, corticobasal degeneration; CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; F, female; FTDP, frontotemporal dementia with parkinsonism; M, male; PSP, progressive supranuclear palsy; RBD, rapid-eye-movement sleep behavior disorder.

in brains affected with LBD is markedly dysfunctional. The neurochemical disruption, but relatively preserved neuronal networks, forms the basis for pharmacotherapy in DLB.

Clinical, Demographic, and Neuropsychologic Features

The criteria for the clinical diagnosis of DLB, according to the Consortium on Dementia With Lewy Bodies (or McKeith criteria), include 4 key features: 1) fully formed visual hallucinations, 2) fluctuations in cognition or arousal, 3) spontaneous parkinsonism, and 4) rapid-eye-movement sleep behavior disorder. Rapid-eye-movement sleep behavior disorder occurs in at least 80% of cases of DLB. Those with 2 or more of these 4 features, particularly if 1 of them includes rapid-eye-movement sleep behavior disorder, is highly predictive of underlying LBD.

The cognitive decline in DLB tends to manifest at 50 to 90 years of age, and is more common in men. The clinical course from onset to death is variable, but it is usually 7 to 8 years; this is similar to the course in Alzheimer disease. Although some studies indicate that as many as 50% of patients with DLB have 1 or more first-degree relatives with dementia or parkinsonism, only a few genetic variants have been identified that are associated with DLB, and most remain to be discovered.

Neuropsychologic testing typically shows impairment on measures of attention and concentration and visuospatial functioning in DLB; performance on delayed recall and language measures is more variable and sometimes more normal than not, especially early in the course.

Neuroimaging Features

Results of structural neuroimaging such as computed tomography (CT) and magnetic resonance imaging (MRI) are usually normal or show only mild generalized cerebral cortical atrophy with or without mild hippocampal atrophy (Figure 32.1). These are in contrast with those of Alzheimer disease, in which hippocampal atrophy is much more common and a helpful diagnostic clue; the absence of hippocampal atrophy in a patient with dementia plus parkinsonism is also a helpful clue and favors DLB.

Parietal and, particularly, occipital hypoperfusion on single-photon emission computed tomography (SPECT) and occipital hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET) are common in patients with DLB. However, the absence of occipital hypometabolism should not dissuade the clinician from suspecting DLB in the appropriate clinical setting.

Dopamine transporter imaging using ioflupane SPECT, also known as DaTscanning, typically shows reduced

Table 32.2 • Neuropsychologic, Neuroimaging, and Neuropathologic Features Differentiating Dementias Associated With Parkinsonism

Feature	DLB	CBS or CBD	PSP	FTDP
Memory	0 to ++	0 to +	0 to ++	0 to ++
Attention, concentration	++ to +++	0 to +++	+ to +++	+ to +++
Executive functioning	++ to +++	0 to ++	+ to +++	+ to +++
Language	0 to +	0 to +++ (Left)	0 to ++	0 to ++
Visuospatial functioning	++ to +++	0 to +++ (Right)	0 to +	0 to +
Social cognition	Often normal	Often normal	Often normal	Usually impaired
Neuropathologic features				
Key proteinopathy	α-Synuclein	Tau	Tau	*MAPT*-tau; *PGRN* and *C9orf72*-TDP-43
Specific hallmarks	Lewy bodies and Lewy neuritis	Neuropil threads, astrocytic plaques, oligodendroglial coiled bodies	Globose neurofibrillary tangles, astrocytic plaques	*MAPT*, tau inclusions *PGRN*, intraneuronal TDP-43 inclusions *C9orf72*, inclusions in cerebrum and cerebellum
Neuroimaging features				
CT or MRI atrophy pattern	Minimal to none	Parietal or frontal	None or frontal Hummingbird sign often present	*MAPT*, symmetric frontotemporal *PGRN*, variable, usually asymmetric *C9orf72*, symmetric frontal>temporal and parietal
SPECT hypoperfusion or FDG-PET hypometabolism pattern	Occipital	Focal or asymmetric parietal or frontal	Mild bilateral frontal, mesial>dorsolateral	*MAPT*, symmetric frontotemporal *PGRN*, variable, usually asymmetric *C9orf72*, symmetric frontal>temporal and parietal
DaTscanning uptake pattern	Moderate to marked bilateral reduction	Moderate to marked focal/asymmetric reduction	Moderate to marked bilateral reduction	Inadequate data

Abbreviations: CBD, corticobasal degeneration; CBS, corticobasal syndrome; CT, computed tomography; DaTscanning, dopamine transporter imaging using ioflupane SPECT; DLB, dementia with Lewy bodies; FDG-PET, fluorodeoxyglucose positron emission tomography; FTDP, frontotemporal dementia with parkinsonism; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy; SPECT, single-photon emission computed tomography; TDP-43, transactive response DNA-binding protein molecular weight 43; 0, absent; +, mild; ++, moderate; +++, marked.

striatonigral uptake, which has been a sensitive and specific finding in DLB compared with Alzheimer disease. Studies from Europe have shown that DaTscanning can be helpful in differentiating DLB from Alzheimer disease in patients with atypical dementia, but DaTscanning is approved by the US Food and Drug Administration only for the differentiation of essential tremor from Parkinson disease.

Several PET radioligands that bind amyloid have been developed and are now in research and sometimes clinical use. Amyloid plaques are one of the pathologic hallmarks of Alzheimer disease, but recent studies have shown that PET is positive for amyloid in not only many patients with DLB, but also in a substantial minority of cognitively normal, elderly persons. Therefore, it is unlikely that amyloid found on PET will have a major role in differentiating DLB from Alzheimer disease.

Management

Cholinesterase inhibitors have been shown to be reasonably well tolerated and often beneficial, likely due to the relatively mild neocortical and limbic neuronal loss but considerable cholinergic deficit. Table 32.3 compares management of DLB with that of other dementias associated with parkinsonism. Memantine has been shown to be reasonably well tolerated and modestly beneficial. Parkinsonism may improve somewhat with levodopa or dopamine agonist therapy, but adverse effects (hallucinations, orthostatic hypotension, hypersomnia) limit their use. Clinicians should always consider physical or occu-

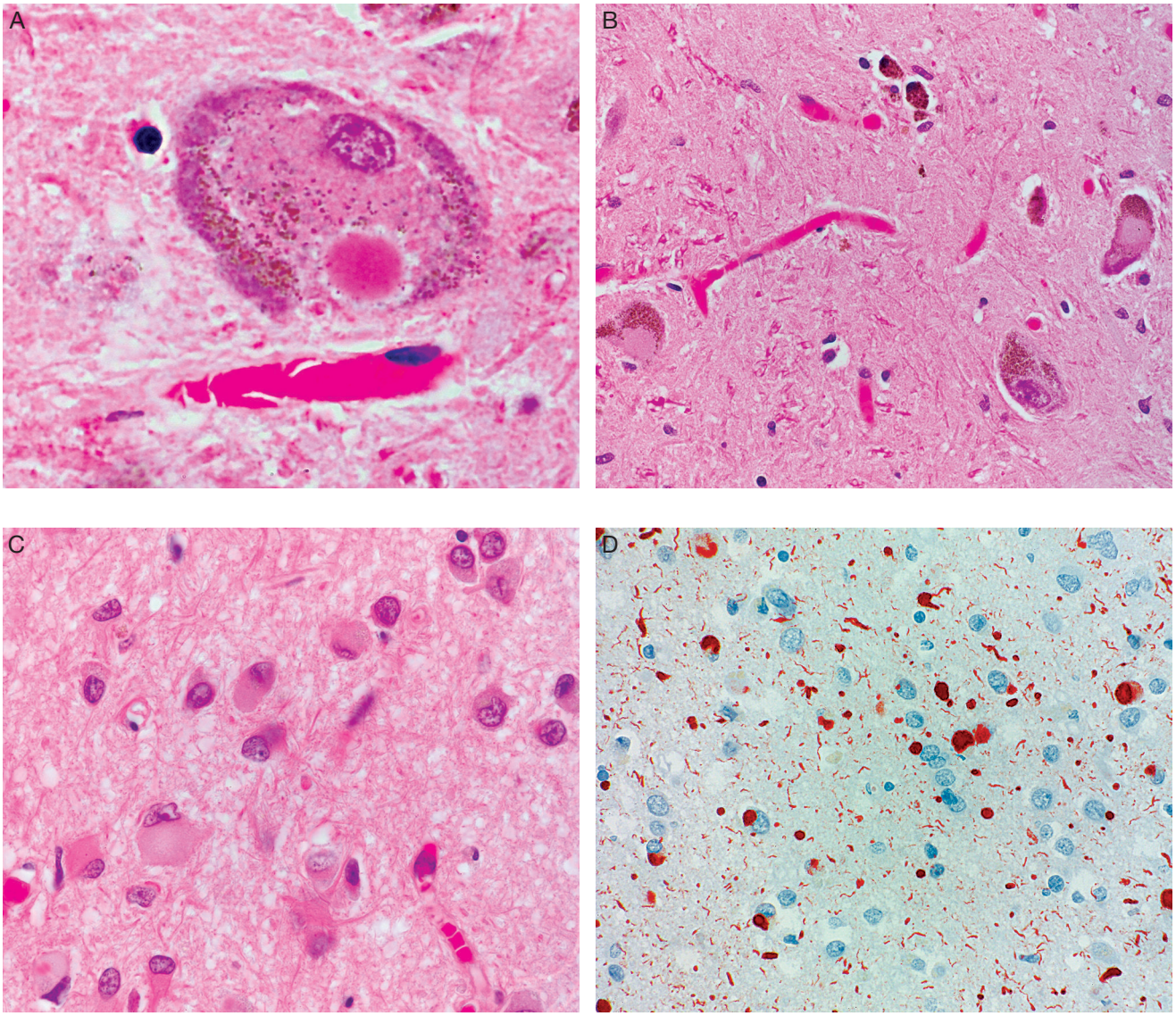

Figure 32.1 *Diffuse Lewy Body Disease.*
A, Typical classic Lewy body is essentially a neuronal inclusion with a hyaline eosinophilic core and pale halo. (Substantia nigra, hematoxylin-eosin stain.). B, Also in the substantia nigra, note the pale bodies that are rounded, granular eosinophilic cytoplasmic inclusions displacing neuromelanin. C, Cortical Lewy bodies are rounded, homogeneous eosinophilic structures usually lacking the classic "halo." Cortical Lewy bodies occupy most of the cytoplasm and appear less eosinophilic than brainstem Lewy bodies. D, α-Synuclein immunohistochemistry demonstrates the inclusions.
(Adapted from Mowzoon N. Behavioral Neurology. Part B: Syndromes of cognitive dysfunction. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 297–332. Used with permission of Mayo Foundation for Medical Education and Research.)

pational therapy, diagnosis and management of sleep disorders, and attention to caregiver education and support.

- The antemortem and postmortem features of DLB and PDD have considerable overlap. The primary differentiating feature is the temporal sequence between the onset of dementia and the onset of parkinsonism.
- Pathologically, Lewy-related disease is caused by abnormal accumulations of the protein α-synuclein.
- The criteria for the clinical diagnosis of DLB include 4 key features: 1) fully formed visual hallucinations, 2) fluctuations in cognition or arousal, 3) spontaneous parkinsonism, and 4) rapid-eye-movement sleep behavior disorder.
- DLB is more common in men.

Table 32.3 • Management of Dementias Associated With Parkinsonism[a]

Feature	DLB	CBS/CBD	PSP	FTDP
Cholinesterase inhibitors	Warranted and often beneficial[b]	Usually not warranted nor beneficial	Usually not warranted nor beneficial	Usually discouraged
NMDA antagonist	Modestly beneficial[b]	Usually not warranted nor beneficial	Usually not warranted nor beneficial	Not beneficial[b]
Levodopa or dopamine agonists	Variably beneficial	Warranted but usually not beneficial	Warranted but usually not beneficial	Warranted but usually not beneficial

Abbreviations: CBD, corticobasal degeneration; CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; FTDP, frontotemporal dementia with parkinsonism; NMDA, *N*-methyl-D-aspartate; PSP, progressive supranuclear palsy.
[a] Comments on management are provided based on clinical experience, anecdotal reports, uncontrolled trials, or controlled trials.
[b] Comments are based on controlled trials.

- The absence of hippocampal atrophy in a patient with dementia plus parkinsonism is a helpful clue and favors DLB.
- Parietal and, particularly, occipital hypoperfusion on single-photon emission computed tomography (SPECT) and occipital hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET) are common in patients with DLB.
- Cholinesterase inhibitors have been shown to be reasonably well tolerated and often beneficial in DLB, likely due to the relatively mild neocortical and limbic neuronal loss but considerable cholinergic deficit.

Corticobasal Syndrome and Corticobasal Degeneration

Overview

The core clinical features that have been considered characteristic of CBD include progressive asymmetric rigidity and apraxia, with other findings suggesting additional cortical and basal ganglionic dysfunction. Because of the considerable clinicopathologic heterogeneity between patients clinically and pathologically diagnosed with CBD, some investigators have suggested that the term corticobasal syndrome (CBS) be used to describe the constellation of features thought to be most characteristic of CBD.

Epidemiology

CBS tends to manifest more as a motor than a cognitive syndrome, usually beginning at 50 to 80 years of age, and there is no apparent sex predilection. The clinical course from onset to death is variable; it is usually 3 to 6 years, but some patients survive for 10 or more years, similar to the course of PSP.

Clinical Features

The core clinical features of CBD include progressive asymmetric rigidity and apraxia, and other findings suggest additional cortical (eg, alien limb phenomena, cortical sensory loss, myoclonus, mirror movements) and basal ganglionic (eg, bradykinesia, dystonia, tremor) dysfunction. The asymmetry of the findings is a key feature. Dystonia, tremor, myoclonus, choreiform movements, and alien limb features are variably present, and these tend to be levodopa-unresponsive.

Neuropsychometric testing typically shows impairment in domains subserved by frontal or frontostriatal and parietal cognitive networks, namely, attention and concentration, executive functions, praxis, language functioning (when the dominant hemisphere is sufficiently affected), and visuospatial functioning (when the nondominant hemisphere is sufficiently affected). Performance on tests of learning and memory tends to be mildly impaired or normal. Underlying atypical Alzheimer disease should be considered if performance on delayed recall measures is markedly abnormal or global cognitive impairment is present in the setting of the CBS.

Further details of the clinical features, diagnostic criteria, and treatment of CBD are discussed in Chapter 23, "Atypical Parkinsonian Syndromes."

- In CBD, neuropsychometric testing typically shows impairment in domains subserved by frontal or frontostriatal and parietal cognitive networks, namely, attention and concentration, executive functions, praxis, language functioning (when the dominant hemisphere is sufficiently affected), and visuospatial functioning (when the nondominant hemisphere is sufficiently affected).

Progressive Supranuclear Palsy

Overview

The core clinical features that have been considered characteristic of PSP are parkinsonism, supranuclear palsy, and postural instability with falls. Because of the

clinicopathologic heterogeneity between the clinical syndromes associated with a pathologic diagnosis of PSP (which include Richardson syndrome—the classic PSP syndrome—and, for example, progressive nonfluent aphasia and progressive freezing of gait), some investigators have suggested that the term *Richardson syndrome* be used to describe the constellation of features thought to be most characteristic of PSP.

Clinical Features

The classic presentation of PSP is the constellation of supranuclear gaze palsy (particularly downward gaze), postural instability and falls, and parkinsonism. Other features include a wide-eyed stare, reduced eyeblink frequency, axial greater than appendicular rigidity, and tendency to walk, turn, and site en bloc.

Notably absent in these core PSP criteria is any mention of cognitive or behavioral changes; yet, almost all PSP patients exhibit some degree of such changes, particularly as the disease evolves. The concept of subcortical dementia has been applied to those with Richardson syndrome-PSP, in which there is slowing of cognitive processing, but cortical signs, such as significant amnesia and aphasia, tend to be mild. Letter fluency (ie, word generation starting with a letter of the alphabet over a specific time period) and cognitive flexibility tend to be particularly impaired. More florid aspects of executive dysfunction occur with disease progression. Apathy, anxiety, and dysphoria are common, and marked obsessive-compulsive or delusionary features can occur in some patients.

Details of the clinical features, pathology, diagnosis, and treatment of PSP are discussed in Chapter 23, "Atypical Parkinsonian Syndromes."

Frontotemporal Dementia With Parkinsonism

Overview

FTDP is the condition of patients who have varying degrees of FTD and parkinsonian features, the majority of whom have an autosomal dominant genetically mediated disorder.

Clinical Features

FTD associated with *MAPT, PGRN,* and *C9orf72* gene defects may have features of parkinsonism. For patients who have FTDP associated with mutations in *MAPT*, symptoms usually involve altered personality and behavior and executive dysfunction, often also with aphasia (particularly as the disease progresses). Parkinsonism tends to be a later feature, with axial more so than appendicular rigidity, generalized bradykinesia, and variable degrees of tremor (which is almost never asymmetric).

The behavioral, cognitive, and motor features associated with mutations in *PGRN* are highly variable, even within families, with the specific phenotypes spanning the spectrum of mild cognitive impairment, Alzheimer-type dementia, primary progressive aphasia, and CBS.

In the hexanucleotide expansion in *C9orf72*, motor neuron disease is common, either in isolation or in combinations with FTD. Bizarre hallucinations and delusions have been described in affected patients. Parkinsonism occurs in up to one-third of cases.

Details of clinical, pathologic, and radiographic features and treatment of FTD are discussed in Chapter 31, "Frontotemporal Dementias."

- FTD associated with *MAPT, PGRN,* and *C9orf72* gene defects may have features of parkinsonism.

33 Nondegenerative Dementias and Encephalopathies

EOIN P. FLANAGAN, MB, BCH

Introduction

The differential diagnosis of dementia is discussed in Chapter 28, "Syndromes of Cognitive Dysfunction." Nondegenerative dementias are a diverse but important group of cognitive disorders because they may be reversible with treatment. Thus, it is important to evaluate for such when suspected.

Many of the causes of nondegenerative dementia result in what is known as a subcortical dementia. Subcortical dementia is thought to be primarily due to damage to the frontal subcortical connections, and typical clinical features include inattention, bradyphrenia (slowed thought process), executive dysfunction (difficulties planning and sequencing tasks), apathy, psychomotor slowing, and mood disorders. Gait apraxia and urinary difficulties may coexist. Cortical features such as agnosia, seizures, aphasia, and ideomotor apraxia are typically absent.

Vascular Dementia

Definition and Epidemiology

Vascular dementia consists of a range of cognitive disorders related to cerebrovascular disease and has generally superseded the term *multi-infarct* dementia. Vascular dementia can be characterized by the size of the vessel involved and location of the infarct and includes large-vessel infarcts (predominantly cortical damage), small-vessel "lacunar" infarcts, and chronic subcortical ischemia. The classic multi-infarct dementia is characterized by recurrent cerebral infarcts producing acute stepwise deteriorations in cognition. However, it is now recognized that patients may present with a more gradual deterioration possibly related to the accumulation of microinfarcts in the brain. Cognitive disorders related to cerebrovascular disease consist of 3 major subtypes: 1) vascular cognitive impairment but not dementia (not yet interfering with day-to-day activities), 2) vascular dementia, and 3) mixed vascular dementia and primary neurodegenerative dementia (usually Alzheimer disease).

Up to 20% of dementia cases are vascular dementia, and this type may be more common in Asian populations. The risk of poststroke dementia after a clinical stroke is approximately 20%.

Causes

Box 33.1 lists vascular diseases that may be most commonly associated with dementia or encephalopathy. Chapter 10, "Ischemic Stroke: Common Causes and Diagnosis," provides a complete differential diagnosis of stroke and information on select diseases.

Clinical Features

The clinical presentation of vascular dementia is diverse. Strategically located cortical or subcortical infarcts can produce specific cognitive and psychiatric syndromes; some examples are outlined in Table 33.1. Numerous clinical and radiographic criteria have been proposed for the diagnosis of vascular dementia, the most common of which is the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale Pour la Recherche et l'Enseignement en Neuroscience (Box 33.2).

Abbreviations: HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; MS, multiple sclerosis

Box 33.1 • Causes of Vascular Dementia

- Hypoperfusion (watershed infarctions)
- Hypoxic-ischemic injury
- Large-vessel disease
  - Vasculitis (granulomatous or systemic)
- Small-vessel disease
  - Binswanger disease
  - Multiple lacunar infarctions
  - CADASIL
  - Spatz-Lindenberg disease
- Coagulation disorders
  - Sneddon syndrome
  - Phospholipid antibody syndrome
- Other
  - Superficial siderosis
  - A beta-related vasculitis

Abbreviation: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Treatment

Treatment of vascular dementia primarily involves management of vascular risk factors, the most important of which is hypertension (see Chapter 13, "Secondary Prevention of Ischemic Stroke"). Acetylcholinesterase inhibitors and memantine have not yet been proven effective for vascular dementia in clinical trials, although benefits may occur in a subset of patients, including those with mixed dementia due to vascular disease and coexistent Alzheimer disease.

Binswanger Disease

The classic syndrome of subcortical dementia from vascular disease is Binswanger disease. Clinical features include early gait apraxia and parkinsonian gait, frequent falls, focal motor deficits and pyramidal signs on examination (extensor plantar responses and exaggerated deep tendon reflexes), urinary urgency and incontinence, apathy and psychomotor slowing, attention and concentration difficulties, executive dysfunction, frontal release signs on examination, and milder memory deficits than those that occur with other dementias.

The magnetic resonance imaging (MRI) findings in vascular dementia often are extensive white matter T2-signal hyperintensities known as leukoaraiosis, which is particularly prominent in Binswanger disease (Figure 33.1). Mild global atrophy with cortical or lacunar infarcts is typical. Multiple lacunes (état lacunaire) and extensive dilated perivascular spaces (étatcriblé) may also be found. Pathologically, lipohyalinosis and microatheroma may be found in the small vessels.

- Up to 20% of dementia cases are vascular dementia.
- The risk of poststroke dementia after a clinical stroke is approximately 20%.

Table 33.1 • Strategic Infarcts and Their Cognitive Syndromes

Location of Lesion and Syndrome Name[a]	Neurologic Features	Notes
Dorsolateral caudate nucleus	Apathy, psychomotor slowing	Recurrent artery of Huebner infarct
Ventromedial caudate nucleus	Psychomotor hyperactivity, disinhibition, impulsiveness	Recurrent artery of Huebner infarct
Hippocampi	Anterograde and retrograde amnesia	Often from hypoperfusion injury, typically bilateral
Paramedian thalamus Artery of Percheron	Altered level of consciousness, lack of spontaneous behavior, and vertical gaze palsy	Artery arises at basilar bifurcation and supplies paramedian thalamus and rostral midbrain
Right parietal lobe	Acute delirium	
Dominant angular and supramarginal gyrus Gerstmann syndrome	Acalculia, agraphia, left-right dissociation and finger agnosia	Located in parietal lobe
Bilateral parieto-occipital lesions Balint syndrome	Optic ataxia, oculomotor apraxia, and simultanagnosia	Often caused by bilateral watershed hypoperfusion infarcts
Anterior corpus callosum	Left-hand apraxia	
Bilateral internal capsule infarcts	Pseudobulbar palsy	
Left frontal lobe	Depression	
Posterior right frontal lobe	Obsessive compulsive disorder	

[a] The location of the lesion identified in the table is traditionally associated with the neurologic features described; however, the associations are not invariably present.

Box 33.2 • NINDS-AIREN Criteria for the Diagnosis of Vascular Dementia

Clinical diagnosis of probable vascular dementia includes all of the following:

- Dementia
  - Defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of 2 or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychologic testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone
- Exclusion criteria
  - Disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychologic testing
  - Systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition
- Cerebrovascular disease
  - Defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke) and evidence of relevant CVD by brain imaging (CT or MRI), including multiple large-vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes, extensive periventricular white matter lesions, or combinations thereof
- A relationship between the above 2 disorders
  - Manifested or inferred by the presence of 1 or more of the following:
    1. Onset of dementia within 3 months following a recognized stroke
    2. Abrupt deterioration in cognitive functions or fluctuating, stepwise progression of cognitive deficits

Abbreviations: ACA, anterior cerebral artery; AD, Alzheimer disease; CT, computed tomography; CVD, cerebrovascular disease; MRI, magnetic resonance imaging; NINDS-AIREN, National Institute of Neurological Disorders and Stroke-Association Internationale Pour la Recherche et l'Enseignement en Neuroscience; PCA, posterior cerebral artery.

Adapted from Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology. 1993 Feb;43(2):250–60. Used with permission.

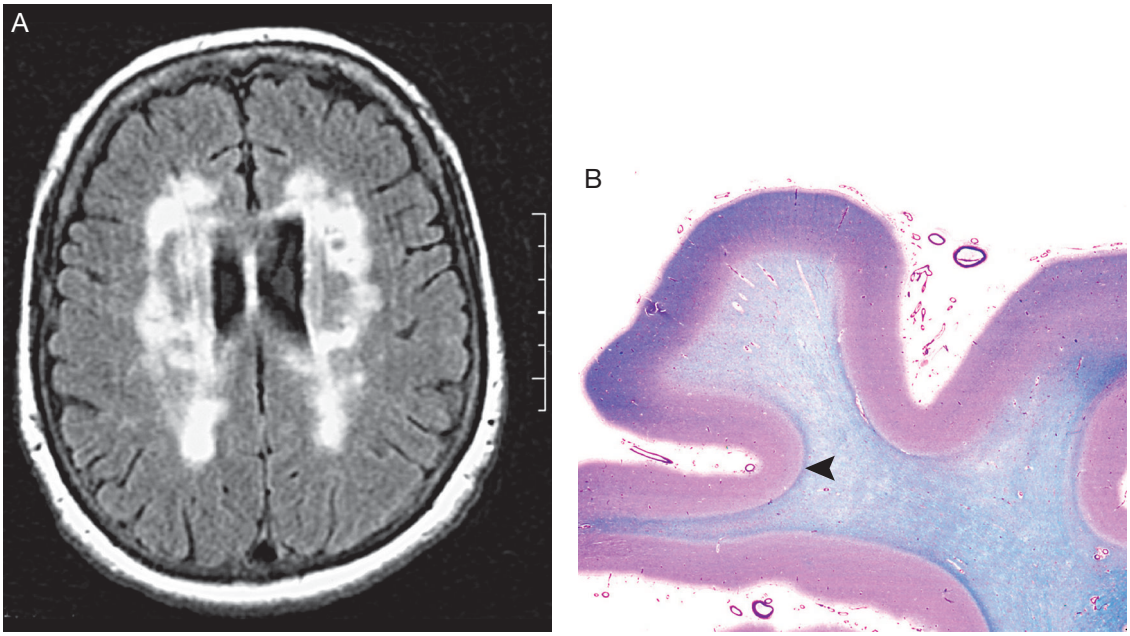

Figure 33.1 *Findings in Binswanger Disease.*
A, Fluid-attenuated inversion recovery image. Note the extensive confluent T2-signal abnormality involving white matter (particularly deep and periventricular white matter) and sparing of gray matter and subcortical U-fibers. B, Low-power microscopy shows diffuse, confluent myelin pallor in subcortical white matter and sparing of U-fibers (arrowhead). These characteristic changes were noted throughout the subcortical white matter.
(Adapted from Mowzoon N. Behavioral Neurology. Part B: Syndromes of cognitive dysfunction. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 297–332. Used with permission of Mayo Foundation for Medical Education and Research.)

- Binswanger disease is characterized by gait apraxia, frequent falls, and pyramidal signs associated with characteristic prominent leukoariaosis.

Infectious Causes of Dementia

Several infectious diseases may cause encephalopathy or dementia. The agents causing encephalitis are discussed in more detail in Chapter 63, "Syndromic Approach to Neuroinfectious Diseases." Select diseases are described here and in Table 33.2.

Human Immunodeficiency Virus

Cognitive deterioration in patients with human immunodeficiency virus (HIV) infection may be due to the infection of the virus itself or to other coexisting brain infections. HIV-associated neurocognitive disorder tends to cause a subcortical type of dementia involving decreased attention, poor working memory, bradyphrenia (slowness in thinking), psychomotor slowing, and psychiatric symptoms including depression, mania, and obsessive compulsive disorder. Motor symptoms include bradykinesia, postural tremors, and pyramidal signs.

The differential diagnosis of dementia in patients with HIV can be broad, because HIV can predispose to other infections (toxoplasmosis, progressive multifocal encephalopathy, cryptococcal meningoencephalitis, tuberculosis, cytomegalovirus infection, and central nervous system lymphoma) that also may present with cognitive difficulties. A careful review of the results of laboratory studies, brain imaging, and spinal fluid studies may be important to help distinguish the cause of memory loss.

In HIV-associated neurocognitive disorder, MRI shows global atrophy and T2-signal hyperintensities in the periventricular and deep white matter.

Treatment is with highly active antiretroviral treatment.

Spirochetes

Neurosyphilis (previously called general paresis of the insane) causes a slowly progressive behavioral syndrome 3 to 40 years after infection with *Treponema pallidum*. It presents with a frontal dysexecutive syndrome with inattention and executive dysfunction. Psychiatric features include psychosis, hallucinations, depression, mania, and irritability. Brain gummas are rare, but concurrent Argyll-Robertson pupils and tabes dorsalis may be found.

Investigations include VDRL studies in the serum and cerebrospinal fluid, and treatment is with penicillin. Treatment does not reverse the dementia. Also see Chapter 66, "Bacterial Infections of the Nervous System."

Autoimmune and Inflammatory Causes of Dementia

Autoimmune Encephalopathies and Dementia

Epidemiology

Autoimmune or paraneoplastic cognitive disorders are increasingly recognized as important, potentially reversible causes of dementia. They can be broadly divided into those infrequently associated with cancer, which are termed *autoimmune encephalopathies* or *dementias*, and those associated with cancer, which are often termed *paraneoplastic encephalitis*. Thyroid peroxidase autoantibodies have been associated with what is termed *Hashimoto encephalopathy* or *steroid-responsive encephalopathy associated with thyroid autoimmunity*. They are a useful marker of autoimmunity but are not thought to be pathogenic and fit best under the overall category of autoimmune encephalopathy. Other neural-specific autoantibodies and associated cancers considered paraneoplastic encephalitides are listed in Table 33.3.

The voltage-gated potassium-channel complex autoantibody is probably the most common cause of autoimmune encephalopathy. The autoantibodies bind to 2 proteins that associate with the channel (leucine-rich glioma inactivated 1, which commonly causes encephalopathy, and contactin-associated protein 2). The clinical and radiologic presentations of Creutzfeldt-Jakob disease may mimic voltage-gated potassium-channel complex autoimmunity, and testing for this reversible cause of dementia should be considered in these cases. Cancers are present in less than one-third of cases, but they should be screened for.

Clinical Presentation

Autoimmune encephalopathies typically present with subacute cognitive decline characterized by fluctuations and are frequently accompanied by tremor or myoclonus. Seizures may also coexist. Subacute to chronic presentations may mimic a neurodegenerative dementia, whereas more acute presentations occur as a classic limbic encephalitis.

Diagnosis

Objective testing with mental status examination or formal neuropsychologic tests before treatment is important to give a baseline from which to judge immunotherapy response.

Supporting features include evidence of an inflammatory process on CSF examination and MRI evidence of T2-signal abnormalities in the mesial temporal lobes (Figure 33.2). Electroencephalography is important to exclude seizures as a contributor to the cognitive decline. Testing for neural-specific autoantibodies is essential because it may confirm an autoimmune basis to the disease

Table 33.2 • Select Infectious Diseases Resulting in Dementia or Encephalopathy

Disease	Infectious Agent	Clinical Presentation	Diagnostic Findings	Treatment
HIV dementia	HIV	Subcortical dementia	(+) HIV Rule out immunocompromised infectious agent	Highly active antiretroviral treatment
Syphilis	*Treponema pallidum*	Frontal dysexecutive syndrome Psychiatric (psychosis, hallucinations, depression, mania)	(+) VDRL (serum and CSF)	Penicillin (does not reverse dementia)
Lyme disease	*Borrelia burgdorferi*	Encephalopathy	(+) Lyme serum (+) Lyme CSF PCR	Doxycycline Ceftriaxone (if considerable CNS involvement)
Whipple disease	*Tropheryma whipplei*	Subcortical dementia Myoclonus Supranuclear gaze palsy Oculomasticatory myorhythmia	Clinical features (neurologic and abdominal) Small bowel biopsy	Ceftriaxone or penicillin (varies due to extent of involvement)
Fungal meningoencephalitides	*Coccidioides* (southwest United States) *Histoplasma* and *Blastomycoses* (Mississippi river valley)	Encephalopathy Headache	Abnormal CSF	
Herpes encephalitis	HSV-1	Encephalitis can be followed by postencephalitic dementia Klüver-Bucy syndrome	(+) HSV PCR in CSF	Acyclovir for encephalitis
HHV type 6	HHV type 6	Limbic encephalitis	Increased serum IgG antibody suggestive	
West Nile meningoencephalitis	West Nile virus	Encephalopathy Tremor Myoclonus Parkinson features Flaccid weakness	Increased serum IgM Increased CSF IgM	Supportive
Prion disease		Rapidly progressive dementia Myoclonus Ataxia	(+) 14-3-3 CSF protein Periodic sharp waves on EEG Restricted diffusion (cortical, pulvinar, or caudate)	Supportive

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; Ig, immunoglobulin; PCR, polymerase chain reaction; (+), positive.

and help guide the cancer search in paraneoplastic cases. Body computed tomography or positron emission tomography may be considered when a paraneoplastic encephalitis is under consideration.

Treatment and Prognosis

Treatment with high-dose intravenous methylprednisolone once daily for 5 days is recommended, and most patients improve within a few weeks. Earlier treatment is associated with better outcomes, but relapse is common, and long-term immunosuppression may be necessary. Paraneoplastic encephalitis may present more acutely and generally has a worse prognosis than autoimmune encephalopathy. Detection and treatment of the underlying cancer are the initial steps. Body computed tomography is recommended, and the addition of positron emission tomography may increase the sensitivity for the detection of cancer in high-risk cases. Sex-specific tests (including mammography and testicular or ovarian ultrasonography) should not be overlooked. Response to immunotherapy is often

Table 33.3 • Neural Autoantibodies Associated With Cognitive Deterioration

Neural Autoantibody	Strong Cancer Association (>70%)	Types of Cancers
AMPA	+	Thymic tumors, lung carcinomas, breast carcinoma
Amphiphysin	+	Breast adenocarcinoma, small cell lung carcinoma
ANNA-1 (anti-Hu)	+	Small cell carcinoma
ANNA-2 (anti-Ri)	+	Small cell lung carcinoma or breast adenocarcinoma
ANNA-3	+	Small cell lung carcinoma
AGNA (SOX-1 antibodies)	+	Small cell lung carcinoma
Calcium channel N or P/Q type	–	Small cell lung carcinoma
CRMP-5 IgG (anti-CV2)	+	Small cell lung carcinoma, thymoma
$GABA_B$	+	Small cell lung carcinoma, other neuroendocrine neoplasia
GAD65	–	Thymoma
Ganglionic acetylcholine receptor autoantibody	–	Adenocarcinoma of breast, prostate, lung and gastrointestinal tract; thymoma
Glycine receptor antibodies	–	Thymoma
Ma-1 (anti-Ma) antibodies	+	Lung, gastrointestinal tract, breast, germ cell, non-Hodgkin lymphoma
Ma-2 (anti-Ta) antibodies	+	Testis
NMDA	+	Teratoma, usually ovarian
PCA-2	+	Small cell carcinoma
VGKC complex		
LGI1	–	Small cell lung carcinoma, thymoma, thyroid, renal cell
Caspr-2	–	Thymoma

Abbreviations: AGNA, antiglial nuclear antibody; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA, antineuronal nuclear antibody; Caspr-2, contactin-associated protein-2; CRMP-5, collapsin-response mediator-protein 5; $GABA_B$, gamma-aminobutyric acid; GAD65, glutamic acid decarboxylase, 65 isoform; Ig, immunoglobulin; LGI1, leucine-rich glioma inactivated 1; NMDA, *N*-methyl-D-aspartate; PCA, Purkinje cell cytoplasmic antibody; VGKC, voltage-gated potassium channel.

less robust than with autoimmune encephalopathy. *N*-methyl-D-aspartate–receptor encephalitis associated with ovarian teratoma is an exception and tends to have a good long-term prognosis despite the severity of the initial illness. This response is possibly related to the ability to completely remove the tumor surgically. It is frequently associated with psychosis, catatonic movements, and autonomic dysfunction.

Multiple Sclerosis

Epidemiology

Cognitive impairment is an underrecognized feature of multiple sclerosis (MS) and affects approximately 60% of patients, although frank dementia occurs in less than 5%.

Clinical Features

Cognitive deficits are more frequent in patients with a progressive rather than relapsing course. MS has been classically thought to cause a subcortical dementia with problems of inattention, working memory, and speed of processing. Coexisting mood disorders and fatigue are also frequent and may contribute to cognitive problems. The lesion burden correlates more with cognitive dysfunction than atrophy does. Recent research has found that cortical lesions in MS are much more common than initially thought and likely contribute to cognitive decline.

Treatment

The diagnosis of MS is discussed in Chapter 18, and the treatment of MS is discussed in Chapter 19. Cholinesterase inhibitors such as donepezil have shown some promise in treating cognitive impairment in MS, but more studies are needed. Some patients with MS may have a chronic, fulminant, predominantly cognitive decline related to progressive cortical demyelination. Others may have tumefactive, demyelinating lesions that cause subacute cognitive deterioration and may mimic tumors radiologically. More fulminant courses, such as the Marburg variant of MS, may cause a rapidly progressive cognitive deterioration that is usually fatal. Large confluent demyelinating lesions may occur with more destructive changes evident pathologically than with typical MS.

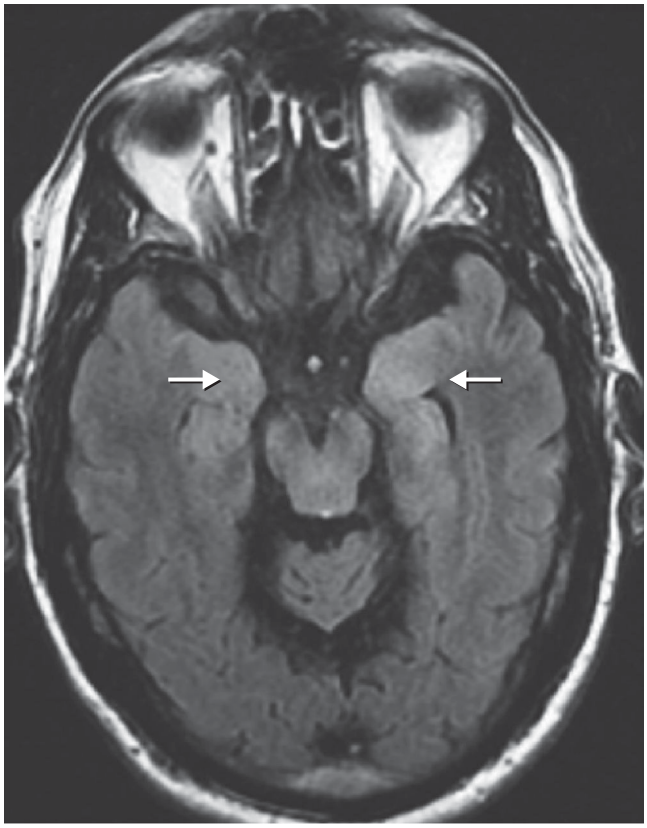

Figure 33.2 *Magnetic Resonance Imaging Findings in Autoimmune Voltage-gated Potassium Channel Complex–associated Encephalopathy.*
T2-signal hyperintensity is greater in the left than the right mesial temporal lobes (white arrows).

Neurosarcoidosis

Neurosarcoidosis may cause cognitive impairment from brain lesions or meningoencephalitis, which typically involves the base of the brain. Systemic features of lung, eye, and skin involvement are often also present. See also Chapter 20, "Mimickers of Multiple Sclerosis."

- Thyroid peroxidase autoantibodies have been associated with what is termed *Hashimoto encephalopathy* or *steroid-responsive encephalopathy associated with thyroid autoimmunity*.
- The voltage-gated potassium-channel complex autoantibody is probably the most common cause of autoimmune encephalopathy.
- Supporting features of autoimmune encephalopathies include evidence of an inflammatory process on CSF examination and MRI evidence of T2-signal abnormalities in the mesial temporal lobes (Figure 33.2).

Toxic and Metabolic Causes of Dementia

A wide range of metabolic conditions, toxins, and drugs (prescription and illicit) may alter cognition. Box 33.3 lists select toxic and metabolic causes of cognitive dysfunction.

Alcohol

Alcohol may result in cognitive changes, but its effect is complicated by its associated comorbidities, which include liver disease, thiamine deficiency, multiple head traumas, and coexisting psychiatric disease. The presentation consists of a frontal-dysexecutive disorder with poor working memory, inattention, impaired judgment, and poor verbal fluency. Assessment requires the patient to be sober for at least 2 months, and treatment with alcohol cessation may result in some improvement.

Wernicke-Korsakoff Syndrome

Wernicke encephalopathy consists of the clinical triad of global confusion, truncal ataxia, and ophthalmoplegia or

Box 33.3 • Toxic and Metabolic Causes of Dementia and Cognitive Changes

- Endocrine
  - Hyperthyroidism (neuropsychiatric manifestations) or hypothyroidism (psychomotor retardation, poor attention)
  - Recurrent episodes of hypoglycemia
  - Cushing or Addison disease
- System failure
  - Hepatic failure
  - Renal failure
  - Dialysis dementia syndrome (likely aluminum excess)
  - Hyperammonemia
- Toxins
  - Alcohol
  - Lead
  - Mercury
  - Manganese
  - Arsenic
  - Toluene
- Nutritional
  - B_{12} deficiency
  - B_3 (niacin) deficiency
  - Chronic malnutrition: Wernicke-Korsakoff syndrome, Marchiafava-Bignami disease
- Medications
  - See Chapter 28, "Syndromes of Cognitive Dysfunction"

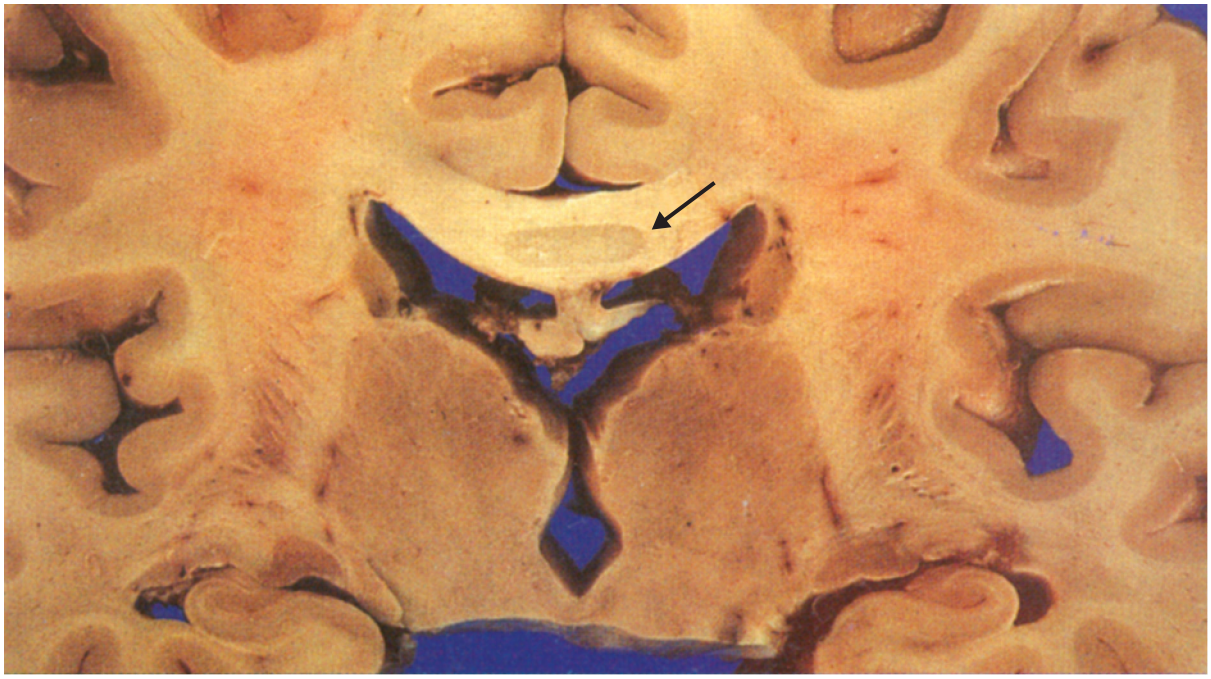

Figure 33.3 *Brain With Marchiafava-Bignami Disease.*
Note discoloration of the central portion of corpus callosum (arrow). Microscopic examination would show demyelination and necrosis.
(Adapted from Ellison D, Love S, Chimelli L, Harding B, Lowe J, Roberts GW, et al. Neuropathology: a reference text of CNS pathology. London [United Kingdom]: Mosby; c1998. Chapter 25, Toxic injury of the CNS; p. 25.1–25.22. Used with permission.)

nystagmus. Wernicke encephalopathy is often followed by Korsakoff syndrome, which consists of anterograde amnesia (inability to form new memories) and retrograde amnesia (inability to remember events in the past; recent memory is usually affected more than remote memory). Patients often confabulate early in the course. Causes of Wernicke-Korsakoff syndrome from thiamine deficiency may include alcohol use or chronic malnutrition, bariatric surgery, hyperemesis gravidarum, dieting or anorexia, malignancy, or AIDS. Early treatment with parenteral thiamine is essential when there is any suspicion and should not await diagnostic confirmation. More details on this syndrome are provided in Chapter 78, "Neurologic Complications of Nutritional Disorders."

Marchiafava-Bignami Disease

Marchiafava-Bignami disease was initially described in drinkers of Italian red wine, but it has since been described in others with chronic alcoholism associated with other alcoholic beverages. Presentation may be acute, with altered consciousness progressing to coma. Presentations may also be subacute and chronic, in which a callosal disconnection syndrome may occur with left-sided apraxia and hemialexia without agraphia. The hallmark finding is demyelination in the corpus callosum, usually involving the central regions (Figure 33.3). This is often followed by necrosis, hemorrhage, and cavitation of the corpus callosum. MRI may show callosal enhancement early on and T2-signal changes and atrophy in the later stages.

Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency is a reversible cause of dementia, and laboratory testing for this is recommended in all patients presenting with dementia. A low-normal vitamin B_{12} value should prompt assessment for an increased methylmalonic acid value, which is more sensitive for the diagnosis of B_{12} deficiency. Patients may present with neuropsychiatric symptoms and a coexisting optic atrophy, peripheral neuropathy, or subacute combined degeneration of the spinal cord. See also Chapter 78, "Neurologic Complications of Nutritional Disorders."

Pellagra (Niacin Deficiency)

Vitamin B_3 (niacin) deficiency is known as pellagra and causes the 3 *d*s of diarrhea, dermatitis (erythematous lesions), and dementia, which at times may be rapidly progressive, mimicking Creutzfeldt-Jakob disease.

- Wernicke encephalopathy consists of the clinical triad of global confusion, truncal ataxia, and ophthalmoplegia or nystagmus.

- Vitamin B_3 (niacin) deficiency is known as pellagra and causes the 3 *d*s of diarrhea, dermatitis (erythematous lesions), and dementia.

Inherited Metabolic Causes of Dementia

Certain inherited metabolic disorders are associated with cognitive decline and may present at a younger age. These include mitochondrial disorders (eg, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes), inherited leukodystrophies (eg, adult onset of X-linked adrenoleukodystrophy), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and other lysosomal storage disorders (Niemann-Pick disease).

Adult Polyglucosan Body Disease

One inherited disorder that deserves mention, because its presentation is often late in adulthood, is that of adult polyglucosan body disease. Its onset is between the fifth and seventh decades of life, and the symptoms are slowly progressive. It most often occurs in the Ashkenazi Jewish population and is due to an autosomal recessive genetic deficiency of the glycogen brancher enzyme. Presenting features include peripheral neuropathy, dementia, neurogenic bladder, and upper motor neuron signs. MRI often shows a leukodystrophy, and spinal cord atrophy is also frequently present. Periodic acid-Schiff–positive polyglucosan bodies are a nonspecific finding in peripheral nerves and may be found occasionally in healthy persons, but extensive amounts may suggest the diagnosis. In the brain, the equivalent corpora amylacea are typically in superficial cortical layers in healthy persons, but they may be scattered more extensively in adults with polyglucosan body disease.

Dementia Due to Trauma

Head trauma may affect cognition in various ways. Severe head injury may result in focal hemorrhage or contusion, shear force injury, and concussion. Repetitive traumatic injury may also result in an increased risk of Alzheimer disease, chronic traumatic encephalopathy, or perhaps other neurodegenerative diseases.

Postconcussive Syndrome

Delayed deterioration after concussion is known as postconcussive syndrome and consists of inattention, impaired working memory, psychomotor slowing, dizziness, posttraumatic headache, and psychiatric symptoms. Treatment involves symptomatic management and reassurance because most patients improve within 3 months.

Cerebral Contusion

The frontotemporal regions are most commonly affected by cerebral contusions. Disinhibition, personality change, and executive dysfunction are common. Unilateral temporal lobe injury may cause learning and memory troubles, whereas bilateral anterior temporal lobe lesions may cause Klüver-Bucy syndrome (hyperorality, hypersexuality, hypermetamorphosis [irresistible impulse to explore everything in environment], and docility [diminished fear and low aggression]).

Posttraumatic epilepsy may also contribute to cognitive difficulties.

Dementia Pugilistica (Chronic Traumatic Encephalopathy)

Progressive cognitive deterioration has been reported in up to 17% of professional boxers and can occur in athletes who participate in other contact sports as a condition called dementia pugilistica or chronic traumatic encephalopathy. Recent neuropathologic studies have shown that chronic traumatic encephalopathy is often associated with underlying tau abnormality and have suggested it be considered a progressive tauopathy.

The presentation may occur many years after retiring from competition. The clinical features include an akinetic rigid form of parkinsonism, pyramidal signs, psychomotor slowing, memory difficulties, and attention problems.

MRI using gradient echo sequences or susceptibility-weighted imaging is sensitive to hemosiderin deposition and may be helpful in the evaluation of suspected chronic traumatic encephalopathy.

Overall, treatment of cognitive difficulties related to trauma mostly involves cognitive behavioral therapy, but the treatment of coexisting psychiatric disorders should not be overlooked.

- Recent neuropathologic studies have shown that chronic traumatic encephalopathy is often associated with underlying tau abnormality and have suggested it be considered a progressive tauopathy.

Dementia Due to Structural Lesions

Structural lesions may cause cognitive deterioration, and thus neuroimaging is important in the initial evaluation of dementia. Causes may include vascular conditions (stroke, subdural, vascular malformations, siderosis), neoplasms (primary or metastases), infections (abscesses, meningoencephalitis, progressive multifocal leukoencephalopathy), and radiation necrosis.

Neoplastic lesions cause about 1.5% of all cases of dementia and may consist of primary malignant cerebral tumors (eg, astrocytoma), central nervous system

lymphoma, metastatic tumors, or benign tumors with symptoms from mass effect. The cognitive syndrome depends on the location and size of the lesion. For example, frontal lobe tumors are often large at presentation, and patients may present with apathy, perseveration, and personality changes. Alternatively, masses in the thalamic or hypothalamic region may present with cognitive symptoms when they are relatively small.

Normal-Pressure Hydrocephalus

Definition

Normal-pressure hydrocephalus is characterized by evidence of hydrocephalus with normal cerebrospinal fluid pressure (although prolonged monitoring may show transient increases of Lundberg waves).

Clinical Presentation

The presentation consists of the insidious onset of a clinical triad of gait disturbance, urinary incontinence, and dementia. Neurologic examination shows gait apraxia or magnetic gait (difficulty lifting feet from floor), decreased stride length, wide-based gait, and the need for multiple steps to turn. Early urinary urge incontinence may be followed by a later lack of concern for incontinence. The cognitive disturbance consists of slowing of thought process (bradyphrenia), decreased attention, impaired working memory, and problems of executive function. This subcortical dementia is thought to be due to the hydrocephalus impinging on periventricular frontostriatal projections. Other features that may be present include parkinsonism, pyramidal signs, and paratonia. Congenital hydrocephalus that becomes symptomatic later in life may contribute to normal-pressure hydrocephalus; thus, asking about hat size and measuring head circumference may be helpful.

Diagnosis

MRI of the brain usually shows ventriculomegaly out of proportion to cortical atrophy, and loss of sulci superiorly may be a helpful sign (Figure 33.4). Other MRI findings may include periventricular white matter changes from transependymal flow and a T2-signal hypointense flow void in the cerebral aqueduct.

A large-volume (30–50 mL) lumbar puncture and video of gait before and after the procedure (needs to be done within 60 minutes after lumbar puncture because cerebrospinal fluid reaccumulates quickly) are used to assess for improvement. A response is considered positive when there is improvement of gait (ideally, this judgment is based on a quantitative measure such as time taken to ambulate a specified distance). This test result has a good predictive value for improvement with shunt. However, rare patients who do not improve with large-volume lumbar puncture may improve with a shunt. Cisternography is sometimes performed by injecting isotope into the lumbar cistern, and the absence of diffusion to convexities at 72 hours is suggestive of normal-pressure hydrocephalus.

Treatment

The definitive treatment of normal-pressure hydrocephalus involves insertion of a shunt, which is usually ventriculoperitoneal. The gait difficulties and urine incontinence are more likely to respond than the dementia. Good

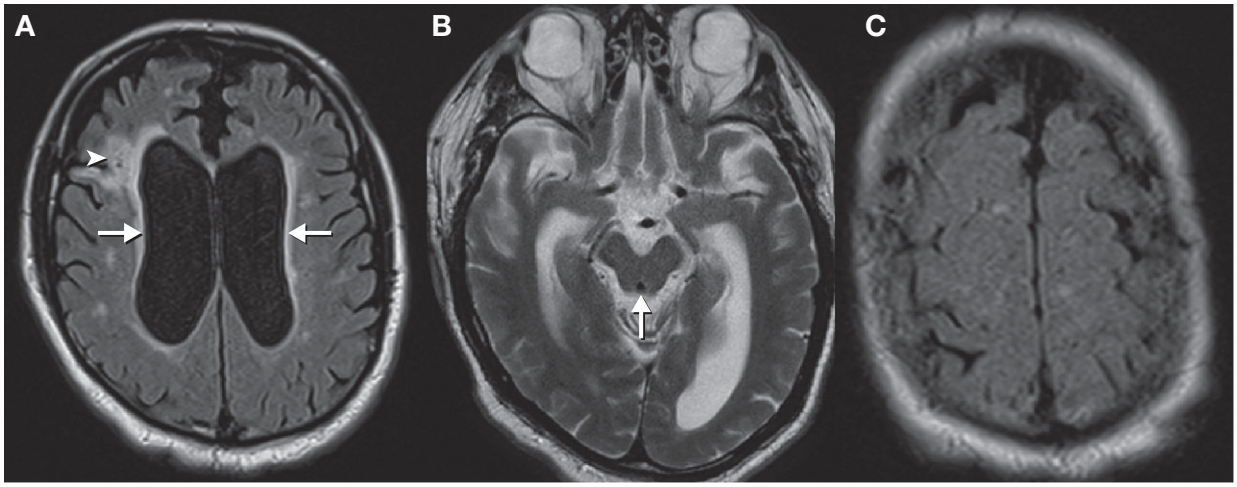

Figure 33.4 *Magnetic Resonance Imaging Findings in Normal-pressure Hydrocephalus.*
Enlarged ventricles are out of proportion to atrophy (A) with transependymal flow (A, white arrows) and incidental old infarct (A, arrowhead). A T2-hypointense flow void is noted (B, white arrow) with prominence of sulci superiorly also evident (C).

prognostic factors include young age, short duration of symptoms (<36 months), prominent early gait disturbance, minimal or no cognitive dysfunction, and positive response to large-volume lumbar puncture. Benefits of shunting may not be sustained long term, raising the possibility of coexistent neurodegenerative disease in some cases.

- The presentation of normal-pressure hydrocephalus consists of the insidious onset of a clinical triad of gait disturbance, urinary incontinence, and dementia.
- A large-volume (30–50 mL) lumbar puncture and video of gait before and after the procedure (needs to be done within 60 minutes after lumbar puncture because cerebrospinal fluid reaccumulates quickly) are used to assess for improvement.

Obstructive Sleep Apnea

Obstructive sleep apnea has been associated with cognitive impairment and tends to affect sustained attention, executive function, and motor planning while preserving language and intelligence. Because many of the comorbidities associated with sleep apnea, such as cigarette smoking, treatment-resistant hypertension, diabetes, cerebrovascular disease, obesity, congestive heart failure, alcohol, use of hypnotic medication, and hypothyroidism, may also cause cognitive impairment in their own right, it is difficult to assess the overall impact of obstructive sleep apnea on cognition. However, it has been shown to be an independent risk factor for cognitive impairment. The suggested pathophysiologic mechanisms have included hypoxemia resulting in subsequent reperfusion brain injury, endothelial dysfunction causing a vascular-type dementia, and excessive daytime somnolence affecting daily functioning.

Treatment with continuous positive airway pressure may help improve symptoms, but residual cognitive dysfunction may remain. It is a possible reversible contributor to cognitive impairment, and asking about its symptoms is important when evaluating patients with dementia.

Other Related Cognitive Disorders

Pseudodementia (Depression)

Depression-associated dementia, or pseudodementia, may mimic dementia, and patients are usually aware of the problem. Depression may also be a prodrome to the diagnosis of Alzheimer disease. Cognitive deficits in pseudodementia are characterized by poor effort and difficulties with attention and working memory (more than delayed recall). Ganser syndrome of approximate answers, in which answers are consistently nearly correct but still incorrect, may occur in pseudodementia but is also present with malingering. Poor sleep hygiene and decreased appetite may coexist with pseudodementia. Dysfunction of noradrenergic pathways from the locus ceruleus may explain anhedonia, apathy, and anorexia. Serotonergic and cholinergic pathways may explain the guilt, depressed mood, and suicidal ideation. Selective serotonin reuptake inhibitors are first-line agents.

Fugue

Fugue is a psychiatric disorder characterized by reversible amnesia for personal identity that may last hours to months. It can be distinguished from transient global amnesia by loss of personal identity (which is preserved in transient global amnesia) and the duration frequently being more than 24 hours (which does not occur with transient global amnesia). Dissociative fugue involves loss of identity that results in unplanned travel and sometimes establishing a new identity in a new location. In transient global amnesia, no treatment is necessary and the prognosis is benign, although up to 25% of patients may have a recurrence.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

V.1. Which of the following is the most significant risk factor for delirium?
a. Age younger than 50 years
b. Underlying cognitive disorder
c. Hypertension
d. Independent living status
e. Diabetes mellitus

V.2. Which of the following is recommended for the treatment of delirium?
a. Administering intravenous thiamine early for patients at risk for nutritional deficiency
b. Administering antipsychotics early to prevent agitation and hallucinations
c. Using physical restraints
d. Deferring management of contributing medical factors until the delirium has resolved
e. Avoiding sensory cues and day-night orientation

V.3. Which of the following is true with regard to Wernicke encephalopathy and Korsakoff syndrome?
a. Thiamine administration is not indicated for patients without the triad of global confusion, truncal ataxia, and ophthalmoplegia or nystagmus
b. Korsakoff syndrome typically consists of both anterograde and retrograde amnesia
c. Magnetic resonance imaging may show abnormalities in medial brain structures such as mammillary bodies, thalamus, and periaqueductal gray
d. Choices *a* and *b* only
e. Choices *b* and *c* only

V.4. Which of the following is a characteristic of the neocortex?
a. Reciprocal connections with the homologous cortical region in the ipsilateral hemisphere
b. Reciprocal connections with the rostral ("forward") and caudal ("backward") proximate ipsilateral cortical regions
c. Eight-layer cytoarchitecture with a differential expansion of specific layers dependent on the neocortical region
d. Subpial "neuropoiesis" that continues until the sixth decade of life
e. Neuronal populations that are uniquely resistant to hypoxia

V.5. Which of the following cortical regions is included in the default network?
a. Inferior prefrontal
b. Precuneus
c. Anterior cingulate
d. Occipital
e. Lateral prefrontal

V.6. Impaired fluency, phonemic paraphasic errors, preserved repetition, and preserved comprehension would characterize which aphasia syndrome?
a. Broca aphasia
b. Wernicke aphasia
c. Transcortical motor aphasia
d. Transcortical sensory aphasia
e. Anomic aphasia

V.7. Which of the following is an example of a perceptual agnosia?
a. Synesthesia
b. Dressing dyspraxia
c. Astereognosis
d. Simultanagnosia
e. Visual hallucinations

V.8. What percentage of amnestic patients who have mild cognitive impairment and who progress to dementia have clinical Alzheimer disease?
a. 90%
b. 75%
c. 50%
d. 25%
e. 15%

V.9. Which of the following is a risk factor for Alzheimer disease?
a. Head trauma
b. Hypothyroidism
c. Higher socioeconomic status
d. Male sex
e. Above-average academic performance

V.10. Which of the following genes provides the greatest risk of developing Alzheimer disease in persons older than 65?
a. *APP*
b. *PSEN1*
c. *PSEN2*
d. *APOE*
e. *TREM2*

V.11. Which of the following is a core clinical feature of diffuse Lewy body disease?
a. Intermittent parkinsonism
b. Anterograde amnesia
c. Rapid eye movement sleep behavior disorder
d. Neuroleptic sensitivity
e. Auditory hallucinations

V.12. Which of the following imaging findings is most typical of dementia with Lewy bodies?
a. Hippocampal atrophy on magnetic resonance imaging
b. Reduced striatonigral uptake on dopamine transporter imaging using isoflupane single-photon emission computed tomography (DaTscanning)
c. Parietal and temporal hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET)
d. Ventriculomegaly on computed tomography
e. Diffusely increased cortical uptake with amyloid-specific PET

V.13. Which of the following are helpful clinical features to differentiate corticobasal degeneration from progressive supranuclear palsy?
a. Asymmetric rigidity and apraxia
b. Postural instability and falls
c. Language dysfunction
d. Choices *a* and *b* only
e. Choices *b* and *c* only

V.14. Parkinsonism is frequently levodopa-responsive in which of the following syndromes?
a. Frontotemporal dementia with parkinsonism associated with *MAPT* mutations
b. Corticobasal degeneration
c. Progressive supranuclear palsy
d. Multiple system atrophy
e. Idiopathic Parkinson disease

V.15. Mutations in which of the following genes are the most common autosomal dominant causes of familial frontotemporal dementia?
a. *PGRN, FUS, MAPT*
b. *PGRN, C9orf72, TARDBP*
c. *PGRN, C9orf72, MAPT*
d. *FUS, TARDBP, VCP*
e. *VCP, MAPT, PGRN*

V.16. Which of the following are common clinical features of behavioral variant frontotemporal dementia?
a. Disinhibition
b. Perseverative, stereotyped, or compulsive behavior
c. Parkinsonism
d. Choices *a* and *b* only
e. Choices *b* and *c* only

V.17. Which histopathologic finding is typically present in logopenic variant primary progressive aphasia?
a. Frontotemporal lobe degeneration (FTLD) with tau-positive inclusions (FTLD-tau)
b. FTLD with ubiquitin and transactive response DNA-binding-43–positive inclusions but tau-negative inclusions (FTLD-TDP) abnormality
c. FTLD with ubiquitin-positive, TDP-43–positive, and *FUS*-positive (FTLD-*FUS*) abnormality
d. Pick body abnormality
e. Alzheimer disease abnormality

Answers

V.1. Answer b.
Flaherty JH. The evaluation and management of delirium among older persons. Med Clin North Am. 2011 May;95(3):555–77. Epub 2011 Mar 31.

V.2. Answer a.
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V.3. Answer e.
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V.4. Answer b.
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V.5. Answer b.
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V.6. Answer c.
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V.7. Answer d.
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V.8. Answer a.
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V.9. Answer a.
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V.10. Answer d.
Ertekin-Taner N. Genetics of Alzheimer's disease: a centennial review. Neurol Clin. 2007 Aug;25(3):611–67.

V.11. Answer c.
Boeve BF. Parkinson-related dementias. Neurol Clin. 2007 Aug;25(3):761–81.

V.12. Answer b.
Taylor JP, O'Brien J. Neuroimaging of dementia with Lewy bodies. Neuroimaging Clin N Am. 2012 Feb;22(1):67–81.

V.13. Answer d.
Boeve BF. Diagnosis and management of non-Alzheimer dementias. In: Noseworthy JH, editor. Neurological therapeutics: principles and practice. 2nd ed. Abingdon (UK): Informa Healthcare; c2006; p. 3156–206.

V.14. Answer e.
Boeve BF. Diagnosis and management of non-Alzheimer dementias. In: Noseworthy JH, editor. Neurological therapeutics: principles and practice. 2nd ed. Abingdon (UK): Informa Healthcare; c2006; p. 3156–206.

V.15. Answer c.
Boeve BF. Diagnosis and management of non-Alzheimer dementias. In: Noseworthy JH, editor. Neurological therapeutics: principles and practice. 2nd ed. Abingdon (UK): Informa Healthcare; c2006; p. 3156–206.

V.16. Answer d.
Boeve BF. Diagnosis and management of non-Alzheimer dementias. In: Noseworthy JH, editor. Neurological therapeutics: principles and practice. 2nd ed. Abingdon (UK): Informa Healthcare; c2006; p. 3156–206.

V.17. Answer e.
Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol. 2010 Jan;119(1):1–4. Epub 2009 Nov 19.

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Section
VI

Epilepsy

Katherine H. Noe, MD, PhD, *editor*

34 Epilepsy Classification

KRISTINE S. ZIEMBA, MD, PHD; KATHERINE H. NOE, MD, PHD

Introduction

A firm understanding of the definitions of *seizures* and *epilepsy*, seizure semiology, and classification is important in the initial approach to a patient presenting with seizure. Characterizing the seizures appropriately helps narrow the differential diagnosis and leads to appropriate diagnostic testing and identification of electroclinical syndromes. *Electroclinical syndromes* are clinical entities that are identified by a cluster of clinical and electroencephalographic (EEG) characteristics that occur together.

This chapter reviews the basic definitions and classifications of seizure disorders and epilepsy. Select epilepsy syndromes are also reviewed.

Basic Definitions

Seizures and Epilepsy

A *seizure* is a transient occurrence of signs or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain. A seizure may be provoked or unprovoked. A *provoked seizure* is a seizure caused by an acute insult to the nervous system or by an acute systemic metabolic derangement. Examples of these insults and derangements include acute intracerebral hemorrhage, hypoglycemia, hyponatremia, alcohol withdrawal, and drugs. *Unprovoked seizure* is a seizure of unknown cause or one arising from a remote symptomatic cause such as a prior stroke, head trauma, metabolic disorder, or developmental abnormality.

Epilepsy refers to a condition in which a tendency to have seizures is present, defined by a history of 2 or more *unprovoked* seizures. Several proposed changes to terminology have been suggested by the International League Against Epilepsy (ILAE). Older terms and proposed terms are reviewed here and summarized in Table 34.1. *Idiopathic epilepsy* refers to epilepsy with a known genetic origin (for which seizures are the sole or primary manifestation) or of unknown cause other than possible hereditary disposition. This term may be replaced by *genetic/presumed genetic epilepsy* or *epilepsy of unknown cause. Symptomatic epilepsy* refers to epilepsy with an identifiable cause, often a structural brain lesion or a disease for which epilepsy is a secondary symptom (eg, tuberous sclerosis). This term may be replaced by *structural/metabolic. Cryptogenic epilepsy* refers to epilepsy that is presumed symptomatic but from an undefined cause. This term may be replaced by *epilepsy of unknown cause. Reflex epilepsy* refers to recurrent seizures precipitated by a stimulus (visual stimulus, eating, music, reading, or startle).

Despite the cause, epilepsy may be characterized by its response to medical therapy. *Medically refractory/intractable epilepsy* refers to epilepsy that does not respond to adequate trials of 2 different antiepileptic medications. Patients with this form of epilepsy should be referred for consideration of surgical intervention.

- *Epilepsy* refers to a condition in which a tendency to have seizures is present, defined by a history of 2 or more *unprovoked* seizures.
- *Symptomatic epilepsy* refers to epilepsy with an identifiable cause, often a structural brain lesion or a disease for which epilepsy is a secondary symptom (eg, tuberous sclerosis). This term may be replaced by *structural/metabolic*.

Abbreviations: EEG, electroencephalographic; ILAE, International League Against Epilepsy; MRI, magnetic resonance imaging

Table 34.1 • Proposed Changes in Seizure and Epilepsy Terminology and Concepts by the International League Against Epilepsy

New Term	Old Term
Genetic—genetic defect directly contributes to the epilepsy, and seizures are the core symptom of the disorder	Idiopathic—presumed genetic
Structural/metabolic—caused by a structural or metabolic disorder of the brain	Symptomatic—secondary to a known or presumed disorder of the brain
Unknown—cause is unknown and might be genetic, structural, or metabolic	Cryptogenic—presumed symptomatic
Focal seizure—seizure semiology described according to specific subjective (auras), motor, autonomic, and dyscognitive features	Complex partial Simple partial
Evolving to a bilateral convulsive seizure	Secondarily generalized

Data from Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010 Apr;51(4):676–85. Epub 2010 Feb 26.

Characterization and Classification of Seizures and Epilepsy

Overview

Seizures and, by extension, forms of epilepsy are classified according to a few key features: mode of seizure onset (generalized seizure or focal or partial seizure), ictal signs and symptoms (semiology), and underlying cause (if known). Age at seizure onset, EEG findings, and other distinctive clinical, pathologic, or metabolic features further help to classify types of epilepsy and syndromes. The ILAE has proposed a simplified scheme for the classification of seizures (Box 34.1).

Focal Seizures

Focal seizures (also referred to as *partial seizures*) are characterized by an onset limited to 1 hemisphere, but the seizures may be discretely localized or more widely distributed within that hemisphere. Focal seizures are further subdivided into those including alterations in consciousness or awareness (*complex partial seizures*) and those in which a normal level of consciousness is maintained (*simple partial seizures*).

Focal seizures may secondarily generalize as synchronous electrical activity spreads to the contralateral hemisphere. The most common type of focal epilepsy is mesial temporal lobe epilepsy, often caused by mesial temporal sclerosis.

Semiology of focal seizures depends on the location of the seizure focus, and different clinical features may appear as the ictal activity spreads to adjacent brain regions. Typical examples of semiology based on location of onset are presented in Table 34.2.

The semiology may also help in lateralizing the seizure. The timing of head turn can be important in distinguishing the localization of the seizure. An early, nonforced head turn may localize seizures to the ipsilateral temporal lobe. A voluntary head turn is often associated with dystonic posturing of the contralateral extremity. A forced head turn (Figure 34.1) is usually due to a seizure focus in the contralateral hemisphere, unless it occurs after a generalized seizure. A forced head turn involves a

Box 34.1 • Classification of Seizures Proposed by the International League Against Epilepsy

- Focal seizures
  - May evolve to bilateral convulsive seizure
  - Characterized according to ≥1 of the following features: aura, autonomic, motor, and awareness or responsiveness
- Generalized seizures
  - Tonic-clonic
  - Absence
    - Typical
    - Absence with special features
    - Atypical
  - Clonic
  - Tonic
  - Atonic
  - Myoclonic
    - Myoclonic
    - Myoclonic-atonic
    - Myoclonic-tonic
- Unknown

Adapted from Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010 Apr;51(4):676–85. Epub 2010 Feb 26. Used with permission.

Table 34.2 • Semiology of Seizures by Location of Onset

Seizure Focus	Typical Features
Mesial temporal lobe	Aura (start of seizure, felt by patient)—psychic phemomena (déjà vu, fear), olfactory or gustatory hallucinations, autonomic features (light-headedness, flushing), vertigo, epigastric rising sensation Observable features—restlessness or agitation, speech arrest or aphasia, confusion, oral or manual automatisms (chewing, lip smacking, picking with hands; usually ipsilateral), dystonic posturing of contralateral limb
Lateral temporal lobe	Auditory auras, visual hallucinations, vertigo
Frontal lobe	Often occurs out of sleep Brief events with hyperkinetic bilateral motor movements (kicking, bicycling, thrashing, clapping, etc) Usually preserved awareness and postictal fatigue May cluster May be confused with psychogenic, nonepileptic events
Motor strip	Contralateral tonic or clonic limb movements May have jacksonian march
Parietal lobe	Subjective sensory symptoms—pins and needles, electric shock sensations, numbness
Occipital lobe	Flashing lights, visual loss or poorly formed visual hallucinations (abstract shapes, etc)

prominent contraction of neck muscle and does not appear voluntary. It tends to occur early in frontal lobe seizures and later in temporal lobe foci. If a forced head turn occurs after a generalized tonic-clonic seizure, it is usually ipsilateral to seizure onset. This is probably due to spread of seizure activity to the hemisphere contralateral to the seizure onset.

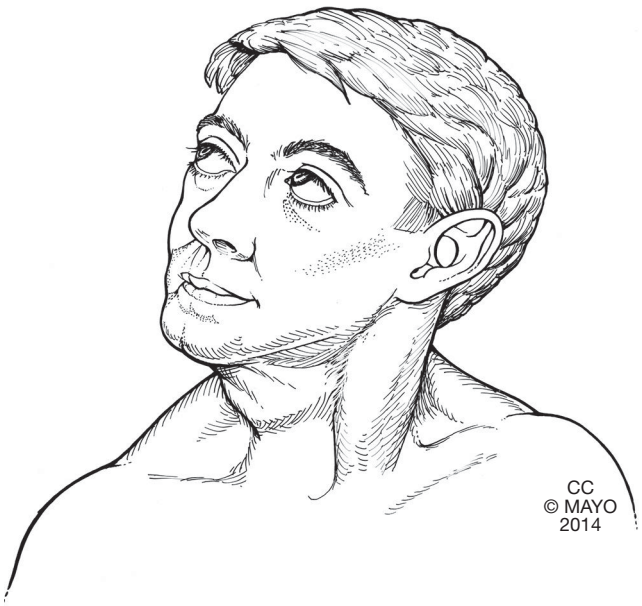

Figure 34.1 *Forced Head Turn and Eye Deviation.*
(Adapted from Bell ML. Epilepsy. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 485–525. Used with permission of Mayo Foundation for Medical Education and Research.)

The figure 4 sign (Figure 34.2) is characterized by tonic extension of 1 arm and flexion of the other. It is often a sign associated with a seizure focus in the contralateral hemisphere to the extended arm. A fencing posture (Figure 34.3) is also a finding in patients with a seizure focus contralateral to the extended arm, often in the supplementary motor area. Additional clues to localization and lateralization based on semiology are summarized in Table 34.3.

Generalized Seizures

Generalized seizures arise in both hemispheres simultaneously. The clinical result is impaired consciousness, with or without bilateral motor manifestations. The seizure types discussed below are included as primary generalized seizures (see also Box 34.1).

Generalized Tonic-Clonic Seizure

The generalized tonic-clonic seizure is characterized by a tonic phase followed by a clonic phase. During the tonic phase, the eyes remain open but roll up, the pupils dilate, the elbows flex, and the arms pronate. Incontinence, moaning, and apnea may occur during this phase. Generalized clonic movements occur during the clonic phase. With time, the amplitude of the tonic movements increases and the frequency decreases. Tongue biting and apnea may occur during this phase. After the seizure, patients may be in a postictal state of confusion and have fatigue, headache, and muscle soreness.

Generalized Tonic Seizure

A tonic seizure is characterized most commonly by increased tone in the axial muscles and the proximal muscles of the limbs. These seizures typically last only seconds.

Figure 34.2 *Figure 4 Sign.*
(Adapted from Bell ML. Epilepsy. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 485–525. Used with permission of Mayo Foundation for Medical Education and Research.)

Figure 34.3 *Fencing Posture.*
(Adapted from Bell ML. Epilepsy. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 485–525. Used with permission of Mayo Foundation for Medical Education and Research.)

Generalized Clonic Seizure
A clonic seizure is similar to the clonic phase of a generalized tonic-clonic seizure.

Absence Seizure
An absence seizure is characterized by the abrupt onset of a brief (seconds) loss of awareness. These seizures may be associated with automatisms or loss of muscle tone. Absence seizures are associated with 3-Hz spike-and-wave discharges on EEG. Patients with atypical absence seizure have absence seizures that last longer (minutes) and often have loss of postural tone.

Myoclonic Seizure
Myoclonic seizures are characterized by a shocklike jerk of any body part, which is often a limb.

Atonic Seizure
Atonic seizures are characterized by a sudden loss of tone of the entire body (drop attacks) lasting seconds.

Infantile Spasms
Infantile spasms are discussed in the "Infantile Spasms and West Syndrome" section.

- Seizures and, by extension, forms of epilepsy are classified according to a few key features: mode of seizure onset (generalized seizure or focal or partial seizure), ictal signs and symptoms (semiology), and underlying cause (if known).
- An early, nonforced head turn may localize seizures to the ipsilateral temporal lobe.
- A forced head turn is usually due to a seizure focus in the contralateral hemisphere, unless it occurs after a generalized seizure.

Table 34.3 • Description and Localization Based on Semiology of Focal Seizures

Finding	Description	Localization
Head turn	Early, nonforced Forced head turn	Ipsilateral temporal Contralateral hemisphere (except if after a generalized seizure)
Eye deviation	May accompany forced head turns (same direction and upward)	Eye deviation in isolation suggests occipital lobe initiation contralateral to direction of gaze
Focal clonic	Clonic movement of a limb	Frontal or perirolandic Sometimes temporal (contralateral to symptoms)
Focal tonic	Extension of limb	Contralateral hemisphere
Figure 4 sign	Tonic posture with 1 arm extended and the other flexed Forced head turn may occur toward the extended arm	Hemisphere contralateral to the extended arm
Focal dystonic	Sustained, contorted posturing of limb	Contralateral hemisphere
Fencing posture	Lateral abduction and external rotation of arm with forced head turn toward that arm	Hemisphere (frontal supplemental motor area more than temporal) contralateral to the extended limb
Ictal paresis	Paresis of a limb	Contralateral hemisphere
Todd paralysis	Hemiparesis after seizure	Extratemporal more than temporal
Unilateral blinking	Appears like winks	Ipsilateral hemisphere
Unilateral limb automatism	Simple or complex automatic behavior (eg, using a pen)	Ipsilateral hemisphere
Postictal nose rubbing	Rubbing nose after seizure	Hemisphere ipsilateral to the hand used Temporal more than frontal
Postictal cough	Cough after seizure	Temporal
Bipedal automatism	Bicycling movement	Frontal more than temporal
Hypermotor	Violent thrashing of extremities	Frontal lobe (supplemental motor area)
Gelastic	Laughter	Hypothalamus or mesial temporal
Ictal spitting	Spitting during seizure	Right temporal
Ictal vomiting	Vomiting or wretching during seizure	Right temporal
Loud vocalization	Grunt, scream, moan	Frontal more than temporal
Speech arrest	Cease speaking	Dominant temporal
Postictal aphasia	Aphasia after seizure	Dominant hemisphere
Ictal drooling	Drooling during ictus	Nondominant hemisphere
Postictal confusion	Confusion after ictus	Temporal more prolonged Frontal—short, if present
Visual symptoms	Elementary visual: circles, spots, flashes, scotoma	Occiptal
Complex visual hallucinations	Complex visual: complex, colorful, previously experienced images; sometimes metamorphopsia (objects appear distorted) or micropsia (objects appear small)	Occipitotemporoparietal junction (nondominant)

- *Generalized seizures* arise in both hemispheres simultaneously. The clinical result is impaired consciousness, with or without bilateral motor manifestations.
- Absence seizures are associated with 3-Hz spike-and-wave discharges on EEG.

Overview of Epilepsy Syndromes

Electroclinical syndromes are clinical entities identified by a cluster of clinical and EEG characteristics that occur together (Box 34.2). Examples include West syndrome, Lennox-Gastaut syndrome, and childhood absence epilepsy.

Box 34.2 • International League Against Epilepsy Classification of Epilepsy Syndromes

Electroclinical syndromes arranged by age at onset[a]

- Neonatal period
  - Benign familial neonatal epilepsy (BFNE)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- Infancy
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy
  - Dravet syndrome
  - Myoclonic encephalopathy in nonprogressive disorders
- Childhood
  - Febrile seizures plus (FS+) (can start in infancy)
  - Panayiotopoulos syndrome
  - Epilepsy with myoclonic-atonic (previously astatic) seizures
  - Benign epilepsy with centrotemporal spikes (BECTS)
  - Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
  - Late-onset childhood occipital epilepsy (Gastaut type)
  - Epilepsy with myoclonic absences
  - Lennox-Gastaut syndrome
  - Epileptic encephalopathy with continuous spike-and-wave discharges during sleep (CSWS)[b]
  - Landau-Kleffner syndrome (LKS)
  - Childhood absence epilepsy (CAE)
- Adolescence to adulthood
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalized tonic-clonic seizures alone
  - Progressive myoclonus epilepsies (PMEs)
  - Autosomal dominant epilepsy with auditory features (ADEAF)
  - Other familial temporal lobe epilepsies
- Less specific age relationship
  - Familial focal epilepsy with variable foci (childhood to adulthood)
  - Reflex epilepsies

Distinctive constellations

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion-hemiplegia-epilepsy syndrome
- Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs focal)

Epilepsies attributed to and organized by structural-metabolic causes

- Malformations of cortical development (hemimegalencephaly, heterotopias, etc)
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc)
- Tumor
- Infection
- Trauma
- Angioma
- Perinatal insults
- Stroke
- Other

Epilepsies of unknown cause

Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se

- Benign neonatal seizures (BNSs)
- Febrile seizures (FSs)

[a] The arrangement of electroclinical syndromes does not reflect etiology.

[b] Sometimes referred to as electrical status epilepticus during slow sleep (ESES).

Adapted from Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010 Apr;51(4):676–85. Epub 2010 Feb 26. Used with permission.

Some syndromes have a characteristic EEG pattern (Table 34.4), and some syndromes are associated with simple genetic inheritance (Box 34.3). Identifying a particular syndrome may help to direct therapy because certain drugs have proven efficacy in some syndromes.

Table 34.4 • Syndromes Associated With Characteristic EEG Patterns

Syndrome	EEG Pattern
Childhood and juvenile absence seizures	3-Hz spike-and-wave
Lennox-Gastaut syndrome	Slow spike-and-wave
Generalized seizures	Atypical spike-and-wave Polyspike-and-wave Paroxysmal fast activity Fast repetitive spikes
Infantile spasms, West syndrome	Hypsarrhythmia

Abbreviation: EEG, electroencephalographic.

Adapted from Bell ML. Epilepsy. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 485–525. Used with permission of Mayo Foundation for Medical Education and Research.

Box 34.3 • Epilepsy Syndromes With Simple Genetic Inheritance

Generalized epilepsy with febrile seizures plus

- Autosomal dominant
  - Sodium channel *SCN1B* (chromosome 19)
  - Sodium channel *SCN1A* (chromosome 2)
  - Sodium channel *SCN2A*
  - $GABA_A$ (chromosome 5)

Benign familial neonatal convulsions

- Autosomal dominant
  - Voltage-dependent potassium channel *KCNQ2* (chromosome 20)
  - Voltage-dependent potassium channel *KCNQ3* (chromosome 8)

Autosomal dominant partial epilepsy with auditory features

- Autosomal dominant
  - *LGI1*, leucine-rich, glioma-inactivated 1 gene (chromosome 10)

Abbreviation: GABA, γ-aminobutyric acid.

Adapted from Bell ML. Epilepsy. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 485–525. Used with permission of Mayo Foundation for Medical Education and Research.

- Electroclinical syndromes are clinical entities identified by a cluster of clinical and EEG characteristics that occur together.

Neonatal and Childhood Epilepsy Syndromes

Overview

Patients with certain epilepsy syndromes present in the neonatal and childhood years (Table 34.5). Select disorders are described below.

Benign Familial Neonatal Convulsions

Overview

Benign familial neonatal convulsions has also been called *fifth day fits* because its onset is in the neonatal period. It can be idiopathic or familial. The benign familial neonatal convulsion syndrome is due to an autosomal dominant channelopathy with mutations of the *KCNQ2* (chromosome 20) and *KCNQ3* (chromosome 8) genes.

Clinical Features

Patients may have clonic or myoclonic seizures that begin in the first few weeks after birth and usually stop by 6 weeks. Neonates are otherwise developmentally normal.

Diagnosis

EEG findings are variable but typically show focal, multifocal, or bilateral sharp waves, spikes, or spike-and-wave patterns.

Treatment and Prognosis

The condition is self-limited, so treatment may not be needed. About 10% to 15% of children may have seizures later, and 33% may have febrile seizures.

Infantile Spasms and West Syndrome

Overview

West syndrome is characterized by infantile spasms (a seizure type), hypsarrhythmia, and developmental arrest. Infantile spasms may be a part of Aicardi syndrome (characterized by infantile spasms, agenesis of the corpus callosum, and retinal malformation).

Clinical Features

Infantile spasms occur typically during infancy. They are characterized by a sudden jackknife-like movement, with flexion of the neck, trunk, and limbs, and may be accompanied by waist flexion and head droop. They often occur in clusters.

West syndrome is characterized by infantile spasm, hypsarrhythmia on EEG, and developmental arrest. It may

Table 34.5 • Common Epilepsy Syndromes of Neonates and Infants

Syndrome	Classification	Clinical Features	EEG Findings	Prognosis	Drugs of Choice and Miscellaneous Pearls
Benign neonatal convulsions	Idiopathic, generalized Familial, genetic form (*KCNQ2* and *KCNQ3* mutations)	Focal clonic or hemiclonic seizures May progress to status epilepticus	Normal, focal, or multifocal	Excellent	Child is normal between seizures Familial form with autosomal dominant inheritance
Ohtahara syndrome (early infantile epileptic encephalopathy)	Symptomatic	Tonic spasms Often hundreds daily	Burst-suppression	Poor Can evolve into West syndrome or Lennox-Gastaut syndrome	Often arising from cortical dysplasia May also be metabolic or associated with *STXBP1* gene mutation
West syndrome	Symptomatic, generalized	Infantile spasms (jackknife spasms) Developmental arrest	Hypsarrhythmia and ictal electrodecrement	Variable, often poor	Defined by triad of findings: infantile spasms, developmental arrest, and hypsarrhythmia Treatment: corticotropin or vigabatrin May be associated with focal cortical dysplasia
Severe myoclonic epilepsy in infancy (Dravet syndrome)	Idiopathic, generalized, genetic (*SCN1A* mutation)	Focal or GTC seizures Often initially with fever or vaccination; later, myoclonic and absence seizures	Slow background, multifocal, generalized spike-and-wave pattern	Poor	Treatment: consider valproate, clobazam, ketogenic diet
Generalized epilepsy with febrile seizures plus (GEFS+)	Idiopathic, generalized, genetic (*SCN1A, SCN1B*, and *GABARG2* mutations)	Febrile seizures; myoclonic, astatic, tonic-clonic, and absence seizures	Normal, generalized spike-and-wave pattern May have focal epileptiform activity	Variable	Variable presentation within families from benign to catastrophic Autosomal dominant inheritance
Benign familial infantile epilepsy	Idiopathic, partial	Focal clonic seizure; may generalize Eye deviation, cyanosis Seizures often cluster	Normal Occipital-parietal spikes	Excellent	Treatment often not required

Abbreviations: EEG, electroencephalographic; GTC, generalized tonic-clonic.

be symptomatic or cryptogenic. In some cases, it has been linked to prenatal, perinatal, or postnatal insults (infections); hydrocephalus; metabolic disturbances; or tuberous sclerosis. Developmental arrest or regression may accompany the infantile spasms and may precede them.

Diagnosis

In patients with West syndrome, interictal EEG shows hypsarrhythmia (high-amplitude, chaotic slow waves with multifocal spikes and sharp waves) (Figure 34.4). During an infantile spasm, there is evidence of electrodecrement.

Treatment

Treatment generally consists of corticotropin and vigabatrin.

- West syndrome is characterized by infantile spasms (a seizure type), hypsarrhythmia, and developmental arrest.
- In patients with West syndrome, interictal EEG shows hypsarrhythmia (high-amplitude, chaotic slow waves with multifocal spikes and sharp waves).

Childhood Epilepsy Syndromes

Overview

Patients with certain epilepsy syndromes present most commonly during childhood years. Select disorders are reviewed in Table 34.6, and common disorders are presented below.

Benign Childhood Epilepsy With Centrotemporal Spikes

Overview

A focal idiopathic epilepsy that is also known as rolandic epilepsy, benign childhood epilepsy with centrotemporal spikes accounts for one-fourth of childhood seizures. Inheritance is thought to be autosomal dominant with variable penetrance.

Clinical Features

Patients typically present during grade-school years (ages 4–12 years). Of the children with rolandic epilepsy, about 70% have seizures only during sleep, and the others have them during wakefulness. The seizures are generally motor or sensory simple seizures, which can have secondary generalization.

Diagnosis

Patients are otherwise normal developmentally. Magnetic resonance imaging (MRI) of the brain is normal. EEG of a patient with rolandic epilepsy shows centrotemporal spikes (Figure 34.5) with a normal background.

Treatment and Prognosis

Seizures are easily controlled with anticonvulsants. Most patients outgrow the seizures in adolescence, and the medication dosage can be tapered and discontinued. Only 10% of patients continue to have seizures 5 years after onset.

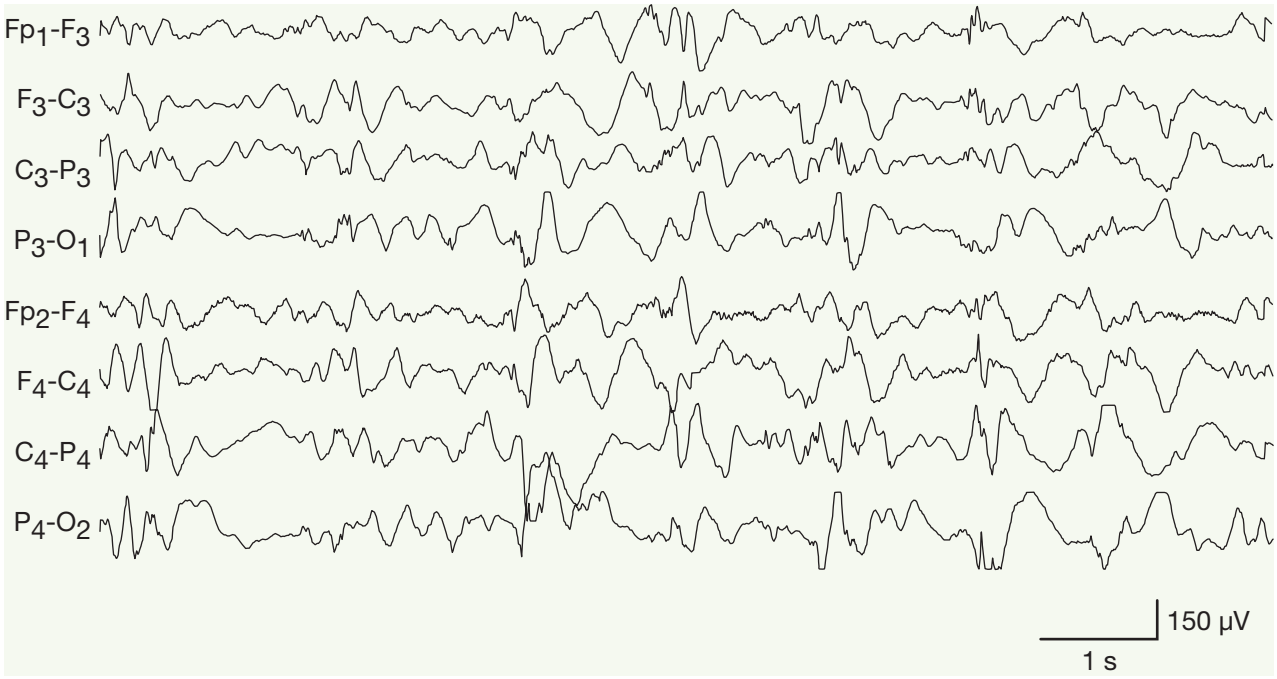

Figure 34.4 *Hypsarrhythmia.*
(Adapted from Ghearing GR. Clinical neurophysiology. Part A: Electroencephalogram [EEG]. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 163–87. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 34.6 • Common Clinical Epilepsy Syndromes of Childhood

Syndrome	Classification	Clinical Features	EEG Findings	Prognosis	Other
Landau-Kleffner syndrome	Symptomatic	Acquired auditory agnosia Often focal motor seizure involving face or arm	Bilateral centrotemporal spikes are much increased during sleep	Seizures generally remit Often permanent language impairment	May present with new "deafness" Treat early to prevent worsening
Panayiotopoulos syndrome (early-onset, benign childhood occipital epilepsy)	Idiopathic, partial	Nocturnal seizures with vomiting and pallor (autonomic) Duration >5 min; may be >30 min (status epilepticus)	Interictal occipital spikes in most, but may be multifocal Increase in non-REM sleep Ictal: low-voltage fast activity	Excellent	Infrequent seizures: about 50% have only 1 Usually no antiepileptic drug is needed
Lennox-Gastaut syndrome	Symptomatic, generalized	Severe seizures of multiple types (tonic, atonic, absence) Mental retardation	Interictal: slow spike-and-wave patterns, ≤2.5 Hz Fast polyspikes with tonic seizures Slow spike-and-wave pattern with absence seizures	Poor	Valproate for all seizure types Lamotrigine and felbamate for drop attacks Carbamazepine and phenytoin for GTC seizures, but these drugs may worsen absence seizures
Myoclonic-astatic (myoclonic-atonic) epilepsy	Idiopathic, generalized	Myoclonic, atonic, tonic, and absence seizures	Normal or slow background, generalized spike-and-wave pattern	Variable	Outcome correlated with seizure control Valproate and lamotrigine
Childhood absence epilepsy	Idiopathic, generalized	Brief (few seconds) staring episodes Behavioral arrest May include automatisms No postictal state	3-Hz spike-and-wave pattern	Excellent	Ethosuximide, valproate, and lamotrigine Often remits by teenaged years Hypoglycemia and hyperventilation provoke absence seizures
Benign epilepsy with centrotemporal spikes (benign rolandic epilepsy)	Idiopathic, partial	SPSs with hemifacial movements are common Drooling, tingling sensations May generalize	Centrotemporal spikes (negative sharp peak, then a positive rounded component) Increase in non-REM sleep	Excellent	Often does not require treatment Resolves by mid-teenaged years

Abbreviations: EEG, electroencephalographic; GTC, generalized tonic-clonic; REM, rapid eye movement; SPS, simple partial seizure.

Lennox-Gastaut Syndrome

Overview and Epidemiology

Lennox-Gastaut syndrome is a clinical triad of mental retardation, slow spike-and-wave (2-Hz) EEG findings, and multiple seizure subtypes. The syndrome may be cryptogenic or symptomatic.

This condition is more common in boys than girls. Children generally present between ages 2 and 8 years.

Clinical Features

Mental retardation often precedes the onset of seizures. Patients may experience multiple seizure types (drop attacks or tonic, atypical absence, atonic, or generalized tonic-clonic seizures).

Diagnosis

The interictal EEG typically shows a slow spike-and-wave pattern (duration, 150 ms; frequency, 1.5–2.5 Hz).

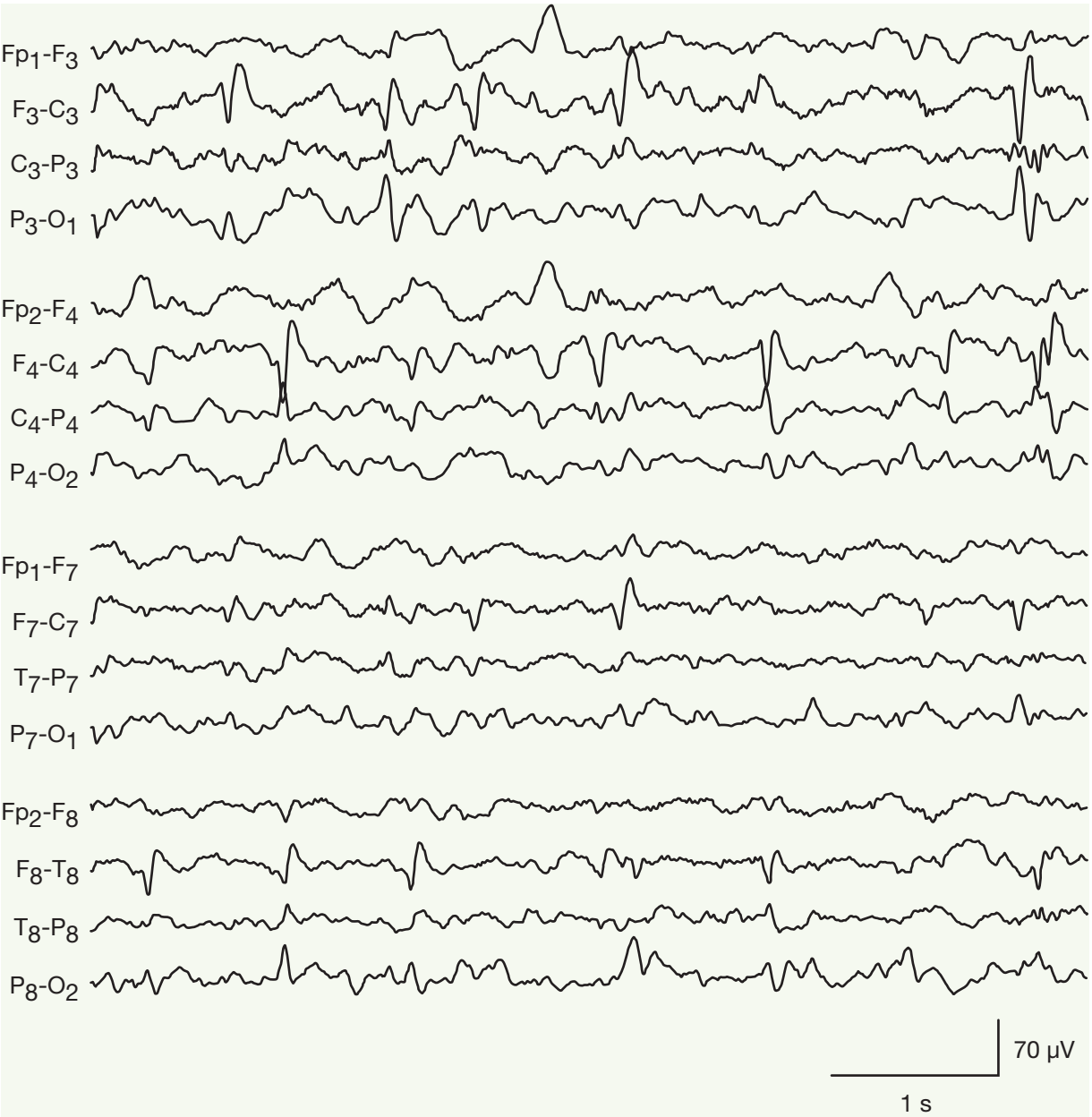

Figure 34.5 *Centrotemporal Spikes.*

(Adapted from Ghearing GR. Clinical neurophysiology. Part A: Electroencephalogram [EEG]. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 163–87. Used with permission of Mayo Foundation for Medical Education and Research.)

Treatment and Prognosis

Valproate is commonly used. Lamotrigine may be used for drop attacks. Carbamazepine and phenytoin may be used for tonic-clonic seizures but may worsen other types (eg, atypical absence seizures).

The prognosis for patients with Lennox-Gastaut syndrome is poor, especially if they are symptomatic. Patients often have progressive deterioration, which is possibly due to an epileptic encephalopathy.

Landau-Kleffner Syndrome

Overview

Landau-Kleffner syndrome is an acquired aphasia accompanied by seizures occurring in children. It is considered a symptomatic epilepsy.

Clinical Features

Aphasia develops in children 3 to 8 years old. They are prone to several seizure types (generalized tonic-clonic, partial complex, and myoclonic).

Diagnosis

MRI of the brain is usually normal. EEG may show variable multifocal spikes, most commonly in the temporal region.

Treatment and Prognosis

Valproate and lamotrigine are often used to treat seizures. Corticosteroids have been tried with some success, although the number of patients is too small to make clear recommendations. In about half the patients, the language disorder persists.

Childhood Absence Epilepsy

Overview and Epidemiology

Absence seizures (previously called petit mal) are brief episodes of loss of awareness occurring multiple times daily. The genetic predisposition is strong, but the exact gene is not known.

The peak age at onset is 6 years. Absence seizures occur more commonly in girls than boys. Children are otherwise developmentally normal.

Clinical Features

Patients with absence seizures have brief episodes of loss of awareness often accompanied by a blank stare. The child's activity at the time is briefly interrupted, thus leading to occasional declines in grades at school. Occasionally the episodes are accompanied by automatisms. Episodes may be provoked by hyperventilation or hypoglycemia. Some patients may also have generalized tonic-clonic seizures.

The cause of atypical absence seizures may be different from the cause of typical childhood absence seizures, and the prognoses may differ.

Diagnosis

EEG shows a symmetric, bilateral, synchronous 3-Hz spike-and-wave pattern. Hyperventilation or photic stimulation may be tried during EEG to provoke absence seizure episodes. This 3-Hz spike-and-wave discharge is thought to be related to the low-threshold T-type channels of the thalamus (Figure 34.6).

Childhood absence seizures should be distinguished from juvenile absence epilepsy, atypical absence seizures, and juvenile myoclonic epilepsy.

Treatment and Prognosis

For the treatment of childhood absence seizures, ethosuximide (inhibits T-type channels), valproate, and lamotrigine are often tried first. Although ethosuximide is useful for absence seizures, it is not recommended if patients have accompanying generalized tonic-clonic seizures. Medication therapy may be discontinued if the child has been free of seizures for 1 to 2 years and the EEG has normalized. By adulthood, absence seizures are in remission in 80% to 90% of patients.

Childhood Occipital Epilepsy (Childhood Epilepsy With Occipital Paroxysms)

Overview

Most children with childhood occipital epilepsy present between the ages of 3 and 6 years with various seizure types. Patients with autonomic seizures may present with ictal vomiting, and patients with visual seizures may present with elementary or complex visual hallucinations. Seizures may generalize.

Diagnosis

Interictal EEG shows frequent or nearly continous bursts or trains of high-voltage rhythmic occipital spikes and spike-and-wave complexes. The frequency is 1 to 3 Hz.

Treatment

Patients with childhood occipital epilepsy have an excellent response to anticonvulsant medications if needed. Treatment may not be needed if the patient has rare, brief seizures.

Progressive Myoclonic Epilepsy

Overview

Progressive myoclonic epilepsy syndromes include several progressive disorders (Box 34.4). Many of these disorders are lysosomal or mitochondrial disorders.

Clinical Features

Children have progressive deterioration in cognition and various generalized seizures (tonic-clonic, tonic, or

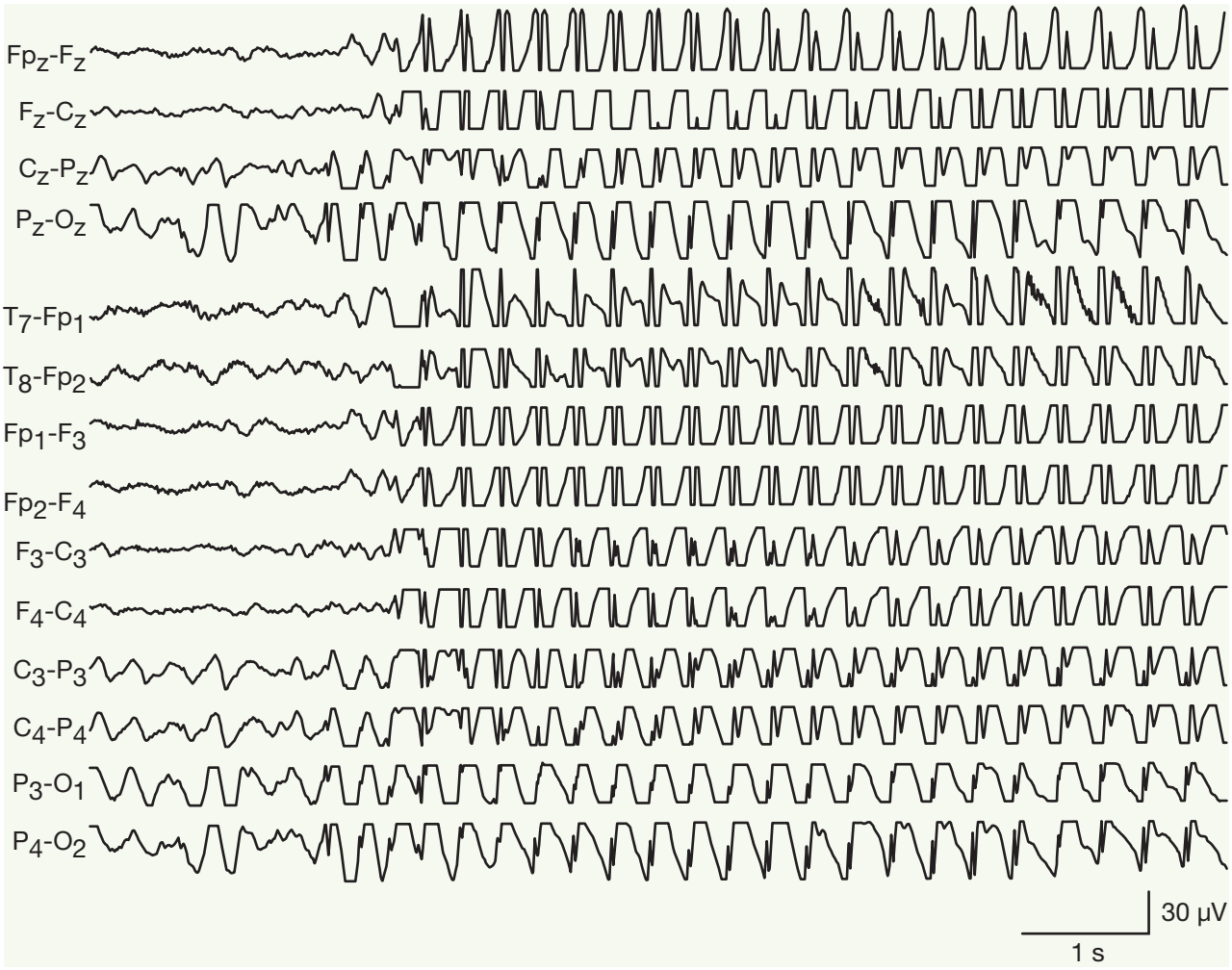

Figure 34.6 *Typical 3-Hz Spike-and-Wave Pattern.*
(Adapted from Ghearing GR. Clinical neurophysiology. Part A: Electroencephalogram [EEG]. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 163–87. Used with permission of Mayo Foundation for Medical Education and Research.)

myoclonic). They may also have nonepileptic myoclonus. Some of these disorders are associated with other neurologic features, including movement disorders and ataxia.

Treatment

Valproate is a common first-line treatment for the generalized seizures accompanying these disorders. Alternatively, clonazepam and lamotrigine can be considered.

- Benign childhood epilepsy with centrotemporal spikes, also known as rolandic epilepsy, accounts for one-fourth of childhood seizures. Inheritance is thought to be autosomal dominant with variable penetrance.
- Of the children with rolandic epilepsy, about 70% have seizures only during sleep, and the others have them during wakefulness.

Box 34.4 • Progressive Myoclonic Epilepsy Syndromes

Lafora body disease
Unverricht-Lundborg disease (initially called Baltic myoclonus)
Neuronal ceroid-lipofuscinosis
Myoclonic epilepsy with ragged red fibers
Sialidoses

Adapted from Bell ML. Epilepsy. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 485–525. Used with permission of Mayo Foundation for Medical Education and Research.

- EEG of a patient with rolandic epilepsy shows centrotemporal spikes with a normal background.
- Lennox-Gastaut syndrome is a clinical triad of mental retardation, slow spike-and-wave (2-Hz) EEG findings, and multiple seizure subtypes.
- The prognosis for patients with Lennox-Gastaut syndrome is poor, especially if they are symptomatic. Patients often have progressive deterioration, which is possibly due to an epileptic encephalopathy.
- Hyperventilation or photic stimulation may be tried during EEG to provoke absence seizure episodes.
- For the treatment of childhood absence seizures, ethosuximide (inhibits T-type channels), valproate, and lamotrigine are often tried first.

Adolescent and Adult Epilepsy Syndromes

Overview

Patients with certain epilepsy syndromes commonly present as teenagers or young adults. Select disorders are reviewed in Table 34.7 and presented below.

Juvenile Myoclonic Epilepsy

Overview

Juvenile myoclonic epilepsy is a syndrome characterized by adolescent onset of several types of generalized seizure: myoclonic, generalized, and absence. It is idiopathic in many. About half have a family history of seizures.

Clinical Features

Patients with juvenile myoclonic epilepsy typically present in the teenaged years (range, 8–24 years). Teenagers are developmentally normal. Patients have a combination of myoclonic, generalized, and absence seizures. The myoclonic type occurs most frequently and at times is triggered by reading, talking, photic stimulation, or other triggers. The generalized type often occurs on awakening.

Diagnosis

MRI is generally normal. EEG may show generalized 4- to 6-Hz polyspike-and-wave discharges interictally. If absence seizures are also present, EEG may show a 3-Hz spike-and-wave pattern.

Treatment and Prognosis

For juvenile myoclonic epilepsy, valproate is first-line treatment. Lamotrigine, levetiracetam, topiramate, and zonisamide can also be tried. Seizures in these patients may *worsen* with the use of carbamazepine or phenytoin. Treatment is generally lifelong. Children do not outgrow these seizures.

Epilepsy With Generalized Tonic-Clonic Seizures on Awakening

Overview and Clinical Presentation

Epilepsy with generalized tonic-clonic seizures on awakening is an idiopathic disorder that often runs in families and presents in the second decade. Patients primarily have generalized tonic-clonic seizures, usually on awakening. They may have myoclonic or absence seizures as well, but not predominantly.

Table 34.7 • Common Epilepsy Syndromes of Adolescence and Adulthood

Syndrome	Classification	Clinical Features	EEG Findings	Prognosis	Other
Juvenile myoclonic epilepsy	Idiopathic, generalized	Myoclonic seizures on awakening GTC Can have absence seizure	Interictal: generalized 4- to 6-Hz polyspike-and-wave discharges in 75% of patients Ictal: trains of spikes	Usually good with treatment	Complex inheritance is linked to multiple genes Valproate works well Lamotrigine for female patients Patients are often photosensitive
Autosomal dominant frontal lobe epilepsy	Idiopathic partial or genetic (*CHRNA4* and *CHRNB2* mutations)	Hyperkinetic seizures at sleep-wake transition May have aura of fear	Normal or frontal spikes	Usually good with treatment	Autosomal dominant Can present in childhood Consider carbamazepine
Familial temporal lobe epilepsy	Idiopathic partial or genetic	Lateral and mesial temporal forms	Temporal spike or sharp waves	Often good with treatment	Autosomal dominant

Abbreviations: EEG, electroencephalographic; GTC, generalized tonic-clonic seizure.

Diagnosis and Treatment

The diagnostic evaluation and treatment are similar to those for juvenile myoclonic epilepsy.

Idiopathic Photosensitive Occipital Lobe Epilepsy

Overview

Idiopathic photosensitive occipital lobe epilepsy is an idiopathic, reflex epilepsy characterized by visually provoked occipital lobe seizures.

Clinical Presentation

Typically, onset occurs during puberty. Patients with this syndrome have occipital lobe seizures that are generally provoked by visual stimuli, which often include video games, movies, or television. Patients may have accompanying autonomic symptoms (epigastric discomfort and vomiting). Occasionally, seizures may secondarily generalize. Symptoms sometimes mimic visual aura in migraine.

Diagnosis

Interictally, patients may have unilateral or bilateral occipital or generalized spike-and-wave discharges that may be enhanced with eye closure. Use of a strobe light during the EEG may help elicit a response.

Treatment

Management involves avoiding potential triggers and consideration of valproate.

Rasmussen Encephalitis

Rasmussen encephalitis is a syndrome characterized by intractable and progressive focal seizures, hemiparesis, and cognitive regression. Children have radiographic characteristics of slowly progressive cortical atrophy. Antibodies to glutamate receptor 3 have been implicated in the pathogenesis of this disorder.

- Juvenile myoclonic epilepsy is a syndrome characterized by adolescent onset of several types of generalized seizure: myoclonic, generalized, and absence.
- Patients with juvenile myoclonic epilepsy have a combination of myoclonic, generalized, and absence seizures. The myoclonic type occurs most frequently and at times is triggered by reading, talking, photic stimulation, or other triggers. The generalized type often occurs on awakening.
- For juvenile myoclonic epilepsy, valproate is first-line treatment. Lamotrigine, levetiracetam, topiramate, and zonisamide can also be tried. Seizures in these patients may *worsen* with the use of carbamazepine or phenytoin.

35 Epidemiology and Pathophysiology of Epilepsy

KATHERINE H. NOE, MD, PHD

Introduction

About 10% of people in the United States have 1 seizure in their lifetime; less than 4% have recurrent seizures or epilepsy. Currently, more than 2 million people in the United States have epilepsy, one of the most common neurologic disorders. Seizures can develop at any age, but the most common times are childhood and after age 60. The greatest incidence is in elderly patients.

- About 10% of people in the United States have 1 seizure in their lifetime; <4% have recurrent seizures or epilepsy.
- Seizures can develop at any age, but the most common times are childhood and after age 60. The greatest incidence is in elderly patients.

Acute Symptomatic Seizures

Acute symptomatic seizures (also called *provoked seizures* or *reactive seizures*) result from new and active insults to the central nervous system. The insults may be toxic, metabolic, infectious, inflammatory, or structural (Box 35.1 and Figure 35.1). By definition, the seizures must occur soon after the provocative cause. For example, accepted time frames include seizures within 1 week of acute stroke or anoxic brain injury or within 24 hours after a metabolic derangement. Acute symptomatic seizures can occur at any age, but they are most common in infants and the elderly. In infants, the leading causes are infection and traumatic brain injury; in elderly patients, the cause of more than half these seizures is related to cerebrovascular disease. Acute symptomatic seizures are typically isolated, nonrecurrent events that do not require ongoing antiepileptic therapy.

Treatment is primarily focused on reversing or removing the underlying cause. Mortality for an acute symptomatic seizure is almost 10 times higher than for a first unprovoked seizure and is determined by the underlying cause.

Box 35.1 • Common Causes of Acute Symptomatic Seizures

- Cerebrovascular
  - Intracerebral hemorrhage
  - Subdural hematoma
  - Stroke
  - Posterior reversible encephalopathy syndrome
  - Cerebral venous thrombosis
- CNS infection (active)
- Metabolic
  - Hypoglycemia or hyperglycemia
  - Hyponatremia or hypernatremia
  - Hypocalcemia
  - Hypoxia
- Toxic
  - Alcohol withdrawal
  - Illicit drugs (cocaine, amphetamine, PCP)
  - Acute drug withdrawal (eg, barbiturates, benzodiazepines)
  - Prescription medications
- Trauma
  - Acute traumatic brain injury
  - Intracranial surgery (perioperative)

Abbreviations: CNS, central nervous system; PCP, phencyclidine hydrochloride.

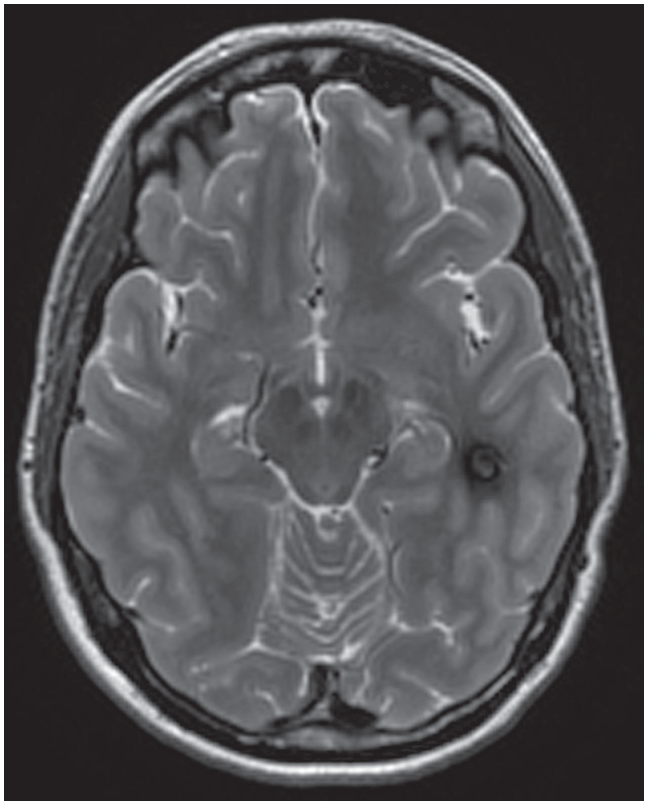

Figure 35.1 *Magnetic Resonance Imaging Scan of the Brain. A cavernous malformation is identified in the left temporal lobe as a cause of this patient's seizure disorder.*

- Acute symptomatic seizures (also called *provoked seizures* or *reactive seizures*) result from new and active insults to the central nervous system. The insults may be toxic, metabolic, infectious, inflammatory, or structural.

Unprovoked Seizures and Epilepsy

Overview

Seizures without an acute symptomatic cause are classified as *unprovoked. Epilepsy* is typically defined as the occurrence of 2 or more unprovoked seizures. Factors such as sleep deprivation, exposure to flashing lights, or illness may lower the threshold for a seizure to occur, but these should not be the sole underlying cause. Determining the cause of epilepsy is important for determining prognosis and treatment. Between 30% and 40% of unprovoked seizures and epilepsy have a remote symptomatic cause. This percentage is lower among young children and higher among the elderly. Compared with idiopathic seizures, those with a remote symptomatic cause are more likely to recur after the first seizure, are less likely to remit once established, and are associated with greater long-term mortality. Remote symptomatic causes include cerebrovascular disease, neurodegenerative conditions, traumatic brain injury, prior central nervous system infection, neoplasm, and developmental abnormalities (congenital brain malformations, neonatal hypoxic-ischemic encephalopathy, mental retardation, and cerebral palsy).

Box 35.2 • Antibodies Potentially Linked With Autoimmune Epilepsy

Thyroid peroxidase (TPO)
Voltage-gated potassium channel (VGKC)
Glutamic acid decarboxylase 65 (GAD65)
N-methyl-D-aspartate (NMDA) receptors
Collapsin response-mediatory protein 5 (CRMP-5)
AMPA

Abbreviation: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

Autoimmune Epilepsy

In recent years, there has been an increasing recognition of autoimmune epilepsy, particularly seizures related to paraneoplastic antibodies. Although a characteristic phenotype is generally lacking, autoimmune epilepsy may be suspected in patients with drug-resistant idiopathic epilepsy, frequent seizures, multifocal or evolving seizure types, or previously defined immune-mediated conditions. In addition to seizures, clinical symptoms may include memory loss, psychiatric disturbances, and movement disorders. Antibodies potentially linked with autoimmune epilepsy are noted in Box 35.2.

Table 35.1 • Selected Idiopathic Epilepsy Syndromes With Autosomal Dominant Inheritance

Syndrome	Genes
Benign familial neonatal seizures	*KCNQ2*
Generalized epilepsy with febrile seizures plus (GEFS+)	*SCN1A* *SCN1B* *SCN9A* *GABRG2* *GABRD*
Severe myoclonic epilepsy of infancy (Dravet syndrome)	*SCN1A*
Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA2* *CHRNA4* *CHRNB2*
Autosomal dominant lateral temporal lobe epilepsy	*LGI1*

Autoimmune epilepsy may respond to immunotherapy, including oral or intravenous corticosteroids, intravenous immune globulin, or plasmapheresis.

Genetic Epilepsy

Idiopathic seizures are presumed to be genetically mediated. Inheritance is often complex and involves polygenic and environmental factors with a high degree of variability in clinical phenotype. However, several monogenic epilepsy syndromes, mostly channelopathies, have been identified (Table 35.1). Genetic testing in appropriate clinical circumstances can assist with prognosis and therapeutic management.

- Seizures without an acute symptomatic cause are classified as *unprovoked*.
- *Epilepsy* is typically defined as the occurrence of ≥2 unprovoked seizures.
- Autoimmune epilepsy may be suspected in patients with drug-resistant idiopathic epilepsy, frequent seizures, multifocal or evolving seizure types, or previously defined immune-mediated conditions.
- Autoimmune epilepsy may respond to immunotherapy, including oral or intravenous corticosteroids, intravenous immune globulin, or plasmapheresis.

36 Evaluating Seizures and Seizurelike Events

JOSEPH F. DRAZKOWSKI, MD

Introduction

Correctly diagnosing seizures and seizurelike events is important for numerous reasons, including safety issues, social consequences, and therapy. Patients with transient neurologic events of unknown cause are commonly admitted to hospitals, and an estimated 10% of the people in the United States have a seizure in their lifetime. These facts highlight the importance of making the correct diagnosis.

History taking is imperfect, but it is still a cornerstone in making the proper diagnosis of transient neurologic events. Focused supporting diagnostic tests may add accuracy in arriving at the proper diagnosis, but even with a good history, diagnostic testing, and physical examination findings, the diagnosis may be inaccurate. Self-reports of seizure frequency are notoriously inaccurate and often miss more than 50% of focal-onset seizures, especially if the seizures begin in the dominant hemisphere (largely because the effects of the event cause an altered level of consciousness).

This chapter reviews the differential diagnosis and a common approach to evaluating the patient with transient neurologic events. It also briefly reviews common neuroimaging and testing for definitive seizures.

The History and Physical Examination

The history is often key to making the correct diagnosis. However, health care providers are often left with incomplete or inaccurate information in the evaluation process. Patients with transient neurologic events typically have altered consciousness before, during, or after the events, so their self-reports provide incomplete data. Witnesses' descriptions may be useful.

If an aura is present in the preictal period of a seizure, its nature may provide clues to the ictal onset zone and the diagnosis (Table 36.1). Potential provoking factors or recent events may provide clues for the diagnosis of seizure. The physical examination and the neurologic

Table 36.1 • Aura Descriptions That May Provide Clues to the Ictal Onset Zone

Lobe	Aura
Frontal	Eye deviation (forced) Speech impairment (dominant hemisphere) Increased motor activity Simple motor activity: primary motor strip Complex motor activity: supplementary motor area
Parietal	Sensory symptoms
Temporal	Psychic symptoms: déjà vu Rising epigastric aura Formed visual images (dominant hemisphere) Powerful emotions (fear or fright) Noxious smell
Occipital	Basic visual images (flashes or colors)

Adapted from Drazkowski JF, Chung SS. Differential diagnosis of epilepsy. Continuum Lifelong Learning Neurol. 2010 Jun;16(3):36–56. Used with permission.

Abbreviations: EEG, electroencephalographic; EMU, epilepsy monitoring unit; MRI, magnetic resonance imaging; PET, positron emission tomography; SISCOM, subtraction ictal single-photon emission computed tomography coregistered to magnetic resonance imaging; SPECT, single-photon emission computed tomography

examination also may provide clues toward the diagnosis of seizure or its mimics.

- If an aura is present in the preictal period of a seizure, its nature may provide clues to the ictal onset zone and the diagnosis.
- Potential provoking factors or recent events may provide clues for the diagnosis of seizure.

Differential Diagnosis and Approach to Suspected Seizure

Considering all the possibilities of causes of seizurelike events is beyond the scope of this chapter; however, common causes of seizurelike events are listed in Box 36.1. Although each patient should be considered on an individual basis, the health care provider should also keep in mind the relative frequencies of the more common imitators of seizures (Box 36.2).

The fine details of the history are often lacking. For example, the workup of suspected new-onset seizures in the emergency department must cover a relatively broad approach because seizures are a true neurologic emergency. The evaluator must quickly assess the situation with an orderly approach and proceed with a rapid workup to help guide therapy (Box 36.3).

For children, the differential diagnosis may include breath-holding spells, kinesigenic chorea, paroxysmal dyskinesia, parasomnia, pseudoseizure, benign myoclonus, and syncope.

Syncope

As noted in Boxes 36.1 and 36.2, syncope is an important diagnosis to consider in the evaluation of patients with transient neurologic events. The history is often the key to proper diagnosis.

Box 36.1 • Common Causes of Seizurelike Events

Syncope (hypotension or arrhythmia)
Transient ischemic attack
Paroxysmal vertigo (otolithic crisis of Tumarkin)
Paroxysmal sleep disorders (cataplexy)
Epilepsy or seizure
Psychiatric disorders (especially panic)
Psychogenic nonepileptic seizure (PNES)
Migraine with complex features

Adapted from Drazkowski JF, Hoerth M. The evaluation of nonepileptic paroxysmal events. In: Cascino GD, Sirven JI, editors. Adult epilepsy. Chichester (West Sussex, United Kingdom): Wiley-Blackwell; c2011, p. 99–111. Used with permission.

Box 36.2 • Incidence of Common Imitators of Epilepsy

Imitator	Incidence per 100,000 Patients
Syncope	3,000
Dizziness	2,000
Migraine	730
Epilepsy	50
Transient ischemic attack	23
Psychogenic nonepileptic seizure (PNES)	3
Transient global amnesia	3

Adapted from Weschler RT, Fisher RS. Introduction: Approach to the diagnosis of possible seizures. In: Kaplan PW, Fisher RS, editors. Imitators of epilepsy. 2nd ed. New York (NY) Demos Publications; c2005 p. 1–13. Used with permission.

Diagnosing syncope and identifying its cause are important because, in addition to self-injury, the 1-year mortality rate is about 30%. Key historic features are often identified in a moment-by-moment history or on examination. For example, an arrhythmia or a murmur consistent with aortic stenosis may be a valuable clue. Convulsive syncope is a particularly perplexing confounder because the associated brief myoclonic motor activity is confused for a seizure. Box 36.4 lists transient neurologic event features that favor the diagnosis of syncope rather than seizure. Diagnostic studies for evaluating patients with suspected syncope are included in Box 36.5.

Seizures

Seizures are typically defined as acute transient neurologic events caused by abnormal electrical activity. Recurrent seizures that are unprovoked are considered to be *epilepsy*. Seizures may also be defined by seizure type and cause. Therefore, the health care provider must consider many aspects of the event while obtaining the history and performing the physical examination.

Features of seizurelike events that favor a diagnosis of epileptic seizures are listed in Box 36.6. As with other conditions discussed in this chapter, the historic features of seizures often lead the clinician to the correct diagnosis. Other features in the history that may favor seizures and epilepsy include 1) family history of epilepsy, 2) history of febrile seizures, 3) history of significant perinatal injury, and 4) history of significant head injury.

Recently, changes have been proposed to the classification of seizures, but this chapter uses major elements of the current classification system. Key features of seizure classification that may be helpful in the evaluation process are 1) focal (partial) or generalized onset, 2) simple

Box 36.3 • Initial Evaluation of Suspected Seizure in the Emergency Department

- Basic evaluation
  - Complete blood cell count
  - Complete metabolic panel (electrolytes, creatinine, liver function tests)
  - Other electrolytes: magnesium, calcium
  - Drug screen
  - Antiepileptic drug levels as appropriate
  - Blood glucose
- Complementary tests as appropriate
  - Computed tomography of the brain
  - Chest radiography
  - Electroencephalography immediately if not awakening
  - Directed investigation if trauma
  - Spinal tap if indicated

symptomatology (no altered consciousness), and 3) complex symptomatology (with altered consciousness). The clinician should keep these general seizure types in mind when completing the workup and taking the history.

Nonepileptic Seizures

Psychogenic nonepileptic seizures are less common than other imitators of seizurelike events, but they are often confounding because they appear to be consistent with epileptic seizures but do not respond to antiepileptic drugs. Results of diagnostic testing are negative. Patients with nonepileptic seizures often appear to have medically refractory epilepsy and require increased medical services. Patients and witnesses often describe events that are remarkably consistent with true epilepsy.

Box 36.4 • Clinical Features of Syncope

- Prior history of cardiac arrhythmia or other cardiac disease
- Event provoked by pain, phlebotomy, exercise, exertion, eating, or haircutting
- Palpitations before an event
- Associated autonomic symptoms: increased sweating, tunnel vision, warmth, or nausea
- Duration: seconds (minutes for other conditions)
- No postictal confusion
- Typically occurs while seated or standing or during a rapid change in position
- Flaccid muscle tone with the event; often the person falls and is injured

Box 36.5 • Studies That May Assist in the Evaluation of Patients With Suspected Syncope

- Standard 12-lead electrocardiography (minimal yield)
- Echocardiography
- Prolonged electrocardiographic recording: 24-h Holter monitor, 30-d event monitor, implanted loop recorder
- Autonomic reflex screen, including tilt table test

Key elements of the history that may favor a diagnosis of nonepileptic seizures over epileptic seizures are listed in Box 36.7. These patients often have a history of prior psychology or psychiatric comorbidity and a past history of physical, emotional, or sexual abuse. The health care provider should not use the presence of past abuse as prima fascie evidence of nonepileptic seizures because many patients with epileptic seizures are vulnerable to similar experiences. Many patients with nonepileptic seizures also have epileptic seizures. The gold standard in making the diagnosis of nonepileptic seizures is recording electroencephalographic (EEG) confirmation of an event with routine EEG or ambulatory EEG or with a long-term epilepsy monitoring unit (EMU). Neurologists typically encounter these patients, who are often referred for medically intractable epilepsy.

Migraine

Migraine headaches are relatively common compared with seizures. An estimated 5% to 10% of epilepsy patients also have migraine. Postictal or peri-ictal headaches are relatively common in temporal lobe seizures. Common migraine headaches typically last many minutes to many hours, in contrast to seizures, which typically last only a few minutes. Migraine aura is often a positive

Box 36.6 • Clinical Features of Seizurelike Events That Favor a Diagnosis of Epileptic Seizure

- Stereotypy
- Duration typically <2 min
- Presence of typical aura
- Postictal confusion with gradual recovery
- Occurring randomly or in a pattern that favors seizure
- Rarely provoked
- Response to antiepileptic drug trial
- Incontinence
- Eyes open at event onset
- Self-injury (eg, lateral tongue biting)
- Postictal Todd paralysis

Box 36.7 • Features of Seizurelike Events That Favor a Diagnosis of Psychogenic Nonepileptic Seizures

- Directly provoked by stress or stimuli not typically associated with reflex epilepsy
- History of abuse
- Psychiatric comorbidity
- Wax and wane
- Prolonged, lasting longer than a few minutes
- Can be stopped by external influences
- Never witnessed
- Seen by only 1 person
- Lack of stereotypy
- Eyes closed at the onset
- Ictal stuttering
- Elevated somatization scales on personality profile testing
- Pelvic thrusting
- Pseudosleep

phenomenon with visual obscurations that might be mistaken for a seizure-related aura, but the seizure-related aura is typically briefer, lasting seconds rather than minutes. Migraine typically does not have altered awareness associated with attacks. In concerning cases, recording an attack with EEG usually distinguishes between migraine and seizure; the EEG during migraine is usually normal or does not show typical epileptiform activity.

Transient Ischemic Attacks

Transient ischemic attacks are common causes of transient neurologic deficits that can be confused with seizure. In general, however, transient ischemic attacks occur with negative phenomena (weakness, lack of sensation, and lack of vision), whereas seizures often occur with positive phenomena (increased tone, tingling, and visual forms or lights).

Movement Disorders

Most movement disorders are continuous, so they generally are not confused with paroxysmal seizure disorders. Less common movement disorders, such as hemifacial spasm, might be confused for simple partial seizures. The spasms of this disorder are typically not regular, and no associated EEG changes are seen. However, caution should be exercised in the presence of clinical uncertainty because in rare cases of simple partial seizures, no EEG changes have been seen.

Myoclonus may be a part of an epilepsy condition, but it can be associated with movement disorders as well. The routine EEG may not show any abnormalities in such cases, and formal movement disorder studies may be necessary for clarification.

Sleep Disorders

Typically, common sleep disorders are not easily confused with seizures except in rare instances, such as less common parasomnias. *Night terrors* can be confused with nocturnal seizures, but night terrors usually occur in children and often last longer than a typical seizure, with the patient falling asleep postictally without recall of the event. Vocalizations, which are common in night terrors, are rare in seizures; when they do occur with seizures, they are usually associated with frontal lobe epilepsy. The EEG shows slow wave sleep with night terrors and epileptiform activity with seizures. *Rapid eye movement sleep behavior disorder* is similar to night terrors in that it can be confused with nocturnal complex partial seizures. However, muscle paralysis usually does not occur in rapid eye movement sleep behavior disorder, which can be distinguished from nocturnal complex partial seizures by recording an event with polysomnography or long-term EEG. Rapid eye movement sleep behavior disorder is more common in men older than 50 years and may be associated with Lewy body dementia with parkinsonism. Somnambulism (sleepwalking) and related disorders occur in 15% of children and 0.7% of adults and are sometimes mistaken for partial seizures, but they are easily differentiated by recording an event.

- Box 36.4 lists transient neurologic event features that favor the diagnosis of syncope rather than seizure.
- Features of seizurelike events that favor a diagnosis of epileptic seizures are listed in Box 36.6.
- Features in the history that may favor seizures and epilepsy include 1) family history of epilepsy, 2) history of febrile seizures, 3) history of significant perinatal injury, and 4) history of significant head injury.
- Key elements of the history that may favor a diagnosis of nonepileptic seizures over epileptic seizures are listed in Box 36.7.
- Many patients with nonepileptic seizures also have epileptic seizures.
- Migraine aura is often a positive phenomenon with visual obscurations that might be mistaken for a seizure-related aura, but the seizure-related aura is typically briefer, lasting seconds rather than minutes.

Testing Related to Distinguishing Seizurelike Events

Routine EEG

The routine EEG has significant utility in the evaluation of the patient with suspected seizure, but a normal EEG does not rule out epilepsy. However, specific abnormalities have been associated with a tendency for seizures. For focal seizures, focal abnormalities, such as temporal

sharp waves and spikes followed by slow waves, have a high correlation with temporal lobe epilepsy. Temporal intermittent rhythmic delta activity is associated with a tendency for seizures in the appropriate clinical setting. The routine EEG can be misleading because a negative EEG does not rule out seizures and a nonspecific finding does not rule in seizures. A wrongly interpreted EEG, with normal variants interpreted as epileptiform activity, is misleading and leads to diagnostic error. The occurrence of overinterpreted EEGs is a serious issue, sometimes exposing the patient to inappropriate therapy. Sleep deprivation and obtaining sleep improve the yield in activating epileptiform abnormalities on routine EEG. The diagnostic yield of routine EEG can be maximized by performing several EEGs up to a total of 4, beyond which the likelihood that any useful information will be discovered is small.

Ambulatory EEG

Technology has improved in recent years, making the use of ambulatory EEG both available and technically reliable. Historically, the use of this technique has been questioned because it has been prone to artifact caused by activities of daily living and other sources of error. However, ambulatory EEG has recently been improved and found to be useful with acceptable diagnostic yield. The same caveats that apply to routine EEG apply to ambulatory EEG regarding abnormalities associated with seizures and overreading or misreading EEGs. The advantage of ambulatory EEG is that the recording length provides a sampling time of 1 day to several days. Coincident use of video with the ambulatory EEG is likely to improve diagnostic yield. The disadvantage of ambulatory EEG compared with long-term video EEG in an EMU is that medication dosage tapering and activation procedures cannot typically be used because the patient is not directly monitored. If an answer is not obtained with routine or ambulatory EEG, prolonged video EEG in an EMU may be necessary for proper diagnosis.

Long-term Video EEG in an EMU

Video EEG is currently the gold standard for recording and diagnosing indeterminate events and for evaluating potential epilepsy surgical patients. The yield of this study can be enhanced within the safety of the EMU by withdrawing seizure medications while the patient is monitored closely for frequent seizures and for other aspects of safety. The underreporting of seizures has been previously noted, making EMU admission reasonable, even if the patient reports "rare" seizures. If an event is recorded in the EMU, the diagnostic accuracy is extremely good. Even if no events are recorded, interictal abnormalities can still be useful in the evaluation process. With EMU admission, the diagnosis of indeterminate events has been shown to change for 25% of patients—the diagnosis of nonepileptic seizures has been reclassified as epileptic seizures and vice versa.

- A normal EEG does not rule out epilepsy.
- Sleep deprivation and obtaining sleep improve the yield in activating epileptiform abnormalities on routine EEG.
- The diagnostic yield of routine EEG can be maximized by performing several EEGs up to a total of 4, beyond which the likelihood that any useful information will be discovered is small.
- With EMU admission, the diagnosis of indeterminate events has been shown to change for 25% of patients—the diagnosis of nonepileptic seizures has been reclassified as epileptic seizures and vice versa.

Additional Neuroimaging and Evaluation in Definitive Seizure Disorders

Structural Imaging

Computed tomography of the brain is useful in emergent settings to rule out acute, serious pathology in a patient with a seizure disorder. Magnetic resonance imaging (MRI) of the brain is more sensitive than computed tomography in evaluating for focal, potentially epileptogenic lesions (eg, lesions from ischemic stroke, traumatic injury, tumors, malformation of cortical development, infections, and mesial temporal sclerosis) (Figure 36.1).

Structural imaging is indicated for a first-time seizure unless there is a clear idiopathic epilepsy syndrome (ie, a clinical story and characteristic EEG with normal examination findings). The sensitivity of MRI is much higher than that of computed tomography, and MRI is the preferred imaging method for evaluating a new seizure disorder. The urgency should reflect other clinical characteristics and examination findings (eg, suspected meningitis, encephalitis, or cerebral ischemia) and whether the semiology or examination suggests a focal seizure rather than a generalized one.

Functional Imaging

Functional imaging is often used in epilepsy surgical evaluation when conventional means of localization (EEG, MRI, video EEG, semiology, and examination) are inconclusive. It can be used to identify targets for intracranial electrode placement and to identify foci of onset. Positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance spectroscopy can be considered.

Positron Emission Tomography

A radioactive ligand used in PET scanning is [18F] fluoro-2-deoxy-D-glucose. Its uptake reflects metabolic

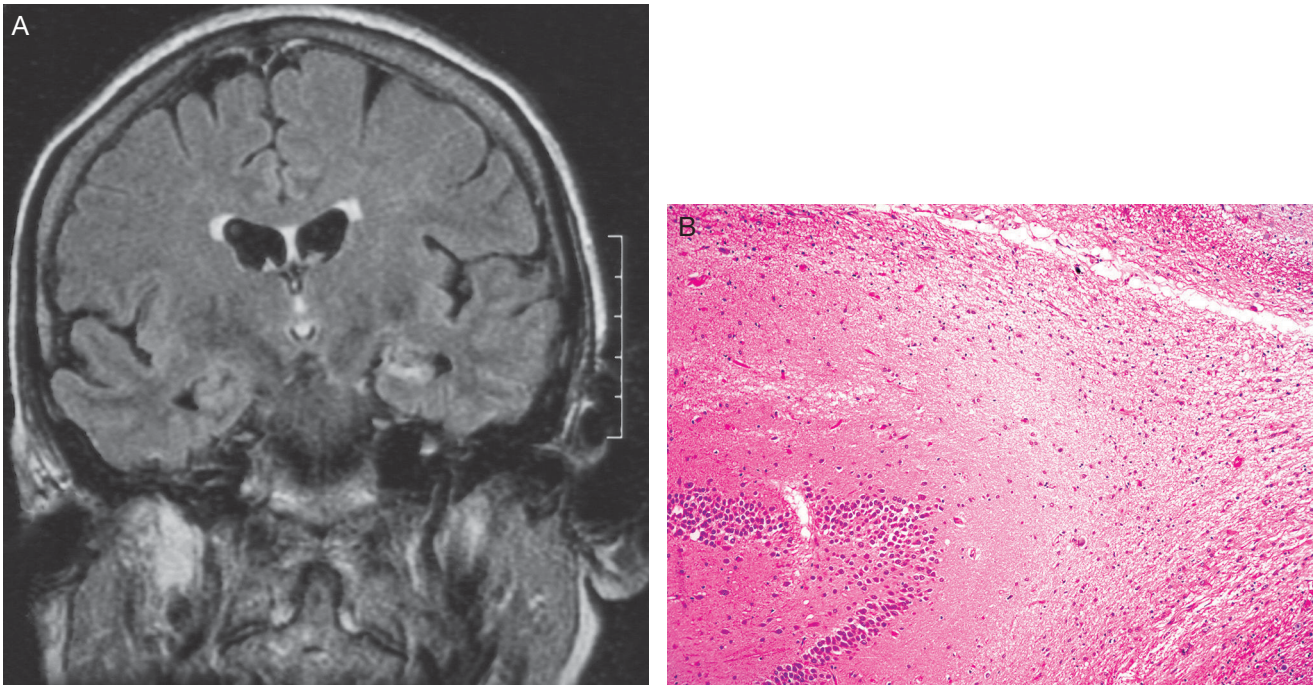

Figure 36.1 *Mesial Temporal Sclerosis.*
A, Magnetic resonance imaging (MRI) from a patient with temporal lobe seizures. The fluid-attenuated inversion recovery sequence shows increased signal in the left mesial temporal lobe and asymmetric hippocampal atrophy (left more than right) best appreciated on quantitative MRI volumetry. B, Histopathologic section shows selective hippocampal neuronal loss and gliosis, with predominant loss of pyramidal cells in the CA1 region. In this specimen, extensive gliosis has replaced the CA1 region.
(Adapted from Bell ML. Epilepsy. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 485–525. Used with permission of Mayo Foundation for Medical Education and Research.)

activity. Interictally, the PET scan may show a hypometabolic region. PET scanning may be used to localize the onset of seizure. When a seizure occurs during PET scanning, a hypermetabolic area may be seen.

Single-Photon Emission Computed Tomography

Ictal SPECT can measure an increase in blood flow at the site of the epilepsy focus. Interictal SPECT may show decreased blood flow in an epileptogenic region.

Subtraction ictal SPECT coregistered to MRI (SISCOM) takes the ictal image and subtracts it from the interictal image (Figure 36.2). This image difference is coregistered to MRI to localize the potential anatomical location of the epileptic focus. SISCOM localization is an independent predictor of epilepsy surgery outcome. However, it requires prompt injection during seizure (within 1 minute).

Functional Cortex Mapping

Wada Testing

Amobarbital is injected into a single carotid distribution through an angiographic catheter. Amobarbital depresses cortical function of the ipsilateral hemisphere. Neuropsychologic testing is then performed to identify the hemisphere with language function. It is poor at identifying specific locations.

Functional MRI

Functional MRI can be used to identify functional cortex through task-specific actions. This is often used in presurgical planning.

Intracranial EEG Monitoring

Patients undergoing evaluation for epilepsy surgery may require intracranial EEG to better localize the region of the brain that is generating the seizures.

- Computed tomography of the brain is useful in emergent settings to rule out acute, serious pathology in a patient with a seizure disorder.
- MRI of the brain is more sensitive than computed tomography in evaluating for focal, potentially epileptogenic lesions (eg, lesions from ischemic stroke,

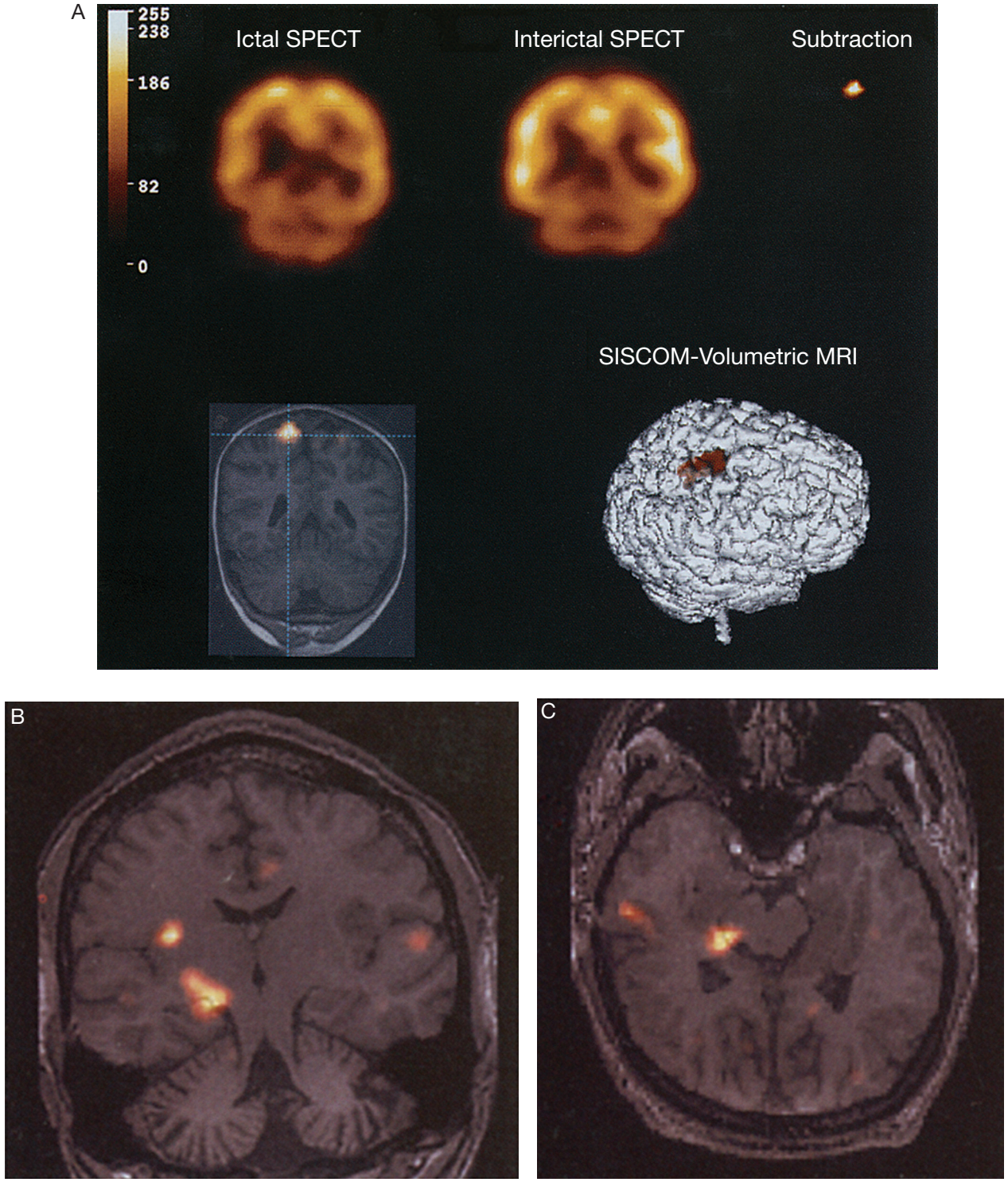

Figure 36.2 *Subtraction Ictal Single-Photon Emission Computed Tomography Coregistered to Magnetic Resonance Imaging (SISCOM).*

A, To obtain a SISCOM image, ictal (upper left) and interictal (upper middle) single-photon emission computed tomographic (SPECT) images are subtracted to obtain a difference (upper right). The difference image is then coregistered with the magnetic resonance image (MRI) in 2-dimensional planes (lower left) or on the surface of a 3-dimensional MRI reconstruction (lower right). B and C, SISCOM images show a focal ictal area of hyperperfusion in the right mesial temporal lobe. D and E, Positron emission tomographic images obtained interictally in the same patient show hypoperfusion (decreased signal intensity) corresponding roughly to the same region in the SISCOM images.

(Adapted from So EL. Role of neuroimaging in the management of seizure disorders. Mayo Clin Proc. 2002 Nov;77[11]:1251–64. Used with permission of Mayo Foundation for Medical Education and Research.)

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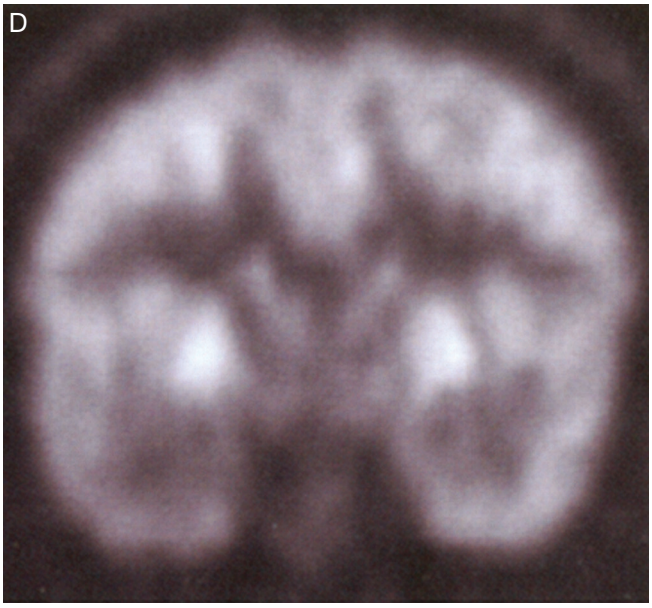

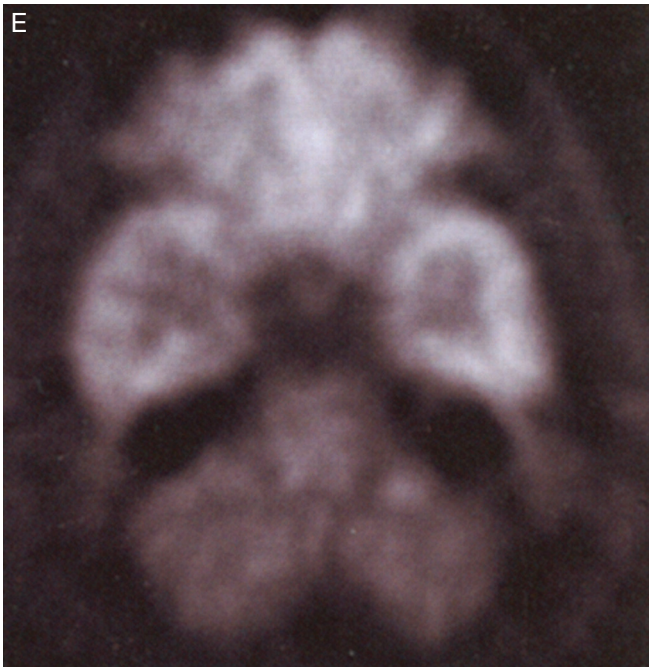

Figure 36.2 *(Continued)*

traumatic injury, tumors, malformation of cortical development, infections, and mesial temporal sclerosis).

- Functional imaging is often used in epilepsy surgical evaluation when conventional means of localization (EEG, MRI, video EEG, semiology, and examination) are inconclusive.
- PET scanning may be used to localize the onset of seizure. When a seizure occurs during PET scanning, a hypermetabolic area may be seen.

37 Treatment of Epilepsy

MATTHEW T. HOERTH, MD

Introduction

A systematic approach can simplify the process of epilepsy treatment, and knowledge of the antiepileptic medications is essential. This chapter summarizes the approach to treatment, presents a summary of medications and alternative therapies, and discusses treatment in special situations.

Epilepsy Drug Selection

A rational approach should be taken when selecting medications for the treatment of seizures associated with epilepsy. The choices for drug selection are ever expanding, which can make the selection process difficult for patients and physicians. With so many choices available, medications can be tailored to each patient's specific situation. The following is a suggested approach for choosing the correct medication for each patient.

Step 1: Confirm the Diagnosis of Epilepsy

Epilepsy is defined as the propensity for recurrent and *unprovoked* seizures. From this definition, neither provoked seizures nor a single seizure requires treatment with anticonvulsants. The differential diagnosis is lengthy and includes syncope and psychogenic events (see also Chapter 36, "Evaluating Seizures and Seizurelike Events"). A detailed history can be helpful. For most patients, the initial workup should include magnetic resonance imaging (MRI) and electroencephalography (EEG). Normal findings do not exclude the diagnosis. Empirical therapy can be started on the basis of a high degree of suspicion; however, reevaluation should always be considered if therapy is ineffective.

Step 2: Determine the Seizure Type

When a decision has been made to begin therapy with a medication, the seizure type should be considered. Effectiveness of each epilepsy medication is established for specific seizure types. At times, seizure types are difficult to determine from history alone (see Chapter 34, "Epilepsy Classification"). MRI or EEG (or both) can be helpful to evaluate for a focal lesion suggestive of partial epilepsy. If the patient has multiple seizure types, or if the seizure type is unclear, a broad-spectrum agent (effective for multiple seizure types) should be considered.

Step 3: Choose the Most Effective Seizure Medication

If the seizure type has been assessed correctly, there is no good evidence to suggest that 1 seizure medication is more effective than any other.

Step 4: Consider Comorbid Conditions

Consideration of comorbid conditions is 2-fold. First, many antiepileptic medications are effective in the treatment of other conditions as well, so that treating 2 conditions with 1 medication would be ideal. Second, antiepileptic medications can cause adverse effects that can worsen other conditions. Most patient counseling is based on these adverse effects. The patient's values and willingness to accept risk have the most influence and need to be weighed against the medication's potential for benefit.

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging

Step 5: Consider the Speed and Ease of Introducing the Medication

Different situations require different speeds of drug introduction. Some antiepileptic medications are available in intravenous formulations, and a patient presenting to the emergency department with multiple seizures may require intravenous administration for rapid effect. A patient presenting to an outpatient clinic with several nondisabling seizures over months or years may be able to use a medication that is titrated to therapeutic levels over several weeks. In general, the more slowly a medication is introduced, the less severe are the dose-dependent adverse effects. The slowness of the introduction depends on the pharmacokinetic properties of the specific medication.

Step 6: Evaluate the Potential for Adherence

Most epilepsy medications require twice-daily dosing. Several are administered only once daily, and others are administered 3 or more times daily. The frequency is linked to the half-life of the medication. Most patients are acceptably adherent to once-daily or twice-daily dosing; however, more frequent administration can be challenging.

Step 7: Consider the Cost of the Medication

Medication can be expensive, and coverage of the cost can vary among different insurance carriers. Differences in coverage can be difficult to predict during discussions with patients in the office. In general, generic drugs are less expensive than brand medications, but evidence has raised concerns related to switching between drugs from different generic manufacturers and resulting in either increased or decreased drug levels. At times, advocacy for patients may be necessary.

- A 7-step approach for initiating antiepileptic therapy is as follows:
  1. Confirm the diagnosis of epilepsy.
  2. Determine the seizure type.
  3. Choose the most effective seizure medication.
  4. Consider comorbid conditions.
  5. Consider the speed and ease of introducing the medication.
  6. Evaluate the potential for adherence.
  7. Consider the cost of the medication.

Overview of Individual Epilepsy Drugs

As noted above, if selected for the correct seizure type, no medication has proved to be more effective than another. Table 37.1 lists epilepsy medications currently available and key characteristics of each. Most newer antiseizure medications are approved by the US Food and Drug Administration for only adjunctive therapy. Commonly, antiseizure medications are used in off-label indications.

Typically, drug levels are not monitored for newer antiseizure medications. Tests for monitoring levels of the older antiseizure medications (phenytoin, phenobarbital, carbamazepine, and valproic acid) are easily ordered. Phenytoin has zero-order kinetics with a nonlinear dose-response curve. Enzyme-inducing medications include phenytoin, phenobarbital, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and possibly zonisamide. Valproic acid is considered an enzyme inhibitor. For the purposes of this chapter's concise review, the pharmacologic properties of each medication are not discussed.

- Phenytoin has zero-order kinetics with a nonlinear dose-response curve.
- Enzyme-inducing medications include phenytoin, phenobarbital, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and possibly zonisamide.

Treatment of Refractory Epilepsy

Medically refractory epilepsy is defined as failure of 2 or more appropriately dosed medications to provide freedom from seizures. It is estimated that seizures in up to one-third of patients are medically refractory. When seizures are deemed refractory, alternatives to traditional medications should be considered, including a ketogenic diet, implantable devices (eg, vagal nerve stimulator), and surgery.

Ketogenic Diet

The only diet that has proved to be effective for the treatment of epilepsy is the ketogenic diet or its derivatives. The theory is to have the brain use ketones rather than glucose for metabolism. In the strictest form, patients must consume almost entirely fat and protein, with only minimal carbohydrates. Many centers admit patients to the hospital during the induction of the diet, since having the patient fast for several days is the most efficient way to have the patient transition to ketone metabolism. This is verified by a urinalysis showing adequate amounts of ketones expelled in the urine. Despite its established efficacy, the ketogenic diet is too restrictive to be a reasonable option for most patients; therefore, it is typically used for patients with refractory seizures.

Therapeutic Device Implantation

Device implantation has been established as an effective strategy for decreasing the number of seizures in patients with refractory epilepsy. Vagus nerve stimulation, the most commonly used stimulation for the treatment of epilepsy, involves the placement of a stimulator lead wrapped around the left vagus nerve in the neck and attached to an implanted stimulator. The stimulation cycles on and off with a programmed duration and

Table 37.1 • Summary of Antiepileptic Medications

Drug	Route of Administration	Frequency of Dose	Seizure Type[a]	Select Adverse Effects	Comorbid Indications[b]
Carbamazepine	po	qid, bid (XR)	Partial	Hyponatremia, aplastic anemia, pancytopenia	Mood stabilization, trigeminal neuralgia
Clobazam	po	bid	Partial, generalized	Somnolence	Anxiety
Ethosuximide	po	bid	Absence	Aplastic anemia	. . .
Ezogabine	po	tid	Partial	Urinary retention	. . .
Felbamate	po	tid, qid	Partial	Aplastic anemia, hepatotoxicity	. . .
Gabapentin	po	tid	Partial	Edema, dizziness	Neuropathy, postherpetic neuralgia
Lacosamide	po, IV	bid	Partial	PR interval prolongation	. . .
Lamotrigine	po	bid, qd (XR)	Partial, GTC	Stevens-Johnson syndrome	Mood stabilization
Levetiracetam	po, IV	bid, qd (XR)	Partial, GTC, myoclonic	Abnormal behavior, depression	. . .
Oxcarbazepine	po	bid	Partial	Hyponatremia, agranulocytosis, pancytopenia	. . .
Perampanel	po	qd	Partial	Aggressive behavior	. . .
Phenobarbital	po, IV	qd	Partial, generalized	Hepatotoxicity, somnolence	. . .
Phenytoin	po, IV	qd	Partial, GTC	Neuropathy, ataxia, gum hyperplasia	. . .
Pregabalin	po	bid	Partial	Edema	Neuropathy, fibromyalgia, neuropathic pain
Primidone	po	tid	Partial, generalized	Ataxia, vertigo	Tremor
Rufinamide	po	bid	Atonic	Shortened QT interval	. . .
Tiagabine	po	qid	Partial	Stevens-Johnson syndrome, agitation	. . .
Topiramate	po	bid	Partial, GTC	Weight loss, cognitive dysfunction, kidney stones	Migraine
Valproate	po, IV	tid, qd (XR)	Partial, generalized, absence	Weight gain, hyperammonemia, thrombocytopenia	Migraine, mood stabilization
Vigabatrin	po	tid	Partial	Irreversible visual field defect	. . .
Zonisamide	po	qd	Partial, GTC	Weight loss, kidney stones	. . .

Abbreviations: bid, twice daily; GTC, generalized tonic-clonic; IV, intravenous; po, by mouth; qd, daily; qid, 4 times daily; tid, 3 times daily; XR, extended-release formulation.

[a] Type of seizure reflects common use of the drug rather than indications approved by the US Food and Drug Administration.

[b] Only the most common indications are listed. Other possible uses for the medications are being investigated.

intensity of stimulation. Adverse effects include the risks of surgery and potentially a hoarse voice (due to stimulation of the recurrent laryngeal nerve). The implanted lead limits patients' ability to have future MRI scans. Other forms of stimulation that have shown effectiveness include transcranial magnetic stimulation, trigeminal nerve stimulation, and thalamic stimulation. *Responsive neurostimulation* is also being used—the implanted device is set to deliver a designated therapy in response to a predetermined EEG pattern.

Epilepsy Surgery

Resection of the epileptogenic tissue is potentially curative for patients with seizures that are otherwise refractory to medical management. This approach should be sought for patients who have medically refractory partial or focal epilepsy. The best possible outcome for patients who undergo a temporal lobectomy with mesial temporal sclerosis is a seizure-free rate of up to 70%. With the alternative of repeatedly prescribing additional medications, the seizure-free rates are far less. Frontal lobectomies, lesionectomies, and focal cortical resections may also be curative. For difficult cases, electrocorticography can be undertaken to further localize the area of seizure onset, and cortical mapping can help establish areas of eloquent cortex that cannot be resected.

Other palliative neurosurgical procedures that can be performed in appropriate situations include cortical subpial transection and corpus callosotomy.

- *Medically refractory epilepsy* is defined as failure of ≥2 appropriately dosed medications to provide freedom from seizures.
- When seizures are deemed refractory, alternatives to traditional medications should be considered, including a ketogenic diet, implantable devices (eg, vagal nerve stimulator), and surgery.
- The best possible outcome for patients who undergo a temporal lobectomy with mesial temporal sclerosis is a seizure-free rate of up to 70%.

Special Situations in the Treatment of Epilepsy

The treatment of epilepsy can be difficult, but there are certain circumstances in which treatment can become even more complicated. This section highlights several of those situations, including prolonged seizures, organ failure, and women's issues.

Status Epilepticus

The definition of *status epilepticus* has changed over time. Previous definitions stated that the duration of continuous seizure activity should be more than 30 minutes to be considered status epilepticus; however, in many definitions the duration has been shortened to 10 minutes. Also included in the definition is a patient whose neurologic functioning does not return to baseline between repetitive seizures. No matter how the term is defined, though, continuous seizure activity is accompanied by high mortality rates—up to one-third in some series. The determinants of mortality are most closely linked to the cause and the duration of the seizures. Therefore, a clear algorithm for the treatment of ongoing seizure activity should be executed quickly by the treating physician (Figure 37.1). (Also see Chapter 3, "Status Epilepticus.")

Organ Failure

Traditional antiseizure medications are metabolized by the liver, and some have been associated with hepatotoxicity. Some of the newer medications are renally metabolized. The mechanism of elimination of the medications can be important when treating patients with kidney failure or liver failure (Box 37.1). These patients may have significant metabolic abnormalities, or they may be taking other medications that put them at risk of seizures. For a patient with liver failure, a medication that is renally metabolized should be considered; for a patient with renal failure, the opposite may be true.

Patients who are receiving dialysis need special consideration. Protein-binding properties of the medication will affect postdialysis drug levels. For simplicity, a medication with minimal protein binding may be a good choice because essentially all the medication would be removed during dialysis. Dosed immediately after dialysis, the drug would be minimally eliminated until the next dialysis treatment.

Hormonal Interactions

Catamenial epilepsy is the term used when the menstrual cycle strongly influences the frequency or severity of seizures. Hormone receptors on neurons have been shown to influence the propensity for a seizure to occur. Estrogen is thought to be more of a proconvulsant; progesterone, more of an anticonvulsant. Therefore, the most susceptible times during a woman's menstrual cycle to have a seizure are immediately before menstruation, during menstruation, and at the time of ovulation. Hormonal contraceptives and acetazolamide have been used to attempt to reduce seizures associated with the menstrual cycle. Hysterectomy or oophorectomy is not a recommended treatment of catamenial epilepsy because the hormones are thought to be an influence and not the cause of the disorder.

Attention should also be given to women who have epilepsy at the time of puberty or menopause, when a change in seizure frequency and severity can occur.

Oral contraceptives are hepatically metabolized by the same enzymes as many of the enzyme-inducing antiepileptic medications, so those medications can reduce the effectiveness of contraception. Any woman of childbearing potential should be counseled on the use of contraception and the potential teratogenicity of antiseizure medications. Folic acid is recommended as a supplement for women with childbearing potential because supplementation can decrease the rate of neural tube defects in the growing fetus. Although there is probably a risk of

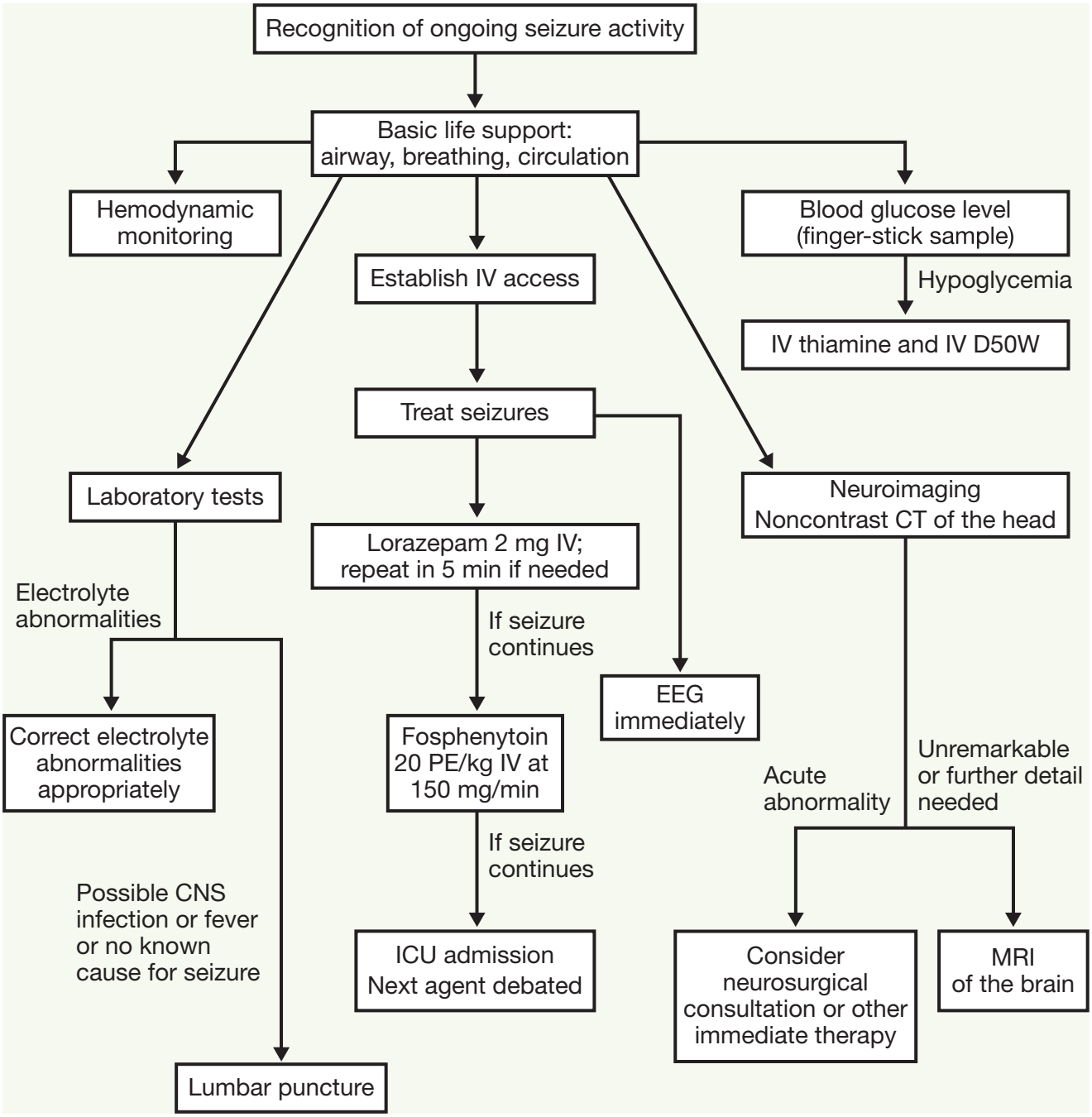

Figure 37.1 *An Example of a Treatment Protocol for Status Epilepticus.*
CNS indicates central nervous system; CT, computed tomography; D50W, 50% dextrose in water; EEG, electroencephalography; ICU, intensive care unit; IV, intravenous; MRI, magnetic resonance imaging; PE, phenytoin sodium equivalent units.

teratogenic adverse effects from essentially all antiseizure medications, valproic acid carries the highest potential harm, especially in combination with other medications and at higher doses. All women who are pregnant and are taking antiseizure medications should be encouraged to enroll in a pregnancy registry so that more data can be collected on the potential risks of these medications. During pregnancy, the dosing of medications may need to be modified as the patient's metabolism and volume of distribution of the medication change. Monitoring drug levels may be helpful. After delivery, the medications need to be adjusted again to avoid potential adverse effects. (Also see Chapter 82, "Neurology of Pregnancy.")

Box 37.1 • Metabolism of Antiepileptic Medications

Hepatic
- Benzodiazepines
- Carbamazepine
- Ethosuximide
- Felbamate
- Lamotrigine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Topiramate
- Valproic acid
- Zonisamide

Renal
- Gabapentin
- Lacosamide
- Levetiracetam
- Pregabalin

Febrile Seizures

Overview

Febrile seizures affect 3% to 5% of children and usually occur between 6 months and 5 years of age. Typically, the patient presents with a generalized tonic-clonic seizure and a fever associated with a common childhood infection.

Risk factors for the development of a febrile seizure include a family history of seizures, delayed development, day care attendance, and a history of prolonged hospitalization in a neonatal intensive care unit.

Clinical Presentation

The seizure associated with fever may be simple or complex. *Simple febrile seizures* consist of a generalized convulsive seizure lasting less than 15 minutes in an otherwise neurologically normal patient. Some patients have a familial predisposition. *Complex febrile seizures* are prolonged (>15 minutes) and may have focal features. Patients may have an abnormal neurologic examination or a postictal neurologic sign such as Todd paralysis. Compared with simple provoked seizures, complex febrile seizures are more likely to be due to an underlying seizure disorder or a central nervous system infection.

Diagnosis

The diagnosis of febrile seizure is made when a child younger than 5 years has a simple febrile seizure during a concurrent illness. Red flags suggesting a more serious underlying pathology, such as meningitis or encephalitis, may include focal neurologic deficits on examination, a focal onset of the seizure, a stiff neck, or a prolonged seizure as described above. These features may suggest the need for imaging of the head; spinal fluid examination should also be performed.

Treatment and Prognosis

Patients with a first simple febrile seizure do not typically require antiseizure medication. Long-term treatment or prophylaxis during febrile illnesses may be considered for patients with prolonged febrile seizures.

The risk of recurrence may be increased for patients with a family history of seizures and for patients younger than 1 year.

Patients may be at risk for epilepsy (ie, recurrent unprovoked seizures) after febrile seizure if they have had developmental delay, a family history of epilepsy, or a personal history of complex febrile seizures.

Alcohol Withdrawal Seizures

Overview

Patients withdrawing from alcohol may be prone to generalized tonic-clonic seizures 12 to 48 hours after their last drink.

Clinical Presentation and Diagnosis

Patients with alcohol withdrawal seizures typically present with a generalized seizure. If the onset or examination suggests a focal lesion, imaging of the head should be considered to rule out a subdural hemorrhage or other pathology.

Treatment

Benzodiazepines may be used to treat the seizure. If a patient has status epilepticus, the appropriate protocol should be followed. The patient may have a long-term risk of further episodes of status epilepticus during alcohol withdrawal.

Bone Health

It has been well established that older antiepileptic medications have adverse effects on bone health, and there is concern with newer medications, particularly enzyme inducers or inhibitors. The bone health problem in patients treated with antiseizure medications probably results from a different mechanism than in patients with osteoporosis. Decreased levels of vitamin D are most common, and bone density evaluations can be abnormal. Patients taking antiepileptic medication should have their vitamin D levels monitored; if levels are low, adequate replacement should be administered. If low levels of vitamin D are severe or refractory, referral to an endocrinologist should be considered.

- Any woman of childbearing potential should be counseled on the use of contraception and the potential teratogenicity of antiseizure medications.

- Folic acid is recommended as a supplement for women with childbearing potential because supplementation can decrease the rate of neural tube defects in the growing fetus.
- Although there is probably a risk of teratogenic adverse effects from essentially all antiseizure medications, valproic acid carries the highest potential harm, especially in combination with other medications and at higher doses.
- Febrile seizures affect 3%-5% of children and usually occur between 6 months and 5 years of age.
- The diagnosis of febrile seizure is made when a child younger than 5 years has a simple febrile seizure during a concurrent illness.
- Patients withdrawing from alcohol may be prone to generalized tonic-clonic seizures 12–48 hours after their last drink.
- Patients taking antiepileptic medication should have their vitamin D levels monitored; if levels are low, adequate replacement should be administered.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

VI.1. A 32-year-old man presents for evaluation of stereotyped spells. He describes a warning that consists of an unpleasant odor followed by fear and loss of awareness lasting several minutes. Clinical examination findings are normal. Which of the following would be the most appropriate in his evaluation and management?
a. Electrocardiography
b. Tilt table testing
c. Empirical treatment with oxcarbazepine
d. Empirical treatment with valproic acid
e. Magnetic resonance imaging (MRI) of the brain with thin coronal sections through the hippocampi

VI.2. Which of the following statements about epilepsy surgery is most correct?
a. Patients with focal electroencephalographic (EEG) abnormalities and no brain lesions on MRI have high rates of seizure control after surgery
b. Single-photon emission computed tomography (SPECT) is not useful for patients with no brain lesions on MRI
c. Patients with mesial temporal sclerosis have poor rates of seizure control after surgery
d. Surgical outcomes are best when clinical, EEG, and imaging findings are concordant
e. Patients without focal EEG abnormalities cannot be considered surgical candidates

VI.3. A 37-year-old man receives a diagnosis of medically refractory temporal lobe epilepsy. Which of the following semiologic features would be most likely to lateralize to the right temporal lobe?
a. Fencing posture with extension of the left upper limb
b. Figure 4 sign with flexion of the left upper limb
c. Speech arrest at seizure onset
d. Postictal nose rubbing with the left hand
e. Postictal dysphasia

VI.4. You are seeing a 12-year-old girl in the clinic for follow-up of her seizure disorder. Her seizures are characterized by brief episodes of staring with an abrupt return to normal cognitive function. She has been seizure free for 3 years while using a single antiepileptic agent. Which of the following would most likely have been seen on her EEG at the time of her diagnosis?
a. Slow spike-and-wave discharges
b. Hypsarrhythmia
c. Generalized 4- to 6-Hz polyspike-and-wave discharges
d. Multifocal spikes and sharp waves
e. Intermittent generalized 3-Hz spike-and-wave discharges

VI.5. A patient you are seeing in the clinic has a new diagnosis of epilepsy and multiple questions about the disorder. Which of the following statements about epilepsy is most correct?
a. Less than 1% of the general population has epilepsy
b. Approximately one-third of unprovoked seizures have a remote symptomatic cause
c. Most patients with epilepsy have refractory disease requiring multiple medication trials
d. About 20% of people in the general population will have a provoked seizure sometime in their lives
e. Likelihood of seizure recurrence is unrelated to the underlying cause of the seizure

VI.6. A 22-year-old woman presents to the clinic for evaluation of a new-onset partial seizure disorder with occasional generalized seizures. Which of the following statements about her evaluation is most correct?
a. If the neurologic examination findings are normal, brain imaging can be deferred unless she does not respond to initial antiepileptic therapy
b. Given the patient's age, lumbar puncture to assess cerebrospinal fluid neurotransmitter levels is required
c. If her seizures are clinically well characterized and controlled with initial antiepileptic monotherapy, prolonged video-EEG monitoring in an epilepsy monitoring unit is generally not required
d. If initial interictal EEG results are normal, there is no additional utility in performing a second recording
e. If the MRI shows no lesions, positron emission tomographic (PET) imaging is usually necessary to ascertain the epileptic focus

VI.7. You decide to start topiramate therapy for a 47-year-old patient with frequent partial seizures. About which of the following potential adverse effects should you counsel the patient?
a. Acral paresthesia
b. Irreversible visual field defect
c. Idiosyncratic hepatic failure
d. Prolonged QT interval
e. Hyponatremia

VI.8. A 23-year-old woman with primary generalized epilepsy has increasing seizure frequency despite good adherence to her lamotrigine monotherapy. As a child she had been treated with phenobarbital, which she tolerated poorly because of sedation. Which of the following agents would be the most appropriate add-on for rapid improvement in seizure frequency?
a. Valproic acid
b. Levetiracetam
c. Felbamate
d. Primidone
e. Carbamazepine

VI.9. You are asked to evaluate an inpatient who now has seizures in addition to multiple medical comorbidities, including severe hepatic failure. Which of the following medications would be most appropriate to manage his seizures?
a. Phenytoin
b. Lamotrigine
c. Clobazam
d. Lacosamide
e. Felbamate

VI.10. A 33-year-old woman with epilepsy requires ongoing medication to manage her seizure disorder. She is planning to have a child in the next year or two. Which of the following medications would place her at the highest risk of teratogenicity?
a. Levetiracetam
b. Valproic acid
c. Topiramate
d. Felbamate
e. Lamotrigine

VI.11. Which of the following patients would be most appropriate for consideration of surgical treatment of epilepsy?
a. A 21-year-old with partial epilepsy that is well controlled with oxcarbazepine
b. A 47-year-old with refractory partial epilepsy and normal findings on MRI of the brain
c. A 28-year-old with refractory generalized epilepsy
d. An 11-year-old with benign epilepsy with centrotemporal spikes
e. A 53-year-old with refractory temporal lobe epilepsy and unilateral medial temporal sclerosis

Answers

VI.1. Answer e.
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VI.2. Answer d.
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VI.5. Answer b.
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VI.6. Answer c.
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VI.7. Answer a.
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VI.8. Answer b.
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VI.9. Answer d.
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VI.10. Answer b.
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VI.11. Answer e.
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Section
VII

Neuromuscular and Spine Disorders

Elliot L. Dimberg, MD, *editor*

38 Myelopathies

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Introduction

A **myelopathy is a** disorder of the spinal cord. The symptoms and signs of myelopathy can vary depending on which part of the spinal cord is affected and on the cause of the myelopathy. Certain causes of myelopathy tend to affect distinct areas of the spinal cord. The severity of myelopathies can vary even when the causes are identical. Also, the severity of symptoms in compressive myelopathies can depend on how quickly the compression occurs; an acute event often causes more severe symptoms than chronic compression. This chapter discusses the clinical features and evaluation of myelopathies in general, followed by a more specific discussion of various forms of myelopathy (Box 38.1).

Diagnostic Approach to Myelopathies

History and Physical Examination

The most common cause of myelopathy in young adults in temperate zones is multiple sclerosis (MS). The most common cause in elderly patients is cervical spondylotic myelopathy. In looking for other, less common causes, one should consider the history.

The onset and course are very important. Causes of acute myelopathy may include vascular and traumatic causes. Subacute onset may imply a possible infectious or inflammatory condition. A progressive decline might imply a growing mass or a degenerative disorder. An exception to the rule might be the chronic, progressive course of a spinal dural arteriovenous fistula.

In the absence of trauma as an obvious cause, the clinician should inquire about a history of cancer, infection, other causes of immunosuppression including medical conditions, medications, risk of human immunodeficiency virus (HIV), a history of travel or residence in certain geographic areas, and family history of similar symptoms.

On examination one should look not only for a pattern of myelopathic features that may suggest a particular cause but also for neurologic findings outside the spinal cord. Care should be taken to distinguish between spasticity and other causes of increased muscle tone in the extremities. The examiner should look for additional findings (such as bulbar dysfunction) that would localize above the spinal cord, suggesting alternative cause or diagnosis. Important nonneurologic findings on examination include skeletal deformities and skin lesions.

Spinal Cord Syndromes

Spinal cord syndromes present specific clinical pictures. Acute complete transverse lesions occurring immediately to over a few hours present with spinal shock that includes paralysis, which is initially flaccid with absent muscle stretch reflexes, loss of sphincter control, and a sensory level. Because of crossing and ascending pain and temperature pathways, as well as the lamination within those pathways, the actual spinal cord level of injury is usually a level or 2 higher than the sensory level on examination.

Central cord syndromes (eg, caused by a syrinx) can present insidiously with a characteristic capelike loss of pain and temperature with sparing of dorsal column function. Eventually the motor neurons and the corticospinal tracts are affected, resulting in lower motor neuron findings at the level of the lesion and spasticity below the

Abbreviations: HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuromyelitis optica

Box 38.1 • Differential Diagnosis of Myelopathy

- Vascular
  - Spinal dural arteriovenous fistula
  - Epidural, subdural, or intramedullary spinal hemorrhage
  - Spinal cord infarction
  - Spinal cord vascular malformation (cavernous malformation, arteriovenous malformation)
  - Vasculitis
- Infectious
  - Spinal epidural abscess or osteomyelitis with compression
  - Syphilitic gumma
  - Tuberculoma
  - Myelitis
    - Viral: enterovirus (polio), flavivirus (West Nile), herpes virus, cytomegalovirus, varicella zoster, Epstein-Barr virus, human immunodeficiency virus, human T-lymphotropic virus 1, hepatitis A
    - Bacterial: *Treponema pallidum* (syphilis), *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*, neuroborreliosis/Lyme disease, dengue, *Bartonella*, Whipple disease
    - Fungal
    - Parasitic: schistosomiasis, cysticercosis, hydatid disease
- Inflammatory or autoimmune
  - Multiple sclerosis
  - Neuromyelitis optica
  - Neurosarcoidosis
  - Sjögren syndrome
  - Systemic lupus erythematosus
  - Behçet syndrome
  - Scleroderma
  - Postvaccinal or postinfectious
  - Arachnoiditis
  - Idiopathic transverse myelitis
- Neoplastic or paraneoplastic
  - Ependymoma
  - Neurofibroma
  - Meningioma
  - Astrocytoma
  - Metastasis
  - Paraneoplastic (CRMP-5, amphiphysin IgG)
- Metabolic
  - Vitamin B_{12} or folate deficiency
  - Vitamin E deficiency
  - Copper deficiency
  - Medications or drugs
    - Zinc toxicity (medications or supplements with zinc; denture cream)
    - Nitrous oxide toxicity
- Degenerative
  - Cervical spondylosis
- Genetic
  - Hereditary spastic paraplegia
  - Adrenomyeloneuropathy
- Traumatic
- Other structural or compressive
  - Spina bifida
  - Syringomyelia or hematomyelia
- Other
  - Radiation
  - Superficial siderosis

Abbreviations: CRMP, collapsin response-mediated protein 5; IgG, immunoglobulin G.

lesion. A unique central cord syndrome can occur more acutely in the setting of limited cervical trauma, particularly hyperextension, often in the setting of cervical stenosis. There is often quadriplegia with early recovery of lower extremity strength but variable remaining upper extremity weakness, urinary dysfunction, and numb, clumsy hands.

Ventral cord syndromes typical of anterior spinal artery distribution ischemia may occur acutely. The clinical picture is one of a complete transverse lesion, except that posterior column function is relatively spared because this is supplied by the posterior spinal artery. This clinical picture can develop less abruptly in demyelinating disease.

Posterior column syndromes can be divided into posterolateral column syndrome, causing both a sensory ataxic and spasticity, or isolated posterior column syndrome, causing sensory ataxia. The former usually develops insidiously, and the classic form is known as subacute combined degeneration, found in metabolic causes of myelopathy or vitamin B_{12} or copper deficiencies. The deficiencies, when occurring in the cervical cord, are usually associated with a Lhermitte sign and often found in MS.

Brown-Séquard syndrome results in loss of pain and temperature contralateral to the lesion and loss of proprioception and weakness ipsilateral to the lesion. It can be found, often partially, in trauma, external compression, or MS. Extrinsic compression of the spinal cord may include radicular pain, and typically the sensory impairment includes the sacral dermatomes because they are

represented more peripherally in the spinothalamic tracts. In fact, with very slowly developing compressive lesions at the cervicothoracic junction, the initial sensory symptoms may be only in the sacral area and in the distal aspect of the legs. This location contrasts with that in intrinsic cord lesions, where there may be sacral sparing.

Diagnostic Evaluation of Myelopathy

Acute myelopathies necessitate urgent or emergency evaluation. If a myelopathy has developed acutely to subacutely, over hours to weeks, imaging should be performed urgently, and the entire spine may have to be imaged, because some causes of compression or inflammation may have multiple sites of disease along the spinal cord. The causes and treatment of acute cord syndromes, including trauma, are reviewed in Chapter 7, "Acute Spinal Cord Compression, Spinal Cord Trauma, and Peripheral Neural Injury."

Myelopathies must be determined to be either compressive or noncompressive. Magnetic resonance imaging (MRI) of the spine is the best study initially. A contrasted study may be useful if the differential diagnosis includes tumor, infection, inflammation, or certain vascular causes. If patients are unable to undergo MRI, computed tomography myelography may be indicated.

Cerebrospinal fluid studies are useful when no compressive cause has been found, particularly to further evaluate potential inflammatory and infectious causes. Additional laboratory or other studies may be necessary depending on the suspicion for individual entities from the differential diagnosis (Box 38.1).

- The most common cause of myelopathy in young adults in temperate zones is multiple sclerosis (MS). The most common cause in elderly patients is cervical spondylotic myelopathy.
- The onset and course of the symptoms and presenting clinical syndrome of myelopathies provide clues to the cause.
- Brown-Séquard syndrome results in loss of pain and temperature contralateral to the lesion and loss of proprioception and weakness ipsilateral to the lesion.

Inflammatory Myelopathies

Multiple Sclerosis

Spinal cord demyelination causes a subacute (days to weeks) myelopathy that is typically asymmetric, with symptoms such as proprioceptive loss or partial Brown-Séquard syndrome. Often there is a Lhermitte sign (exacerbation of symptoms with forward flexion of the neck).

The responsible lesions on MRI are small, typically less than 2 vertebral segments long and located peripherally. They may enhance with gadolinium in the acute or subacute phase. If there is no previous diagnosis of MS, MRI of the brain should be performed to look for evidence of typical white matter lesions of MS. The presence of at least 2 of these lesions predicts a risk of just under 90% conversion to MS during the next 14 years.

Treatment is with high-dose intravenous corticosteroids, usually 1 g of methylprednisolone daily for 3 to 5 days. Plasmapheresis should be considered in patients who have significant neurologic impairment and no response to high-dose corticosteroids. Consideration should be given to treatment with immunomodulatory agents in patients who are found to have brain lesions on MRI and are considered at high risk for development of MS. Patients with known primary progressive MS can sometimes present with an acute worsening of their chronic myelopathy in the setting of a medical problem, typically an underlying infection or with heat exposure. See also Chapter 19, "Treatment of Multiple Sclerosis."

Neuromyelitis Optica

Neuromyelitis optica (NMO) presents with symmetric and severe complete spinal cord syndrome with symptoms of paraparesis, a sensory level, and bladder and bowel dysfunction. The patient may have a history of optic neuritis or have concurrent optic neuritis. The MRI appearance is that of a longitudinally extensive area of T2 signal change, extending over at least 3 or more vertebral segments. In this setting, serum NMO immunoglobulin G testing is indicated. However, one must rule out other causes of longitudinally extensive myelitis, including idiopathic transverse myelitis, sarcoidosis, and myelitis associated with systemic autoimmune diseases. Additional details on NMO are provided in Chapter 20, "Mimickers of Multiple Sclerosis."

Sarcoidosis

Significant neurologic symptoms will develop in approximately 10% of patients with sarcoidosis, and 10% of those have spinal disease.

The clinical presentation is varied because sarcoidosis can cause intramedullary, subdural, or epidural disease. Subacute progressive myelopathy, or waxing and waning myelopathy, is typically found.

MRI with gadolinium usually shows leptomeningeal enhancement with nodular or linear lesions on the surface of the cord as well as the nerve roots. Intramedullary areas of increased T2 signal show patchy enhancement and may be longitudinally extensive. The cervical cord is most commonly affected. Suspicion of sarcoidosis should prompt evaluation for extraneural disease as a source to biopsy, although in some patients (those who have atypical MRI appearance, are at risk for tuberculosis, or do not respond to treatment of sarcoidosis) biopsy of nervous system tissue is necessary. Treatment of sarcoid and

involvement of other central nervous system structures is discussed in Chapter 20, "Mimickers of Multiple Sclerosis."

Postvaccinal, Postinfectious, and Idiopathic Myelopathy

Absent a history of infection or immunization, there is no way to readily distinguish between postvaccinal myelitis, postinfectious myelitis, and idiopathic transverse myelitis. By definition, postvaccinal and postinfectious myelitis occur within 3 weeks of the vaccination or systemic infection. The vaccines associated with myelitis include influenza, hepatitis B, rubella, and rabies. Postinfectious causes include many viruses, *Mycoplasma*, and *Chlamydia*. It may be that both vaccines and infections function as immune activators, triggering a clinical episode of a more defined disorder such as MS or NMO, and patients should be evaluated with that in mind. Treatment of these conditions is with high-dose intravenous corticosteroids.

Paraneoplastic myelopathies may also present as an inflammatory myelopathy and are discussed in Chapter 62, "Paraneoplastic and Other Autoimmune Neurologic Disorders."

- Spinal cord demyelination due to MS often involves small lesions, less than 2 vertebral segments long.
- In neuromyelitis optica, MRI shows longitudinally extensive T2 signal change, generally extending over 3 vertebral segments.

Infectious Myelopathies

Overview

A myelopathy may result from an infectious agent for various reasons (see also Chapter 63, "Syndromic Approach to Neuroinfectious Diseases.") The infection may result in an abscess (epidural, subdural, rarely intramedullary) or destruction of a vertebral body with subsequent cord compression (eg, tuberculosis), or there may be infection of the spinal cord or meninges.

Viral and Bacterial

Acute infectious myelitis is typically associated with viral or bacterial infection and only rarely with fungal or parasitic infection. There is often evidence of systemic infection with fever and meningoencephalitis.

Enteroviruses (eg, poliovirus, coxsackievirus, and echovirus) and flaviviruses (eg, West Nile virus) have a predilection for affecting the anterior horn cells and present with a flaccid paralysis. Only about 1% of infected patients have spinal cord symptoms, which may develop over 2 days to more than a week. (See Chapter 64, "DNA and RNA Viral Infections of the Nervous System," for further discussion of poliomyelitic syndromes.)

The herpesviruses can cause myelopathy with herpes simplex virus 2, Epstein-Barr virus, and cytomegalovirus, occasionally presenting with acute myelitis at the time of the primary infection. Cytomegalovirus also causes a different clinical picture with a progressive ascending flaccid weakness, paresthesia, and urinary retention in the immunocompromised host, particularly those with concurrent HIV.

Varicella zoster virus can cause a chronic progressive myelopathy in the immunocompromised host, or it may cause an acute necrotizing myelitis 1 to 2 weeks after an outbreak of shingles at the level of the affected dermatome.

Diagnosis in all of these cases is with cerebrospinal fluid analysis, confirming the presence of viral DNA by polymerase chain reaction. Appropriate antiviral therapy is indicated for herpex simplex virus, cytomegalovirus, and varicella zoster virus.

Rarely, bacteria can cause an infectious myelitis with intramedullary abscess formation via direct spread of infection or hematogenous spread from endocarditis or pulmonary infections. Myelitis can also occur uncommonly in cat-scratch disease (*Bartonella henselae*), Lyme disease, and Whipple disease.

Human Immunodeficiency Virus

HIV-associated vacuolar myelopathy usually occurs late in the course of HIV infection and typically presents with symmetric paresthesia, weakness, gait impairment due to spasticity and sensory ataxia, and bowel and bladder incontinence (see also Chapter 65, "Retroviral Infections of the Nervous System"). It is a diagnosis of exclusion, because there are many other infectious and noninfectious causes of myelopathy in HIV. In patients with known HIV who present with myelopathy, MRI should be performed to exclude tumor or abscess, then cerebrospinal fluid should be evaluated for bacterial and fungal cultures, studies for cytomegalovirus, herpex simplex virus, varicella zoster virus, and cryptococcal antigen. Likewise, patients with undiagnosed myelopathies should have HIV testing. There is no specific treatment for HIV-associated vacuolar myelopathy.

Human T-Cell Lymphotrophic Virus Type I

Human T-cell lymphotrophic virus type I is not common in the United States, although it is endemic in the Caribbean, Japan, Central America, equatorial Africa, and the South Pacific. Transmission is parenteral or through sexual contact, intravenous drug use, or breast milk. In about 1 in 250 infected persons, a chronic progressive myelopathy can develop with spastic lower extremity weakness and spastic bladder. More rarely, there is a rapid course occurring over weeks to months. Human T-cell lymphotropic virus type II

can cause similar neurologic disease, primarily in intravenous drug abusers and, for unknown reasons, in the Native American population. Diagnosis is made with tests for antibodies in the serum and antibody and polymerase chain reaction testing in cerebrospinal fluid. There is no clear effective treatment (see also Chapter 65, "Retroviral Infections of the Nervous System").

Spinal Epidural Abscess

Presentation of myelopathy acutely to subacutely in the setting of back pain and fever should prompt immediate MRI with and without contrast to exclude spinal epidural abscess. Spinal epidural abscess is an uncommon entity found sporadically or in the setting of intravenous drug use; spinal abnormalities; chronic medical problems such as diabetes, renal disease, or cancer; or the immunosuppressed patient. Treatment usually consists of surgical débridement, identification of the organism, and targeted antibiotics. An occasional patient with minimal disease may be managed conservatively with neuroradiologic needle aspiration, with appropriate antibiotics and surgery reserved for treatment failures.

Tuberculosis

Tuberculosis most commonly causes myelopathy from tuberculous spondylitis with inflammation from the affected vertebrae putting pressure on the anterior spinal cord, vascular thrombosis, and spinal instability (Gibbus deformity). There can also be intramedullary or extramedullary tuberculomas. This diagnosis should be considered in immunocompromised patients and in those who have come from regions of the world where the disease is common. Treatment usually involves surgery and long-term courses of antitubercular drugs (see also Chapter 66, "Bacterial Infections of the Nervous System").

Syphilis

Syphilis can affect the spinal cord in multiple ways (meningomyelitis, tabes dorsalis, and syphilitic gumma), with the most common now being syphilitic meningomyelitis.

Syphilitic meningomyelitis occurs after the primary infection, anywhere from 1 to 30 years later. Patients note a sense of heaviness in the legs with paresthesias, and spastic weakness and bladder dysfunction are identified. Eventually, a small-vessel vasculitis may cause spinal cord infarction.

Tabes dorsalis is a form of syphilitic spinal cord disease occurring at least 10 years after the primary infection. It begins with severe lightning pains in the legs associated with impotence and bladder dysfunction. Patients will be areflexic with multimodality sensory loss and Argyll Robertson pupils. This phase lasts about 3 years. The second phase lasts between 2 and 10 years and has worsening pain and sensory loss, particularly for deep pain and proprioception, often leading to arthropathies. In the last phase, also lasting 2 to 10 years, there is significant spastic paraparesis and autonomic dysfunction.

Syphilitic involvement of the spinal cord can also occur with intramedullary or extramedullary gummas or hypertrophic pachymeningitis.

Two important points to note are the frequent coexistence of syphilis in a patient with HIV and the fact that syphilitic meningomyelitis clinically presents very similarly to cervical spondylotic myelopathy.

The diagnosis and treatment of syphilis are discussed in Chapter 66, "Bacterial Infections of the Nervous System."

Parasitic

Although rare in the United States, parasitic myelopathy due to schistosomiasis is common in South America, Africa, and Asia. Exposure occurs with bathing or swimming in contaminated freshwater. This infectious myelopathy presents acutely or subacutely with leg pain, weakness, sensory loss, and bowel and bladder dysfunction.

Cysticercosis, in which the spinal cord is involved in up to 5% of cases, is endemic in Latin America, sub-Saharan Africa, India, and Asia. It presents as a slowly progressive myelopathy from intramedullary cysts or direct subarachnoid invasion. Hydatid disease causes myelopathy from either intramedullary cysts or extrinsic cord compression from bone disease. (See also Chapter 68, "Parasitic Infections of the Central Nervous System.")

Fungal

Fungal myelopathies are rare and present as either cord compression related to vertebral osteomyelitis, cord infarction from related vascular inflammation, or granulomatous meningitis. They should be considered particularly in the immunocompromised host. (See also Chapter 67, "Fungal Infections of the Central Nervous System.")

- Enteroviruses (eg, poliovirus, coxsackievirus, and echovirus) and flaviviruses (eg, West Nile virus) have a predilection for affecting the anterior horn cells and present with a flaccid paralysis.
- Spinal epidural abscess is an uncommon entity found sporadically or in the setting of intravenous drug use; spinal abnormalities; chronic medical problems such as diabetes, renal disease, or cancer; or the immunosuppressed patient.
- Syphilis can affect the spinal cord in multiple ways (meningomyelitis, tabes dorsalis, and syphilitic gumma), with the most common now being syphilitic meningomyelitis.

Vascular Myelopathies

Spinal Cord Infarction

Spinal cord infarction causes an acute, painful myelopathy. The majority of cases present as a ventral cord syndrome, in that the anterior spinal artery distribution is the most commonly affected. Pain usually occurs first, in a radicular pattern in the lower thoracic or lumbar level. Weakness follows within minutes to hours, accompanied by bladder and bowel symptoms. About half of patients have substantial recovery of function, especially if they have improved motor function in the first 24 hours. Patients are often left with considerable central pain syndromes. See Chapter 11, "Ischemic Stroke: Uncommon and Special Situations" for a review of the causes, diagnosis, and treatment of spinal cord infarction.

Spinal Cord Hemorrhage

Spinal cord hemorrhage also presents with sudden onset of back pain followed by cord dysfunction. Spinal cord hemorrhage can be epidural, subdural, or diffuse subarachnoid hemorrhage and presents over hours to days. The main risk factors for hemorrhage are impaired clotting from medications or hematologic disorders, trauma, spinal surgery, lumbar puncture, and vascular malformation. As with other acute myelopathies, MRI should be performed immediately. Spinal cord hemorrhage with neurologic deficit from hematoma mass effect is a surgical emergency.

Spinal Dural Arteriovenous Fistula

Spinal dural arteriovenous fistula is a treatable condition, but it is commonly diagnosed long after considerable neurologic dysfunction has accrued. It is the most common vascular anomaly of the spine. Patients are typically men in the sixth or seventh decade of life. The disorder is slowly progressive, sometimes with stepwise deterioration, which early on does not necessarily demonstrate findings classically found in myelopathy. No matter the level of the fistula, the caudal end of the spinal cord is affected first by venous congestion leading to initial sensory-motor symptoms ascending from the feet, gait difficulties, radicular pain, and eventually bowel, bladder, and sexual dysfunction. Patients may report acute transient worsening with exercise or prolonged standing. The majority of patients have a mixture of upper and lower motor neuron findings on examination.

MRI should be done to look for increased T2 signal in the central spinal cord, typically involving the conus and extending longitudinally over 5 to 7 vertebral segments. Flow void abnormalities are also found on the surface of the cord (Figure 38.1). MR angiography can help determine the level of the spinal dural arteriovenous fistula, and spinal angiography is necessary for planning treatment, either endovascular embolization or surgical ligation of the fistula.

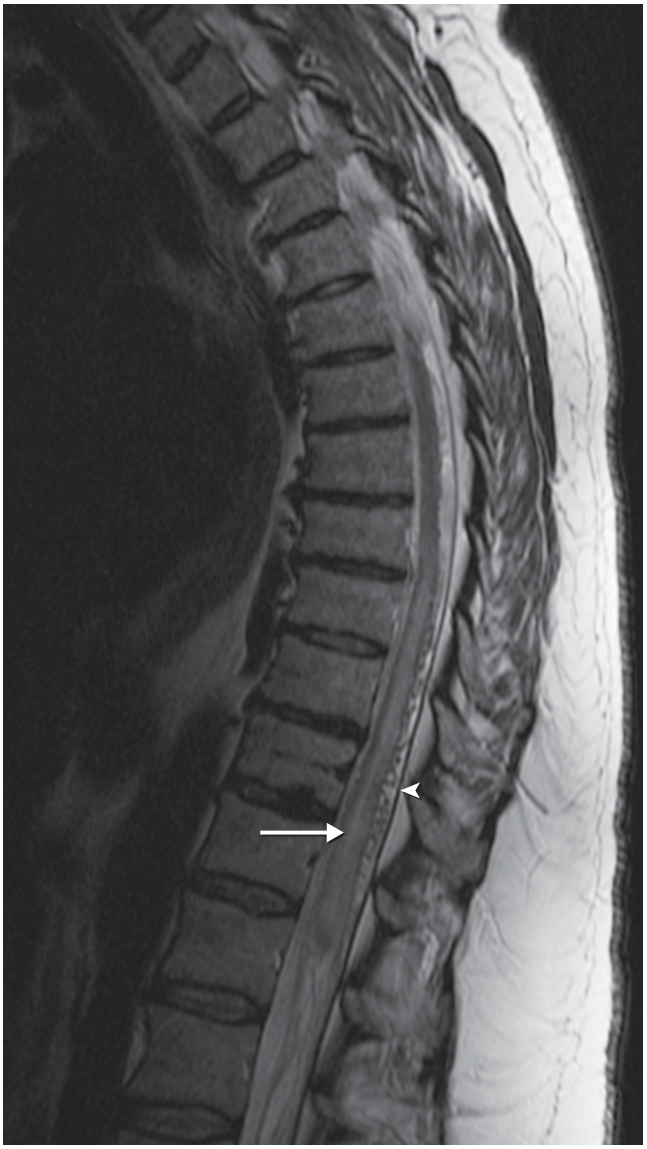


Figure 38.1 *Spinal Dural Arteriovenous Fistula.*
Sagittal thoracic T2 magnetic resonance imaging shows a thoracic-level dural arteriovenous fistula. Note the flow voids dorsal to the cord (arrowhead), representing the fistula. The fistula results in cord edema, evidenced by the high T2 signal (arrow).

Response to treatment depends on how long symptoms have been present and the degree of disability; thus, it is important to keep this diagnosis in mind.

Compressive Myelopathies

Cervical spondylotic myelopathy results from a common degenerative condition causing changes in the disks with disk extrusion, hypertrophic osteophytes, and hypertrophy of the ligamentum flavum. It occurs in elderly persons, but patients with a congenitally small spinal canal will present with symptoms earlier in life.

The myelopathy that may be associated with cervical spondylosis usually presents chronically, with gait unsteadiness, a sense of weakness or stiffness in the legs, difficulty with fine motor skills in the hands, and sensory symptoms in the upper and lower extremities. There is often neck pain or stiffness and eventually bladder symptoms. The natural history of this disorder is not absolutely known.

Patients who have substantial myelopathy or progressive symptoms should undergo decompressive surgery. Patients who have minimal myelopathy on examination, no T2 signal change in the cervical cord on MRI, and no spinal instability can be followed with neurologic examinations to document myelopathic progression. Surgery is performed primarily to prevent progression of symptoms; therefore, patients being treated conservatively must be followed closely. Spondylotic myelopathy can also develop acutely, with seemingly minor trauma in the setting of cervical stenosis.

Various metastatic and primary neurologic malignancies may present with myelopathy. For review of myelopathy related to neoplastic diseases and their treatments, see Chapter 58, "Spinal Cord Tumors."

Traumatic spine injury commonly causes abrupt, severe deficits. Patients with trauma must be assumed to have a spinal injury and be immobilized until this diagnosis is ruled out (see Chapter 7, "Acute Spinal Cord Compression, Spinal Cord Trauma, and Peripheral Neural Injury").

- Patients with spinal dural arteriovenous fistula are typically men in the sixth or seventh decade of life. The disorder is slowly progressive, sometimes with stepwise deterioration.
- MRI should be done to look for increased T2 signal in the central spinal cord, typically involving the conus and extending longitudinally over 5 to 7 vertebral segments.

Hereditary Myelopathies

Hereditary Spastic Paraplegia

Epidemiology

Inheritance of hereditary spastic paraplegia can be autosomal dominant, autosomal recessive, or X-linked, and the age at onset can range from infancy to the seventh decade of life. Autosomal dominant inheritance occurs in 75% to 80% of cases, and one-quarter of these cases are thought to be spontaneous mutations.

Clinical Features

Hereditary spastic paraplegia presents as a chronic progressive spastic weakness in the lower extremities. There may be some loss of vibratory function and bladder dysfunction. The rate of progression varies considerably between different genetic types and even within families. Some types of hereditary spastic paraplegia are considered "complicated," in which neurologic findings are outside the spinal cord. These are usually inherited recessively.

Other Inherited Myelopathies

Hereditary ataxias may initially present with progressive spasticity, but oculomotor abnormalities or dysarthria eventually develops. Patients may also have lower extremity areflexia in the setting of an elicited Babinski sign.

Hereditary neurometabolic disorders can atypically present in adulthood with symptoms similar to those of hereditary spastic paraplegia. Late-onset Krabbe disease may have associated dementia. Assay for activity of galactosylceramide β-galactosidase is diagnostic. Adult-onset metachromatic leukodystrophy is often associated with psychiatric symptoms. MRI of the brain can show dysmyelination, but diagnosis is made by assaying arylsulfatase A levels in the serum.

Adrenoleukodystrophy is an X-linked disorder in which a peroxisomal enzyme deficiency results in accumulation of very long-chain fatty acids. Phenotypic variations of the disease include a childhood cerebral form, an adult cerebral form, a predominantly myelopathic form, and isolated adrenal insufficiency, and these can present in the same family. Adrenomyeloneuropathy usually presents in the third decade of life with a gradual onset of paraparesis and sphincter dysfunction and progresses slowly over decades. There is an associated demyelinating peripheral neuropathy; however, the peripheral nerve symptoms are overshadowed by the myelopathic symptoms. Adrenocortical insufficiency is present in 70% of patients with adrenomyeloneuropathy and should be looked for and treated. For details of this disease and its diagnosis and treatment, see Chapter 75, "Inherited Leukoencephalopathies."

Structural Myelopathies

The spina bifida disorders have a wide range of anatomic and neurologic presentations. The presence of meningomyelocele is typically associated with other neurologic abnormalities, such as hydrocephalus, and is noted at birth (Figure 38.2). Diastematomyelia is a malformation characterized by a split spinal cord with either a fibrous strand or bony spur running between the 2. Patients often have no symptoms, but traction on the cord during rapid growth spurts or compression by the bony spur can cause chronic progressive myelopathy that is usually asymmetric and associated with prominent sphincter dysfunction.

Idiopathic spinal cord herniation occurs with an anterior dural defect, which allows for thoracic cord herniation. This condition typically occurs in midlife, more commonly in women. It usually presents as a chronic, slowly progressive Brown-Séquard syndrome. It is easily seen on MRI and treated surgically.

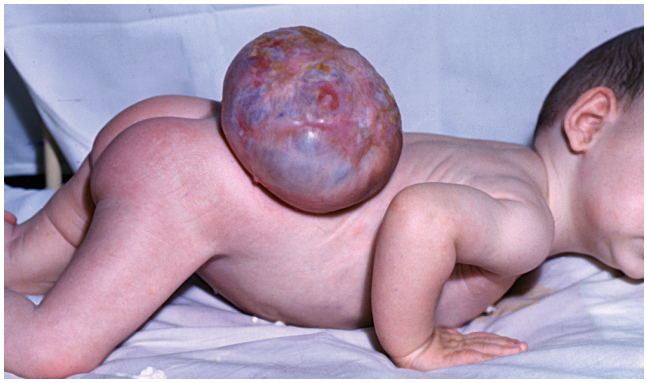


Figure 38.2 *Myelomeningocele (Spina Bifida Cystica). The spinal cord and meninges herniate through a congenital defect in the vertebral arch. It is covered with skin.*
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

Adults with tethered cord, unlike children with the disorder, do not have other associated skeletal deformities. They rarely become symptomatic, but symptoms can be precipitated by development of central canal narrowing or trauma. They present with diffuse sacral and leg pain, sensorimotor deficits, and bowel and bladder dysfunction. Treatment is surgical release of the conus and may improve all symptoms, but less so the bowel and bladder symptoms. The most common causes in adults are tight filum terminale, spinal lipoma, lipomyelomeningocele, and diastematomyelia. In the pediatric population, tethered cord may develop after surgery for spinal dysraphisms or other occult spinal lesions.

Metabolic Myelopathies

Metabolic causes of myelopathy also often affect peripheral nerve function. In the spinal cord, the dorsal columns and corticospinal tracts are preferentially affected. Most patients have a subacute presentation, and treatment does not necessarily reverse all deficits.

Vitamin B_{12} deficiency and copper deficiency may present with clinical manifestations of myelopathy characterized by dorsal column and corticospinal tract involvement

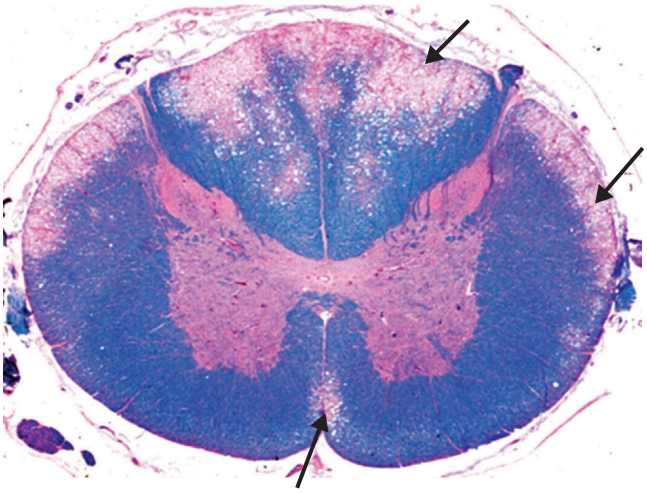


Figure 38.3 *Effect of Vitamin B_{12} Deficiency. Coronal section of the cervical cord stained with hematoxylin-eosin shows degeneration of the dorsal columns in combination with that of the lateral and anterior corticospinal tracts (arrows).*
(Adapted from Benarroch EE, Daube JR, Flemming KD, Westmoreland BF. Mayo Clinic medical neurosciences: organized by neurologic systems and levels. 5th ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. Chapter 14, The spinal level; p. 547–94. Used with permission of Mayo Foundation for Medical Education and Research.)

(Figure 38.3). In vitamin B_{12} deficiency, initial symptoms are usually paresthesia followed by development of myelopathy. Patients particularly at risk for vitamin B_{12} deficiency include those who have had gastric bypass surgery or have inflammatory bowel disease or those with low levels exposed to nitrous oxide. Copper deficiency may result from gastric surgery or excess zinc ingestion, although often the cause is not identifiable. These disorders are discussed in more detail in Chapter 78, "Neurologic Complications of Nutritional Disorders."

Vitamin E deficiency can cause a subacute combined degeneration, but it usually presents as a progressive spinocerebellar syndrome with associated dysarthria and visual symptoms. For additional details, see Chapter 78, "Neurologic Complications of Nutritional Disorders."

- Vitamin B_{12} deficiency and copper deficiency may present with clinical manifestations of myelopathy characterized by dorsal column and corticospinal tract involvement.

39 Motor Neuron Diseases

ERIC J. SORENSON, MD

Introduction

The motor neuron disorders are a clinically diverse group of diseases that share a pathologic loss of the motor neurons. The most common adult-onset disorder is amyotrophic lateral sclerosis (ALS). Other forms include the spinal muscular atrophies, infectious motor neuronopathies, and rare focal forms of anterior horn cell loss.

Amyotrophic Lateral Sclerosis

Epidemiology of ALS

Overall, the incidence rate is believed to be between 1.5 and 2.0 cases per 100,000 person-years, and the prevalence rate is 4 to 6 cases per 100,000 population. Other than the sparsely populated geographic clusters (Guam and the Kii Peninsula of Japan), the incidence rate seems consistent across ethnic and geographic boundaries. It has been suggested recently that a higher-than-expected prevalence of the recently identified *C9orf72* causative mutation within the Kii Peninsula may have created a founder effect and explains, in part, the increased incidence in that region.

There is a male preponderance, with 1.2 to 1.5 males per affected female. The incidence of ALS varies by age. Cases of ALS in persons younger than 30 years are rare, but notable examples include the rare forms of juvenile ALS. The incidence increases with age, peaking in the seventh decade of life, and the risk decreases after that.

Case-control studies have suggested an association between ALS and a history of smoking or prior military service. In general, the odds ratios for these associations have been weak (<2.0) and lacked a dose-response effect. These findings raise the possibility of confounding effects, and the true risk factor behind these statistical associations has yet to be identified. Trauma, and particularly head trauma, has recently been reported as a significant risk for later development of ALS. The strongest evidence in support of this has been from a cohort study of former professional athletes, in which the odds ratio for development of ALS was 4 times higher than in matched controls and the risk increased as the severity of the trauma increased.

Genetics of ALS

The majority of cases are sporadic; only 5% to 10% of all cases are familial. The familial cases have a slightly younger age at onset but are otherwise clinically indistinguishable from the sporadic cases. Nearly all adult-onset familial cases are inherited in an autosomal dominant manner. The first genetic mutation described in familial ALS was within the superoxide dismutase (Cu/Zn), or *SOD1*, gene on chromosome 21. Since then, more than 80 unique mutations have been identified within this gene. In total, mutations within the *SOD1* gene represent about 20% of all familial cases of ALS.

Recently, a hexanucleotide repeat expansion was identified in the *C9orf72* gene on chromosome 9 that seems to account for up to 40% of familial forms of ALS. Interestingly, this same genetic mutation has also been associated with frontotemporal dementia, providing the strongest evidence to date for a common cause between frontotemporal dementia and ALS.

Several other genes have been identified in a small proportion of familial ALS cases (Table 39.1). Interestingly, there is no commonality in the function of these genes;

Abbreviations: ALS, amyotrophic lateral sclerosis; SBMA, spinal and bulbar muscular atrophy; SMA, spinal muscular atrophy; TDP-43, transactive response DNA-binding protein 43

Table 39.1 • Currently Known Genes Responsible for Familial Forms of Amyotrophic Lateral Sclerosis and Their Protein Product

Gene	Protein
SOD1	Superoxide dismutase (Cu/Zn)
C9orf72	Uncharacterized
FUS	Fused in sarcoma
TARDBP	TDP-43
ALS2	Alsin
ANG	Angiogenin
SETX	Senataxin
VAPB	Vesicle-associated protein B
UBQLN2	Ubiquilin

Abbreviation: TDP-43, transactive response DNA-binding protein 43.

thus, the molecular pathogenesis of the disease is elusive. How each of these mutations leads to the final common pathway of motor neuron degeneration remains unknown, but it is a very active area of research.

Pathology of ALS

On gross pathologic examination, ALS generally demonstrates motor roots that may appear atrophic, but no other specific pathologic features are present. Histologic examination of the brain and spinal cord shows a marked loss of the Betz cells of the motor cortex. Less-marked loss of other pyramidal neurons in other regions of the brain can be seen. Gliosis is also prevalent within the affected regions. Within the spinal cord, there is a marked loss of the large motor neurons within the anterior horn. Here, too, there is a reactive gliosis. Additionally, there is a loss of myelinated fibers, with the lateral columns corresponding to degeneration of the corticospinal tracts.

Within the surviving motor neurons, cytoplasmic inclusion bodies have been described. Historically, the Bunina body has represented the primary pathologic finding within the motor neurons (Figure 39.1). Bunina bodies are eosinophilic cytoplasmic inclusions that represent ubiquinated protein aggregates. These are thought to be sensitive but not entirely specific for ALS.

Ubiquinated aggregates containing transactive response DNA-binding protein 43 (TDP-43) are highly sensitive and specific for ALS and frontotemporal dementia (Figure 39.2). Although the exact role of TDP-43 in ALS is yet to be defined, it is known that TDP-43 binds DNA and RNA as a transcription inhibitor and plays a role in presplicing regulation of RNA expression. The relationship between the Bunina bodies and the TDP-43 inclusions is not entirely clear. Many, but not all, of the Bunina bodies are TDP-43–positive.

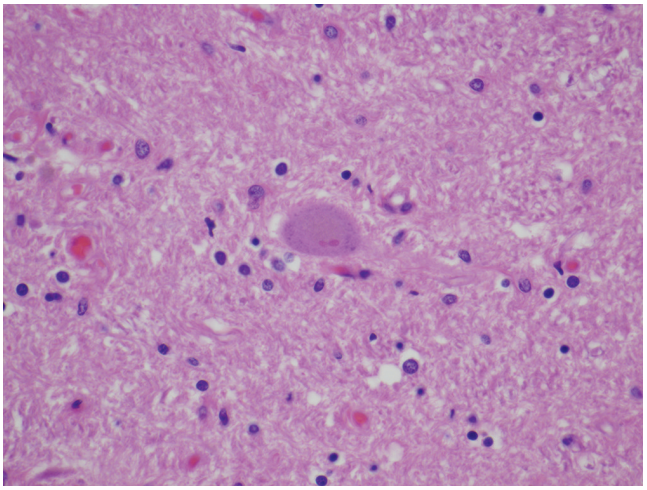


Figure 39.1 *The Bunina Body.*
This is an eosinophilic cytoplasmic inclusion body.

Also evident on pathologic study is activation of microglia cells and a T-cell infiltration. This has led to speculation that the inflammatory response may be important in the pathogenesis of the disease. Alternatively, this may represent a reactive process, with little contribution to the disease initiation or propagation.

Etiology of ALS

The cause of ALS remains unknown. Several theories have been proposed, but there is little definitive evidence pointing to any specific one. Neuronal apoptosis is generally believed to be the final event leading to cell death. Despite this commonly held theory, there is little experimental evidence in support of this.

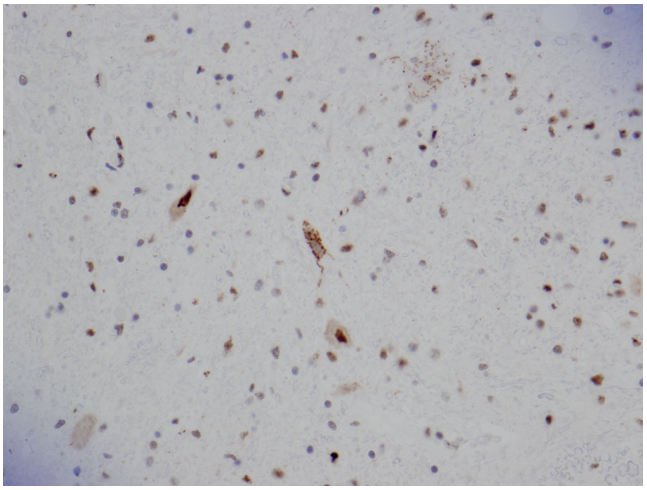


Figure 39.2 *Transactive Response DNA-Binding Protein 43 (TDP-43)–Positive Neurons.*
These show the protein aggregate within the cytoplasm of the neurons.

Clinical Features of ALS

The classic presentation of ALS is that of progressive weakness, without other neurologic features of sensory loss or pain. Objective signs include evidence of upper motor neuron and lower motor neuron loss (Box 39.1). The clinical signs of upper motor neuron loss include hyperreflexia, the Babinski signs, muscle spasticity, and slowness of movements. Signs of lower motor neuron loss include muscle weakness, muscle atrophy, and muscle fasciculations.

ALS typically begins regionally and asymmetrically. In about one-third of cases, ALS begins unilaterally in 1 hand, another one-third unilaterally in 1 leg, and one-third with progressive bulbar dysfunction most commonly noted first with dysarthria followed by dysphagia.

For reasons that remain unclear, ALS typically does not affect the extraocular muscles or the voluntary sphincter muscles until very advanced stages of the disease. Traditionally, cognitive issues were thought to develop in only a small proportion of patients with ALS. In recent years, it has become known that patients with ALS commonly have various forms of executive dysfunction and other cortical cognitive syndromes as the relationship between ALS and frontotemporal dementia has become apparent.

Although the clinical features of ALS are similar among cases, there is considerable variability in the rates of progression. The median survival from symptom onset is typically 3 years, and from diagnosis it is just under 2 years (Figure 39.3). The strongest predictor of survival at presentation is the age of the patient; a younger age at onset offers a longer survival. Bulbar-onset disease also has a slightly poorer prognosis. A small minority of patients have a prolonged survival. Approximately 5% of patients survive longer than 5 years, and occasionally patients survive longer than 10 years.

A unique presentation is the pure upper motor neuron phenotype that has been labeled *primary lateral sclerosis*. It remains debated whether this should be classified as a unique disorder, given its slower evolution and more benign prognosis. However, today, most investigators consider primary lateral sclerosis to be a more benign variant of ALS.

Box 39.1 • Clinical Features of Amyotrophic Lateral Sclerosis, by Motor Neuron Manifestations

Motor Neuron Features	
Lower	**Upper**
Weakness	Spasticity
Atrophy	Slowed movements
Fasciculations	Hyperreflexia
	Babinski signs

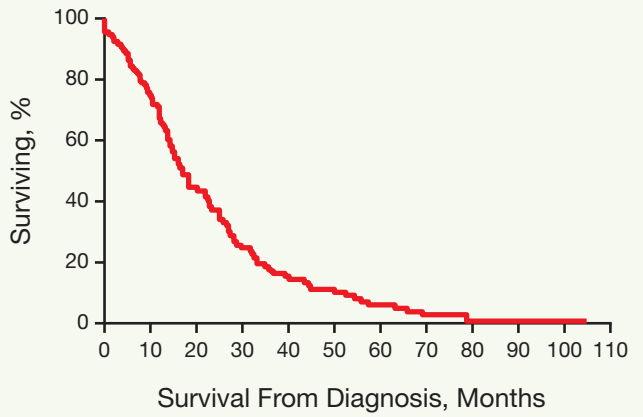


Figure 39.3 *Survival From Diagnosis in Amyotrophic Lateral Sclerosis.*
Data are from a population-based sample from Olmsted County, Minnesota.

Evaluation of ALS

There is no single standardized evaluation when ALS is suspected. The work-up should be directed at the specific differential diagnosis for each case. The most important ancillary examination is nerve conduction studies and needle electromyography. The principal role of these tests in ALS is to confirm the suspected diagnosis and to exclude potential mimickers.

The El Escorial criteria have become the standard of care in diagnosing ALS. These criteria provide guidelines for the diagnosis, along with a level of diagnostic certainty (Table 39.2). The criteria divide the body into 4 regions: bulbar, cervical, thoracic, and lumbar. Within each segment, lower motor neuron findings should be present in 2 muscles innervated by 2 different peripheral nerves and in 2 different myotomes. Along with these findings, upper

Table 39.2 • El Escorial Criteria for Amyotrophic Lateral Sclerosis

Criterion	Level of Diagnostic Certainty
Lower motor neuron only	Clinically possible
Upper motor neuron only	Clinically possible
One region with upper and lower motor neuron involvement	Clinically possible
One region with upper and lower motor neuron involvement, with EMG evidence in a second region	Clinically probable, laboratory supported
Two regions with upper and lower motor neuron involvement	Clinically probable
Three or four regions with upper and lower motor neuron involvement	Clinically definite

Abbreviation: EMG, electromyographic.

motor neuron features need to be present clinically. If 3 or 4 of these regions meet these guidelines without another explanatory cause, then the diagnosis is classified as "clinically definite." If 2 regions are affected, then the diagnosis is classified as "clinically probable." If only 1 region is affected, then the diagnosis is classified as "clinically possible." In the unique situation of pure upper motor neuron or pure lower motor neuron involvement, the diagnosis is also classified as "clinically possible."

Electromyography can also be very useful for identifying an alternative cause. For example, multifocal motor neuropathy is commonly misdiagnosed as ALS. A hallmark of multifocal motor neuropathy is the presence of motor conduction block, a finding that can be reliably identified only on motor nerve conduction studies. Other contributions of the nerve conduction studies include the interrogation of the sensory nerves. In ALS, the sensory neurons are spared, and abnormalities in the sensory nerve action potentials should lead to further investigation for explanation. Needle electromyography is important for documenting the supportive findings of large, complex, and varying motor unit potentials associated with fibrillation and fasciculation potentials. Inclusion body myositis is a chronic degenerative muscle disorder that clinically may resemble ALS. The needle examination is important for distinguishing this disorder from ALS. In inclusion body myositis, the typical finding is mixed large and small motor unit potentials with associated fibrillation potentials, but it lacks the fasciculation potentials characteristic of ALS.

Pharmacologic Management of ALS

Currently, the only therapy approved by the US Food and Drug Administration for slowing the progression of ALS is riluzole. This medication was approved in 1995 for the indication of ALS on the strength of 2 large randomized, placebo-controlled clinical trials with similar results. There was a small but significant benefit in the median survival (3–4 months) of the riluzole-treated patients when compared with placebo. Also found was a small dose-dependent response with the maximal benefit, occurring at 50 mg twice daily. The primary adverse effect was hepatoxicity, requiring patients to have their liver function monitored at a recommended frequency of every 3 months. The precise mechanism of riluzole is unknown; however, it is believed to act by inhibiting the release of glutamate from presynaptic neurons, thus reducing the excitotoxicity in the postsynaptic motor neuron.

Clinical Management of ALS

All other therapies in ALS should be considered palliative and administered to improve each patient's quality of life. Because progressive limb weakness is common, adaptive equipment and orthoses can be helpful. Small studies have suggested that low-intensity strengthening exercises through physical therapy may have a modest benefit in preserving strength. A multidisciplinary approach to supportive management should be undertaken. These recommendations are listed in Box 39.2. In addition, 2 important aspects of care—feeding and respiratory dysfunction—are further described here.

Dysphagia is a major quality-of-life issue for patients with ALS. Dysphagia typically occurs soon after other bulbar signs appear. Early in the dysphagia, compensatory swallowing mechanisms such as upright posture, small food boluses, and chin-tuck maneuvers can minimize aspiration risk. Eventually, patients alter their food consistencies and ultimately avoid certain foods because of swallowing difficulties. At this stage, weight and nutritional status should be monitored closely.

If signs of significant weight loss appear or the subject is at high risk of aspiration, a percutaneous endoscopic

Box 39.2 • Clinical and Supportive Management for Patients With Amyotrophic Lateral Sclerosis

- Mobility equipment for weakness
  - Cane, walker, wheelchair
  - Bed and transfer equipment
  - Orthotic devices
- Dysarthria
  - Speech therapy
  - Speech augmentation devices (computer, eye-gaze boards, eye-gaze retinal scanners)
- Dysphagia
  - Swallowing compensatory maneuvers
  - Nutritional status monitoring
  - PEG tube placement
- Sialorrhea
  - Amitryptiline or glycopyrrolate
  - Suction device (if severe)
  - Botulism toxin to minor salivary glands (if PEG tube placed)
- Pseudobulbar palsy
  - Combination drug of dextromethorphan and quinidine
  - Amitryptiline may be useful
- Respiratory dysfunction
  - Monitor maximum inspiratory and expiratory pressures, spirometry, and overnight oximetry
  - Noninvasive ventilation
  - Tracheostomy in some
- General support and resources
  - ALS Association
  - Social work (disability)

Abbreviation: PEG, percutaneous endoscopic gastrostomy.

gastrostomy tube should be considered. The tube offers several advantages, including a portal for hydration, medications, and supplemental nutrition. It is generally recommended to place the tube before the patient's lung forced vital capacity decreases below 50% predicted. The complication rate for tube placement increases as the forced vital capacity decreases. This increase is apparent below the 50% predicted threshold.

Progressive respiratory failure is perhaps the most feared effect of ALS. Respiratory function is often monitored through serial spirometry with maximal inspiratory and expiratory pressures and overnight oximetry. Because the maximal respiratory pressures directly correlate with the strength of the respiratory muscles, commonly the first abnormality noted is a decrease in the pressure generated with maximal inspiration and expiration. Subsequently, the respiratory volumes begin to decrease. The overnight oximetry often has the strongest correlation to symptom onset and can be very helpful when trying to guide the initiation of noninvasive ventilation. Typically, the characteristic sawtooth pattern appears on the oximetry graph during sleep, indicative of periodic nocturnal desaturations. The initiation of noninvasive ventilation is best performed early in the evolution of pulmonary symptoms because the mask and equipment are better tolerated at that stage.

As respiratory function deteriorates, the use of noninvasive ventilation will become necessary while the patient is awake. At this stage, a tracheostomy and invasive ventilation may become necessary. Approximately 5% of patients with ALS elect to undergo tracheostomy with invasive ventilation. Discussions should be established early in the disease regarding the issue of tracheostomy, invasive ventilation, and other complications of ALS. Advanced directives should be discussed with patients early in the disease course so that appropriate plans can be enacted at this stage of the disease. For patients who have elected not to proceed with tracheostomy with invasive ventilation, hospice should be discussed and referral for services should be done when appropriate.

Other devices have been developed to help with clearance of pulmonary secretions. A mechanical vest with oscillatory pneumatic pressures and another device that delivers a rapid pressure reversal through an oral tube (cough assist) are 2 such examples.

- Histologic examination of the brain and spinal cord of patients with ALS shows a marked loss of the Betz cells of the motor cortex.
- Bunina bodies are eosinophilic cytoplasmic inclusions that represent ubiquinated protein aggregates. These are thought to be sensitive but not entirely specific for ALS.
- The classic presentation of ALS is that of progressive weakness, without other neurologic features of sensory loss or pain.
- The clinical signs of upper motor neuron loss include hyperreflexia, the Babinski signs, muscle spasticity, and slowness of movements. Signs of lower motor neuron loss include muscle weakness, muscle atrophy, and muscle fasciculations.
- For reasons that remain unclear, ALS typically does not affect the extraocular muscles or the voluntary sphincter muscles until very advanced stages of the disease.
- In ALS, the median survival from symptom onset is typically 3 years, and from diagnosis it is just under 2 years.
- The El Escorial criteria have become the standard of care in diagnosing ALS.

Spinal Muscular Atrophy

Overview

The spinal muscular atrophies (SMAs) are inherited disorders that affect the anterior horn cells in isolation. They occur in 3 forms: proximal SMA, distal SMA, and X-linked spinal and bulbar atrophy (also known as Kennedy disease) (Table 39.3). In contrast to ALS, these disorders affect only the lower motor neurons and, in general, are symmetric in their presentation.

Proximal SMA

The proximal SMAs are caused by a common genetic mutation consisting of a deletion or point mutation in exon 7 of the survival motor neuron (*SMN1*) gene on chromosome 5 (5q13). Among northern European descendants, approximately 1 in 50 carry this mutation with an inheritance pattern that is autosomal recessive.

Proximal SMA has 4 phenotypes: type 1 (infantile), type 2 (intermediate), type 3 (juvenile-onset), and type 4 (adult-onset). All forms share the same underlying genetic mutation. The phenotypic differences are due to the *SMN2* pseudogene. The age at onset and the clinical course are correlated with the functionality and number of copies of this *SMN2* pseudogene. A low number of copies of a nonfunctional protein results in the infantile onset of type 1 (also referred to as Werdnig-Hoffmann disease). This is the most severe form of the disease, and the life expectancy is less than 1 year. A higher number of copies of a partially functional protein results in an older age at onset, an indolent progression, and a normal life expectancy.

Symptoms of the proximal SMAs are similar; the primary differences are age at onset and rate of progression. Symmetric proximal weakness and areflexia are the rule. These symptoms involve the axial and proximal limb muscles. Because of the proximal weakness, these SMAs may be mistaken for myopathy or muscular dystrophy. Increased levels of serum creatine kinase may also be

Table 39.3 • Forms of Spinal Muscular Atrophy

Form of Spinal Muscular Atrophy	Eponym	Gene	Phenotype
Infantile	Werdnig-Hoffmann	*SMN1*	Proximal weakness
Intermediate	Dubowitz	*SMN1*	Proximal weakness
Juvenile	Kugelberg-Welander	*SMN1*	Proximal weakness
Adult	None	*SMN1*	Proximal weakness
Distal	Spinal form of CMT	Varied	Distal weakness
X-linked SBMA	Kennedy	Androgen receptor	Proximal weakness with bulbar palsy, males only

Abbreviations: CMT, Charcot-Marie-Tooth disease; SBMA, spinal and bulbar muscular atrophy.

present. The areflexia and the presence of fasciculations should suggest anterior horn cell localization.

Distal SMA

In contrast to the proximal SMAs, the distal SMAs occur with weakness and atrophy in the distal aspects of the upper and lower limbs. These are genetically more heterogeneous, with multiple causative mutations. Clinically, they resemble the inherited sensorimotor peripheral neuropathies (Charcot-Marie-Tooth disease); however, they spare the sensory neurons and axons. They result in only modest neurologic deficits; ankle-foot orthoses are often necessary, but little other adaptive equipment or lifestyle modification is necessary. The distal SMAs do not shorten life expectancy.

X-linked Spinal and Bulbar Muscular Atrophy (Kennedy Disease)

X-linked spinal and bulbar muscular atrophy (also known as SBMA or Kennedy disease) is, as the name implies, an X-linked disorder caused by a trinucleotide repeat within the androgen receptor gene. In general, only men are clinically affected, and women are carriers for the gene. However, in rare cases, women may be mildly affected.

The clinical phenotype is that of symmetric proximal weakness with a flaccid bulbar palsy that typically begins in the third or fourth decade of life, but it can have its onset at a later age. Fasciculations are particularly prominent in SBMA, especially among the orofacial muscles. This disorder may bear a striking resemblance to ALS and can be distinguished by the absence of upper motor neuron involvement and by subclinical sensory loss that may be apparent on neurophysiologic testing in approximately 50% of cases.

Survival is only minimally diminished, but disability may accumulate and necessitate lifestyle modifications and adaptive equipment. Androgen insensitivity is common, and patients with SBMA may also have gynecomastia or testicular atrophy. For reasons that are not well understood, patients with SBMA may have markedly increased levels of serum creatine kinase, including asymptomatic female carriers.

- Spinal muscular atrophy occurs in 3 forms: proximal SMA, distal SMA, and X-linked spinal and bulbar atrophy (also known as Kennedy disease) (Table 39.3).
- In proximal SMA, the age at onset and the clinical course are correlated with the functionality and number of copies of the *SMN2* pseudogene.
- Clinically, distal SMAs resemble the inherited sensorimotor peripheral neuropathies (Charcot-Marie-Tooth disease); however, they spare the sensory neurons and axons.
- Spinal bulbar and muscular atrophy (SBMA, or Kennedy disease) is an X-linked disorder caused by a trinucleotide repeat within the androgen receptor gene.
- In spinal bulbar and muscular atrophy, androgen insensitivity is common, and patients with SBMA may also have gynecomastia or testicular atrophy.

Infectious Motor Neuron Syndromes

The classic infectious motor neuron syndrome is paralytic poliomyelitis. This enterovirus has its primary infection within the gastrointestinal tract. In a minority of patients, the virus infects the anterior horn cells, resulting in cell death and an acute syndrome of flaccid paralysis. This is classic in a focal distribution but, if severe, can be more widespread. The disease has been eradicated from North America. Isolated outbreaks in sub-Saharan Africa, the Middle East, and Southeast Asia still occur.

The Salk vaccine was introduced in the 1950s and is a killed vaccine. The Salk vaccine requires injection for effectiveness. It was replaced by the live-attenuated oral vaccine because of its lifelong immunity advantage. Unfortunately, because the oral vaccine is live, it retains its virulent potential. Each year a very small number of vaccine-related cases of paralytic polio occur. Although

this relationship of the vaccine and polio has been controversial, in the United States the practice has returned to the killed Salk vaccine to prevent these cases. Although the polio virus has the highest affinity for the central nervous system, the syndrome of an acute paralytic flaccid paralysis can occur with infection from any of the enteroviruses.

The West Nile virus has been associated with motor neuron disease. This virus, unrelated to the enteroviruses, often presents in a manner that is indistinguishable from that of acute polio. Because of the loss of anterior horn cells, recovery is poor, and the likelihood of lifelong deficits is high.

- The West Nile virus has been associated with motor neuron disease.

Hirayama Disease

A very rare disorder that superficially resembles ALS is Hirayama disease (monomelic motor neuron disease or Sobue disease). This was first described by Hirayama in Japan, where the condition is more common. Hirayama disease has a fairly characteristic presentation. It occurs almost exclusively in young persons and has a marked male predominance (often with an athletic background). Typical age at onset is between 18 and 25 years. The presentation is typically unilateral hand weakness and atrophy. It may be bilateral, but it is almost always markedly asymmetric. It affects primarily the C8 and T1 myotomes and spares the sensory nerves. The weakness presents and progresses over about 5 years, followed by a plateau and stability of the deficits. There are no upper motor neuron findings, and the disease does not generalize.

The mechanism of injury is not well understood. Cervical magnetic resonance imaging studies with neck flexion suggest a narrowing in the anteroposterior diameter and an expansion of the epidural space. Attempts at surgical correction have not yielded any benefit.

- Hirayama disease has a marked male predominance.
- The presentation of Hirayama disease includes unilateral hand weakness and atrophy.

40 Peripheral Nerve Disorders

SARAH E. BERINI, MD; NATHAN P. STAFF, MD, PHD

Introduction

Disorders of the peripheral nerves are some of the most common conditions that neurologists face in clinical practice. The wide differential diagnosis that often accompanies peripheral nerve disorders may be narrowed by careful attention to the history (time course, preexisting disease, and family history), peripheral neuroanatomy, patient symptomatology (sensory loss, paresthesia, pain, and weakness), and the neurologic examination (sensory loss, weakness, atrophy, and reduced muscle stretch reflexes).

Electromyography (EMG) assesses large-diameter myelinated axons (touch, pressure, vibration, proprioception, and motor) and aids in localization while further narrowing the differential diagnosis by predicting axonal or demyelinating pathophysiology. Autonomic testing and epidermal nerve quantification assess the small, unmyelinated axons (pain, heat, and autonomic). Final diagnosis may rely on blood tests, genetic analyses, or nerve biopsy.

This chapter provides an overview of peripheral nerve disorders as they occur in their various forms: diffuse (polyneuropathy), multifocal (plexopathy), and focal (mononeuropathy and radiculopathy).

Polyneuropathy

Epidemiology

Polyneuropathy is a common disorder, with a prevalence of 2.4% in the general population and 8% in persons older than 55. In the developed world, the most common cause is diabetes mellitus, and the most common manifestation is a length-dependent sensorimotor peripheral neuropathy, although diabetes mellitus can be associated with other types of neuropathy (Box 40.1).

Inherited Polyneuropathy

Inherited neuropathies (Table 40.1) can be primarily demyelinating or axonal, and they occur in patients with or without a clear family history; an estimated 30% of mutations are de novo. The list of genes that cause inherited neuropathies is ever expanding, and this chapter focuses on the more classic forms.

Charcot-Marie-Tooth disease (CMT) (also known as hereditary motor and sensory neuropathy [HMSN]) is the most common inherited neuropathy, occurring in 1 per 2,500 people. Duplication of the *PMP22* gene, which encodes a myelin protein, is the most common cause of inherited demyelinating neuropathy (CMT type 1) (Figure 40.1). The most frequent axonal forms of inherited neuropathy (CMT

Box 40.1 • Neuropathies Associated With Diabetes Mellitus

- Subclinical neuropathy
- Polyneuropathy (distal symmetric sensorimotor)
- Small-fiber neuropathy
- Polyradiculoplexopathy
- Autonomic neuropathy
- Mononeuropathy or mononeuritis multiplex
- Cranial mononeuropathy

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; CMT, Charcot-Marie-Tooth disease; EMG, electromyography; HMSN, hereditary motor and sensory neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; MMN-CB, multifocal motor neuropathy with conduction block

Table 40.1 • Abbreviated List of Inherited Neuropathies

Condition	Inheritance	Genes	NCS	Comments
HMSN1	AD	*PMP22* duplication *MPZ*	D	Onion bulbs
HMSN2	AD	*MFN2, MPZ, Rab7*	A	. . .
HSMN10	XLD	*GJB1*	D more than A	. . .
HNPP	AD	*PMP22* deletion	D	Tomacula
HSAN1	AD	*SPTCLC1*	A	Onset in second decade of life or later
HSAN2	AR	Many	A	Onset in childhood
HSAN3	AR	*IKBKAP*	A	Riley-Day syndrome; autonomic failure
HSAN4 and HSAN5	AR	*NTRK1-IV* and *NTRK1-V* *NGFβ-V*	A	Congenital insensitivity to pain with anhidrosis
Fabry disease	XLR	Galactosidase A	A	Angiokeratoma Cardiomyopathy Treat with replacement enzyme
Refsum disease	AR	Phytanoyl-CoA hydroxylase	D	Retinitis pigmentosa Treat by restricting phytanic acid
Transthyretin (TTR) amyloidosis	AD	*TTR*	A	Congophilic Treat with liver transplant
Gelsolin amyloidosis	AD	Gelsolin	A	Congophilic Finnish descent Cranial nerve VII palsy, corneal lattice dystrophy
Apolipoprotein A-I amyloidosis	AD	Apolipoprotein A-I	A	Congophilic
Tangier disease	AD	ATP-binding cassette 1 gene (*ABCA1*)	A	α-Lipoprotein deficiency; very low HDL; orange tonsils; sensory neuropathy

Abbreviations: A, axonal; AD, autosomal dominant; AR, autosomal recessive; ATP, adenosine triphosphate; D, demyelinating; HDL, high-density lipoprotein; HMSN, hereditary motor and sensory neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; NCS, nerve conduction studies; XLD, X-linked dominant; XLR, X-linked recessive.

type 2) result from mitofusin-2 mutations. Mutations in the genes for connexin 32 (*GJB1*; X-linked CMT) and myelin protein zero (*MPZ*) are also common causes of inherited demyelinating or axonal neuropathies. Each of these causes of inherited neuropathy is autosomal dominant, with the exception of *GJB1*, which is X-linked recessive.

The inherited neuropathies present as slowly progressive, length-dependent peripheral neuropathies. A notable exception is hereditary neuropathy with liability to pressure palsies (HNPP) (due to *PMP22* deletion), which typically presents with asymmetric mononeuropathies resulting from focal compression (Figure 40.2). Pes cavus (Figure 40.3) and hammer toe are often present in inherited neuropathies, as is atrophy of the anterior compartment of the leg, causing the "inverted champagne bottle" appearance (Figure 40.4).

On nerve conduction studies, inherited demyelinating neuropathies are characterized by uniformly slow conduction velocities and can often be distinguished from acquired demyelinating neuropathies (eg, chronic inflammatory demyelinating polyneuropathy [CIDP]) by the lack of conduction block and temporal dispersion. HNPP is characterized by evidence of conduction block but only at common sites of compression.

Inherited conditions causing predominantly sensory, autonomic, and small-fiber neuropathies include the hereditary sensory and autonomic neuropathies (HSANs), familial amyloidosis, Fabry disease, and Tangier disease. The HSANs are autosomal recessive with the exception of HSAN type 1, which is autosomal dominant. HSAN type 1 is the most common type; patients present with distal sensory loss in adult life. HSAN types 2, 4, and 5 are characterized by congenital insensitivity to pain, and HSAN type 4 is characterized by prominent anhidrosis (Figure 40.5). Patients with HSAN type 3 (Riley-Day syndrome) present with autonomic failure.

Familial amyloidosis results from autosomal dominant mutations in the transthyretin (*TTR*), gelsolin (*GEL*), or

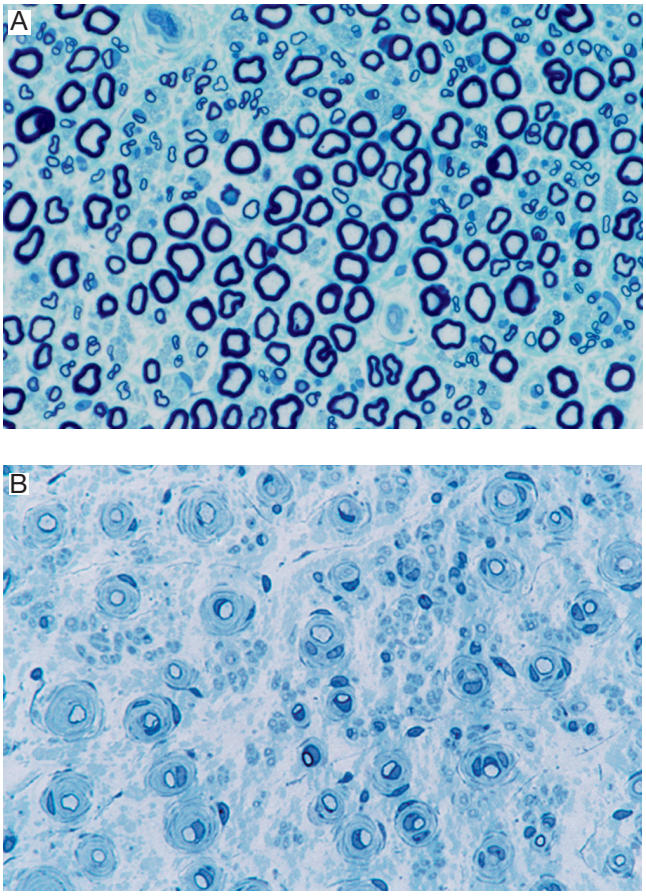


Figure 40.1 *Semithin Sections of Peripheral Nerve.*
A, Control. B, Charcot-Marie-Tooth Disease Type 1 with Onion Bulbs.
(B, Adapted from Dyck PJ, Dyck PJB, Giannini C, Sahenk Z, Windebank AJ, Engelstad J. Peripheral nerves. In: Graham DI, Lantos PL, editors. Greenfield's neuropathology. 7th ed. London [United Kingdom]: Arnold; New York [NY]: distributed in the U.S. by Oxford University Press; c2002. p. 551–675. Used with permission.)

apolipoprotein A-I genes that cause these proteins to form amyloid deposits throughout the body, including the peripheral nerves (see Chapter 44, "Autonomic Disorders," for further discussion of autonomic dysfunction in inherited and acquired amyloidosis). Tissue biopsy shows the amyloid as congophilic material with apple-green birefringence under polarized light (Figure 40.6). Mutant transthyretin is produced in the liver, and liver transplant is a treatment option. Gelsolin amyloidosis is more common in Finnish populations and often occurs with progressive bilateral cranial nerve VII palsies and corneal lattice dystrophy.

Fabry disease (X-linked recessive) is characterized by α-galactosidase deficiency, angiokeratomas, and cardiomegaly; treatment includes enzyme replacement.

Orange tonsils are a unique examination finding in Tangier disease (autosomal dominant; *ABCA1* mutation),

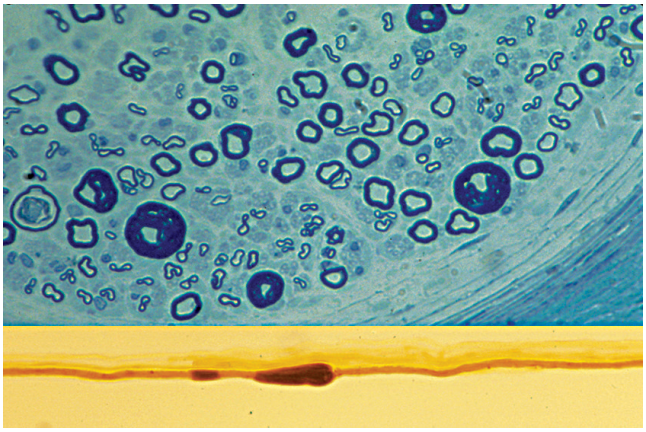


Figure 40.2 *Sural Nerve Biopsy Specimen From Patient With Hereditary Neuropathy With Liability to Pressure Palsies (HNPP).*
Upper, Multiple focal thickenings of myelin sheaths (tomacula) (methylene blue). Lower, Sausage-like appearance of tomacula in a teased-fiber preparation.
(Courtesy of Guillermo A. Suarez, MD.)

which is associated with α-lipoprotein deficiency and very low levels of high-density lipoprotein.

Acquired Polyneuropathy

Acquired forms of polyneuropathy can result from metabolic, inflammatory, infectious, toxic, neoplastic, or paraneoplastic conditions. Acquired polyneuropathies that

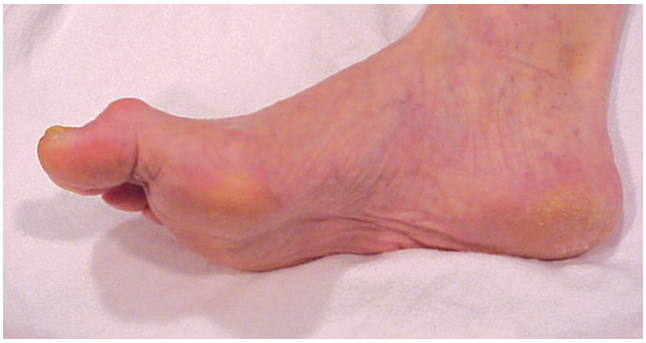


Figure 40.3 *Skeletal Abnormalities of a Foot of a Patient With Hereditary Neuropathy.*
Prominent features are pes cavus (high longitudinal arch of the foot) and hammer toe.
(Adapted from Kilfoyle DH, Jones LK, Mowzoon N. Disorders of the peripheral nervous system. Part B: Specific inherited and acquired disorders of the peripheral nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 799–845. Used with permission of Mayo Foundation for Medical Education and Research.)

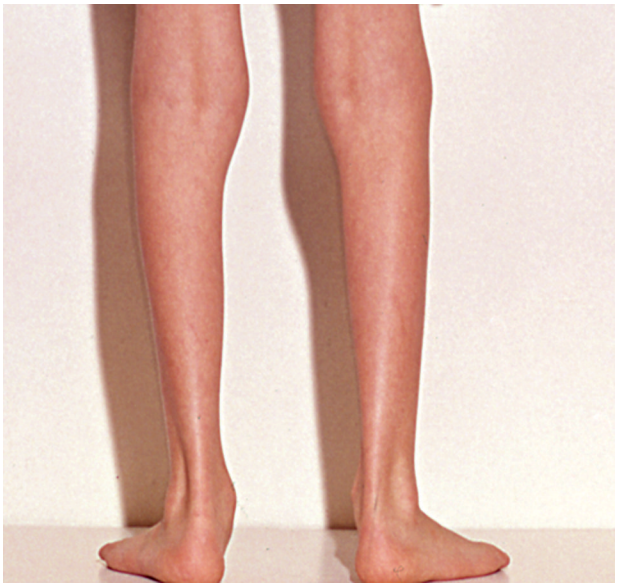


Figure 40.4 *Distal Atrophy With "Inverted Champagne Bottle" Legs of a Patient With Hereditary Motor and Sensory Neuropathy Type 1 (HMSN1).*
(Adapted from Kilfoyle DH, Jones LK, Mowzoon N. Disorders of the peripheral nervous system. Part B: Specific inherited and acquired disorders of the peripheral nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 799–845. Used with permission of Mayo Foundation for Medical Education and Research.)

affect the nerve root are *polyradiculoneuropathies*. Disorders selectively or exclusively affecting sensory ganglia (*ganglionopathies*) are characterized by isolated, diffuse, multimodal sensory loss and can be idiopathic or occur with Sjögren syndrome or paraneoplasia. The potential acquired causes of polyneuropathy are numerous, and the time course, distribution of deficits, and types of fibers involved are useful for directing the evaluation. Nerve conduction studies and EMG are helpful in distinguishing axonal from demyelinating polyneuropathies (Table 40.2 and Figure 40.7).

Features such as demyelination or multifocality can significantly narrow the differential diagnosis. An acquired demyelinating neuropathy raises the possibility of acute inflammatory demyelinating polyneuropathy (AIDP) (also known as Guillain-Barré syndrome), CIDP, or multifocal motor neuropathy with conduction block (MMN-CB). Paraproteinemia due to monoclonal plasma cell expansion is another important cause of acquired demyelinating neuropathy, often due to an IgM monoclonal gammopathy of undetermined significance. A multifocal presentation raises the possibility of vasculitis (mononeuritis multiplex) (Figure 40.8), multifocal CIDP (also known as multifocal acquired demyelinating sensory and motor neuropathy), or MMN-CB.

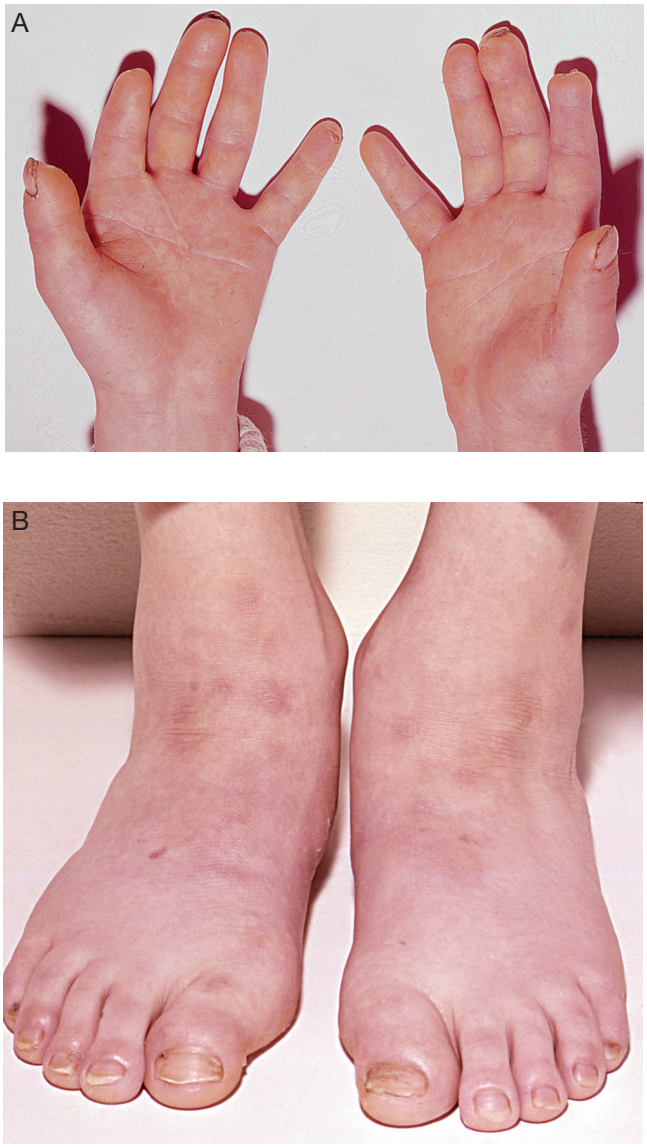


Figure 40.5 *Mutilating Acropathy Typical of Hereditary Sensory and Autonomic Neuropathy (HSAN).*
A and B, Patient's hands (A) and feet (B) were affected.
(Adapted from Kilfoyle DH, Jones LK, Mowzoon N. Disorders of the peripheral nervous system. Part B: Specific inherited and acquired disorders of the peripheral nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 799–845. Used with permission of Mayo Foundation for Medical Education and Research.)

- The most common cause of polyneuropathy is diabetes mellitus.
- CMT (also known as HMSN) is the most common inherited neuropathy, occurring in 1 per 2,500 people.

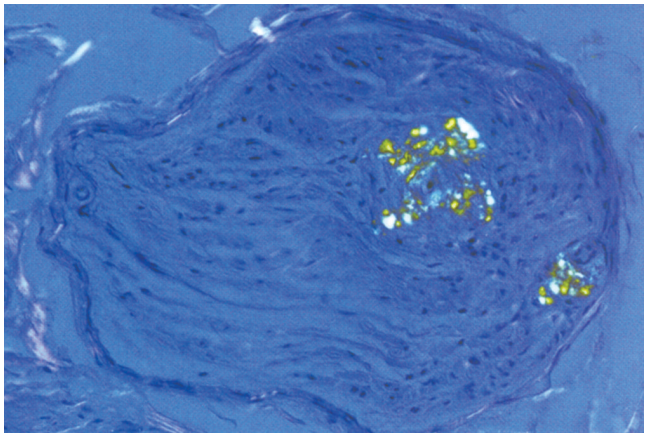


Figure 40.6 *Congo Red–Stained Section of Sural Nerve From Patient With Familial Amyloid Polyneuropathy.*
Use of polarizing filters shows the apple-green birefringence of amyloid deposits.
(Adapted from Kyle RA, Dispenzieri A. Amyloidosis. In: Noseworthy JH, editor-in-chief. Neurological therapeutics: principles and practice. Vol 3. 2nd ed. Abingdon, Oxon [United Kingdom]: Informa Healthcare; c2006. p. 2415–25. Used with permission.)

- Duplication of the *PMP22* gene, which encodes a myelin protein, is the most common cause of inherited demyelinating neuropathy (CMT type 1).
- On nerve conduction studies, inherited demyelinating neuropathies are characterized by uniformly slow conduction velocities and can often be distinguished from acquired demyelinating neuropathies (eg, CIDP) by the lack of conduction block and temporal dispersion.
- Acquired forms of polyneuropathy can result from metabolic, inflammatory, infectious, toxic, neoplastic, or paraneoplastic conditions.
- Nerve conduction studies and EMG are helpful in distinguishing axonal from demyelinating polyneuropathies.

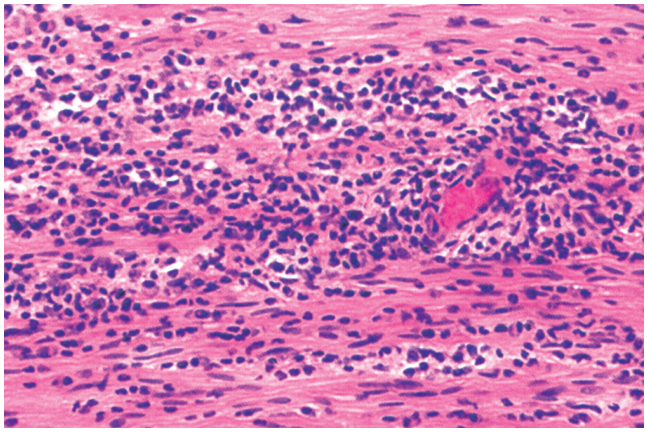


Figure 40.7 *Sural Nerve Biopsy Specimen From Patient With Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP).*
Endoneural inflammation is present with prominent mononuclear cellular endoneurial infiltration.
(Adapted from Hahn AF, Hartung H-P, Dyck PJ. Chronic inflammatory demyelinating polyradiculoneuropathy. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Vol 2. 4th ed. Philadelphia [PA]: Elsevier Saunders; c2005. p. 2221–53. Used with permission.)

Plexopathies

Traumatic Plexopathy

Erb palsy is a traumatic plexopathy involving the upper trunk of the brachial plexus, often related to stretch injury at birth. Because of weakness of the muscles innervated by spinal nerves C5 and C6 (including the deltoid, biceps, brachioradialis, and supinator muscles), affected patients present with a "waiter's tip" sign, with the arm adducted and internally rotated. In contrast, Klumpke palsy is associated with injury to the lower trunk (C8 through T1), which causes weakness and atrophy of the intrinsic hand muscles, resulting in a clawhand.

Neoplastic and Radiation-Induced Plexopathy

Neoplastic plexopathies invade the lower brachial plexus, most often by direct extension of a primary lung tumor (Pancoast tumor) or by extension of breast cancer or lung cancer metastasis from adjacent lymph nodes. Neoplastic brachial or lumbosacral plexopathies are typically painful and rapidly progressive.

In contrast, radiation-induced plexopathies are slowly progressive and relatively painless. There is no known effective treatment. Myokymic discharges may be seen on EMG when patients have radiation damage.

Inflammatory Plexopathy

Patients with inflammatory plexopathies (eg, Parsonage-Turner syndrome affecting the brachial plexus) frequently present with acute or subacute onset of pain. As the pain resolves, weakness and atrophy become prominent. The pattern of damage to nerves is patchy, and pure motor nerves, such as the long thoracic nerve and the anterior and posterior interosseous nerves, are often affected. Inflammatory plexopathies can occur after viral illness, pregnancy, surgery, or vaccinations (eg, hepatitis B). Magnetic resonance imaging of the affected plexus is helpful to rule out structural causes. Corticosteroids are the most commonly used treatment. Patients typically have a relatively good recovery, with an average of 89% improvement in function over 3 years.

Table 40.2 • Acquired Polyneuropathies

Cause	Presentation	Evaluation	Treatment
Metabolic			
Diabetes mellitus	Chronic, length-dependent PN, often affecting small fibers and autonomic fibers	Fasting blood glucose, OGTT, and hemoglobin A_{1c}	Blood glucose control
Hypothyroidism	Chronic, length-dependent PN	Thyrotropin, free thyroxine	Thyroid hormone replacement
Vitamin B_{12} deficiency	Chronic, length-dependent PN, myeloneuropathy	Vitamin B_{12}, methylmalonic acid	Vitamin B_{12} replacement
Copper deficiency	Chronic, length-dependent PN, myeloneuropathy	Serum copper, ceruloplasmin, urinary copper	Copper replacement
Thiamine deficiency	Chronic, length-dependent PN, Wernicke encephalopathy	Whole-blood thiamine	Thiamine replacement
Alcohol	Chronic, length-dependent or small-fiber PN	Liver function testing	Alcohol cessation
Uremia	Chronic, length-dependent PN	Serum urea nitrogen, creatinine, creatinine clearance	Dialysis, kidney transplant
Hyperlipidemia Hypertriglyceridemia	Chronic, painful small-fiber PN	Fasting lipid panel, triglycerides	Medication and dietary management
Inflammatory			
AIDP	Acute onset of demyelinating, polyradiculoneuropathy, ascending weakness and numbness, areflexia	CSF: cytoalbuminologic dissociation NCS: loss of F waves	IVIG, PLEX
CIDP	Chronic, inflammatory polyradiculoneuropathy; motor more than sensory; usually symmetric but asymmetric forms exist (MADSAM)	CSF: cytoalbuminologic dissociation NCS: demyelination, conduction block, temporal dispersion Biopsy (Figure 40.7)	IVIG, PLEX, corticosteroids
Multifocal motor neuropathy	Chronic, asymmetric weakness of hands and distal portions of arms without sensory involvement; affects males more than females	NCS: conduction block Antiganglioside antibodies	IVIG
Vasculitis: systemic and nonsystemic	Acute to subacute onset, multiple mononeuropathies, painful, with or without systemic symptoms (fevers, weight loss) Systemic vasculitides: polyarteritis nodosa, Wegener granulomatosis, rheumatoid arthritis, Churg-Strauss syndrome	NCS, EMG: multiple mononeuropathies Nerve biopsy: necrotizing vasculitis ANA, ENA, RF, ANCA, MPO, PR3	Corticosteroids, cyclophosphamide
Sarcoid	Polyradiculoneuropathy	CXR, CT of the chest: hilar lymphadenopathy Biopsy: noncaseating granulomas ACE level	Corticosteroids
Sjögren syndrome	Sensory ganglionopathy; small-fiber and autonomic neuropathy; associated with sicca syndrome	Lip biopsy: sialadenitis SSA, SSB	Immunotherapy; poorly responsive to treatment

Toxic			
Lead	Motor predominant; wrist drop	Urine: heavy metals	Chelation: dimercaprol, EDTA, D-penicillamine
Mercury	Motor neuropathy; tremor	Urine: heavy metals	Chelation: DMSA, dimercaprol, D-penicillamine
Arsenic	Painful sensory neuropathy; gastrointestinal tract upset	Urine: heavy metals	Chelation: dimercaprol
Thallium	Painful sensory neuropathy, alopecia	Urine: heavy metals	Chelation: Prussian blue, hemodialysis
Vitamin B_6	Painful sensory neuropathy	Vitamin B_6 level	Stop vitamin B_6 supplementation
Chemotherapy			
Cisplatin, oxaliplatin Vincristine Suramin Cytarabine Bortezomib Paclitaxel, docetaxel Thalidomide	Typical presentation: symmetric, length-dependent sensory predominant PN Cisplatin: sensory ataxia Oxaliplatin: exacerbated by cold Bortezomib: small-fiber involvement	NCS, EMG: sensorimotor PN Exceptions: cisplatin is pure sensory with normal CMAPs and EMG Cytarabine and suramin can be demyelinating	Monitoring and modification of treatment regimen
Neoplastic, paraneoplastic, paraprotein			
MGUS	Chronic demyelinating or axonal PN	Skeletal survey: sclerotic, lytic lesions SPEP with immunofixation, UPEP	Depends on presentation; observation vs IVIG or rituximab
POEMS syndrome	Demyelinating neuropathy with plasmacytoma, organomegaly, endocrinopathy Monoclonal protein Skin changes	Skeletal survey: sclerotic, lytic lesions SPEP with immunofixation, UPEP, thyrotropin	Bone marrow transplant, IVIG
Neurolymphomatosis	Painful, rapidly progressive polyradiculopathy with weight loss, fever, night sweats	CSF: cytology and flow cytometry Imaging: MRI plexus, PET Biopsy: targeted nerve or fascicular biopsy if imaging is positive and CSF is negative	Chemotherapy
Paraneoplastic	Often associated with small cell lung cancer Anti-Hu (ANNA 1 and 2): sensory ganglionopathy Antiganglionic antibody: autonomic neuropathy	Paraneoplastic panel Imaging: CT of chest, abdomen, and pelvis; PET scan Routine health screening: mammogram, prostate and testicular examination, colonoscopy	Treatment of malignancy; consider trial of corticosteroids, IVIG, or PLEX
Primary amyloidosis	Painful sensory and autonomic neuropathy; can present with carpal tunnel syndrome	Monoclonal protein Biopsy (fat pad, bowel, or nerve): congophilic with apple-green birefringence	Chemotherapy, bone marrow transplant

(*continued*)

Table 40.2 • Continued

Cause	Presentation	Evaluation	Treatment
Infectious			
HIV	Multiple presentations: AIDP or CIDP presentation at seroconversion, sensorimotor PN, and mononeuritis multiplex Causes: HIV, opportunistic infection, antiretroviral medications	HIV testing, medication review	Optimize antiretroviral medications; rule out iatrogenic causes (nucleic acid analogues) and infection
Syphilis	Polyradiculoneuropathy, tabes dorsalis	RPR, VDRL	Penicillin V
Lyme disease	Cranial neuropathy (cranial nerve VII), radiculopathy, polyradiculoneuropathy, erythema migrans rash, meningitis	CSF: Lyme PCR Lyme serology	CNS or PNS involvement: ceftriaxone No CNS or PNS involvement: doxycycline
Leprosy	Sensory-predominant neuropathy Tuberculoid form: multifocal anesthesia Lepromatous form: widespread anesthesia in cooler areas of skin	Biopsy (skin, nerve): granulomas and organism visualization	Multidrug therapy: dapsone, rifampin, clofazimine, minocycline, fluoroquinolones

Abbreviations: ACE, angiotensin-converting enzyme; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ANNA, antineuronal nuclear antibody; CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest radiograph; DMSA, dimercaptosuccinic acid; EMG, electromyography; ENA, extractable nuclear antigen; HIV, human immunodeficiency virus; IVIG, intravenous immunoglobulin; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MGUS, monoclonal gammopathy of undetermined significance; MPO, myeloperoxidase; MRI, magnetic resonance imaging; NCS, nerve conduction studies; OGTT, oral glucose tolerance test; PCR, polymerase chain reaction; PET, positron emission tomography; PLEX, plasma exchange; PN, peripheral neuropathy; PNS, peripheral nervous system; PR3, proteinase 3; RF, rheumatoid factor; RPR, rapid plasma reagin; SPEP, serum protein electrophoresis; SSA, anti–Sjögren syndrome A; SSB, anti–Sjögren syndrome B; UPEP, urine protein electrophoresis.

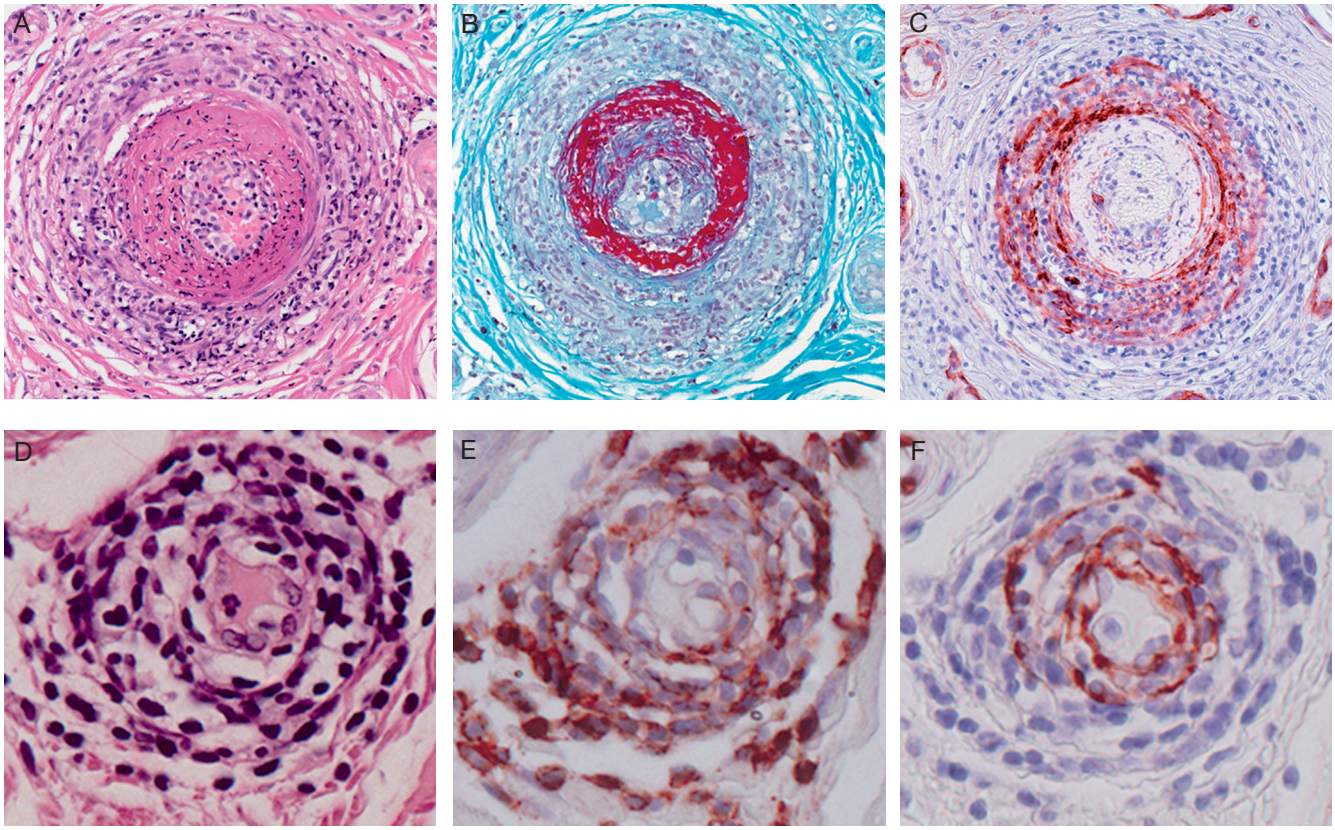


Figure 40.8 *Nerve Pathology of Microvasculitis and Large-Vessel Vasculitis.*
A, B, and C, A large epineurial arteriole in a sural nerve shows necrotizing vasculitis with fibrinoid degeneration. A, Hematoxylin-eosin. B, Fibrinoid necrosis stains red with trichrome stain. C, Antihuman smooth muscle actin staining shows the separation and fragmentation of the muscle layers. D, E, and F, Microvasculitis is present in a sural nerve from a patient with lumbosacral radiculoplexus neuropathy. D, Hematoxylin-eosin. E, CD45 staining of lymphocytes shows significant inflammation. F, Antihuman smooth muscle actin staining shows the separation and fragmentation of the muscle layers.
(A-C, Adapted from Dyck PJB, Engelstad J, Dyck PJ. Microvasculitis. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Vol. 2. 4th ed. Philadelphia [PA]: Elsevier Saunders; c2005. p. 2405–14. Used with permission. D-F, Adapted from Dyck PJ, Windebank AJ. Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. Muscle Nerve. 2002 Apr;25[4]:477–91. Used with permission.)

Diabetic Lumbosacral Radiculoplexus Neuropathy

Diabetic lumbosacral radiculoplexus neuropathy (also known as diabetic amyotrophy) usually occurs in patients with newly diagnosed or mild diabetes mellitus and, often, weight loss. Patients with diabetic lumbosacral radiculoplexus neuropathy typically present with severe pain followed by asymmetric weakness and atrophy of proximal muscles, most frequently the quadriceps. Involvement of other body regions (cervical, thoracic, and bulbar) may also occur, and nondiabetic forms of this condition have been described. Microvasculitis and ischemic injury are seen on nerve biopsy. Treatment with methylprednisolone is considered to help treat pain and prevent progression.

- Erb palsy is a traumatic plexopathy involving the upper trunk of the brachial plexus, often related to stretch injury at birth.
- Klumpke palsy is associated with injury to the lower trunk (C8 through T1), which causes weakness and atrophy of the intrinsic hand muscles, resulting in a clawhand.
- Radiation-induced plexopathies are slowly progressive and relatively painless.
- Myokymic discharges may be seen on EMG when patients have radiation damage.
- Patients with inflammatory plexopathies (eg, Parsonage-Turner syndrome affecting the brachial plexus) frequently present with acute or subacute onset

of pain. As the pain resolves, weakness and atrophy become prominent.
- Patients with diabetic lumbosacral radiculoplexus neuropathy typically present with severe pain followed by asymmetric weakness and atrophy of proximal muscles, most frequently the quadriceps.

Mononeuropathy

Overview

Mononeuropathy refers to involvement of a single peripheral nerve. The distributions of individual peripheral nerves are shown in Figure 40.9. The cause of mononeuropathies is diverse and includes compression, metabolic derangements, and hereditary predisposition.

Median Mononeuropathy

Carpal tunnel syndrome is common, with a prevalence of about 50 cases per 1,000 people. The incidence of carpal tunnel syndrome is higher among patients who are pregnant or who have diabetes mellitus, hypothyroidism, amyloidosis, renal failure, acromegaly, or HNPP. Caused by compression of the median nerve within the carpal tunnel, carpal tunnel syndrome is characterized by hand paresthesias and sometimes pain. The symptoms are often worse at night. Sensory fibers are affected first, and more severe cases result in atrophy of the thenar eminence, with weakness of thumb abduction and opposition. The Tinel sign (paresthesias elicited by tapping over the median nerve at the wrist) and Phalen sign (paresthesias produced by passive wrist flexion) are often present on examination. The diagnosis is made clinically, but the severity can be assessed on electrodiagnostic studies. Conservative treatments include the use of wrist splints and anti-inflammatory medications. Corticosteroid injections and surgical release are options in severe or refractory cases.

Ulnar Mononeuropathy

Ulnar mononeuropathies at the elbow are most often due to mechanical compression or arthritis at the ulnar groove or at the cubital tunnel. Fibrous bands, tumors, and accessory muscles can also contribute to ulnar nerve compression. Injury leads to weakness and atrophy of hand muscles innervated by the ulnar nerve, with paresthesias in the fourth and fifth digits. On nerve conduction studies, an ulnar neuropathy at the elbow can result in focal slowing at the elbow or partial conduction block and temporal dispersion. Conservative measures include elbow pads, avoidance of compression, and physical therapy. Surgical options include cubital tunnel decompression, transposition of the ulnar nerve, and medial epicondylectomy.

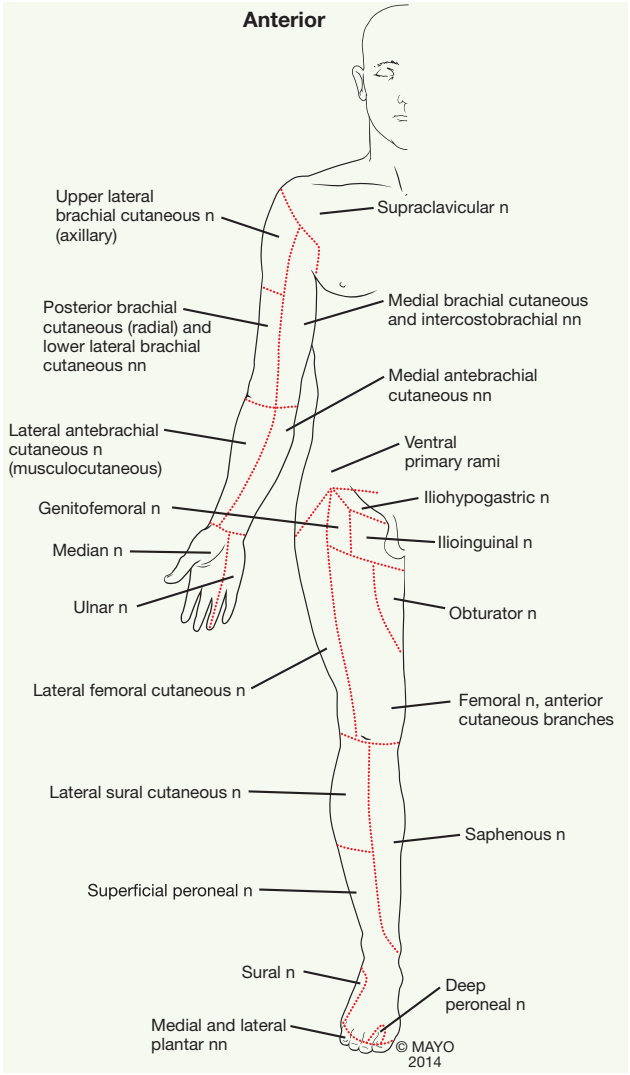


Figure 40.9 *Cutaneous Distribution of Peripheral Nerves. n indicates nerve; nn, nerves.*
(Adapted from Benarroch EE, Daube JR, Flemming KD, Westmoreland BF. Mayo Clinic medical neurosciences: organized by neurologic systems and levels. 5th ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. Chapter 13, The peripheral level; p. 491–546. Used with permission of Mayo Foundation for Medical Education and Research.)

Radial Mononeuropathy

Radial mononeuropathies can occur at the level of the axilla when crutches are fitted incorrectly. This results in weakness of all radial muscles and sensory deficits in the radial distribution. Radial injury at the spiral groove can occur with humeral fracture or with "Saturday night palsy" (compression of the nerve while sleeping, often with intoxication). The presentation is similar to that of an axillary lesion, with sparing of the triceps brachii muscle and sensation to the posterior arm. Lesions of the posterior

interosseous nerve often occur in Parsonage-Turner syndrome and MMN-CB; patients present with finger drop.

Peroneal Mononeuropathy

Peroneal mononeuropathies commonly occur at the fibular neck due to compression and nerve trauma. Common causes of peroneal mononeuropathy are leg crossing, operative positioning, prolonged bed rest, casts, pneumatic compression stockings, weight loss, diabetes mellitus, ganglionic cysts, Baker cysts, synovial cysts, tumors, and hematomas. The deep peroneal branch is most often affected, and patients present with foot drop. The Tinel sign or sensory deficits in the peroneal distribution may be seen on examination. Nerve conduction studies may show focal slowing or partial conduction block across the knee. Axonal lesions present with a low-amplitude compound muscle action potential (CMAP). The superficial peroneal sensory nerve conduction is often normal. The short head of the biceps femoris muscle is the most proximal muscle innervated by the peroneal portion of the sciatic nerve proximal to the common peroneal nerve; if the needle EMG is abnormal, a sciatic neuropathy must be considered.

Lateral Femoral Cutaneous Mononeuropathy

Meralgia paresthetica is frequently caused by compression of the lateral femoral cutaneous nerve by the inguinal ligament. Predisposing factors for meralgia paresthetica include truncal obesity, diabetes mellitus, and pregnancy. Symptoms include pain and paresthesias of the anterolateral thigh, which are exacerbated with walking or standing. Medications, corticosteroid injections, and surgical interventions such as neurectomy or surgical decompression can be considered, depending on the severity of symptoms.

- The incidence of carpal tunnel syndrome is higher among patients who are pregnant or who have diabetes mellitus, hypothyroidism, amyloidosis, renal failure, acromegaly, or HNPP.
- Common causes of peroneal mononeuropathy are leg crossing, operative positioning, prolonged bed rest, casts, pneumatic compression stockings, weight loss, diabetes mellitus, ganglionic cysts, Baker cysts, synovial cysts, tumors, and hematomas.
- Predisposing factors for meralgia paresthetica include truncal obesity, diabetes mellitus, and pregnancy.

Radiculopathy

Radiculopathies involve the ventral or dorsal spinal roots and frequently involve both. Structural causes such as disk herniation and degenerative spine disease (spondylosis and spondylolisthesis) are the most common etiologic factors. Patients with radiculopathies frequently present with radiating back or neck pain that worsens with coughing or the Valsalva maneuver. Weakness in a specific myotome (muscles innervated by a specific nerve root), dermatomal sensory loss, and loss of an associated reflex are common. On nerve conduction studies, the sensory responses should be normal because the spinal pathology is usually proximal to the dorsal root ganglion.

The most common nerve roots affected by intervertebral disk extrusions include C5, C6, and C7 in the cervical spine and L5 and S1 in the lumbar spine and sacrum. The most common radiculopathy in the cervical region is a C7 radiculopathy, leading to weakness of the triceps, finger extension, and forearm pronation, with a loss of the triceps reflex. The most common lumbosacral radiculopathy is an L5 radiculopathy, leading to weakness of ankle dorsiflexion, inversion, and eversion. In contrast, a peroneal neuropathy does not cause ankle inversion weakness.

Lateral disk protrusions affect the exiting nerve root. For example, a lateral disk protrusion at the L4–5 disk space affects the exiting L5 nerve root. In contrast, a central disk protrusion at the L4–5 disk space affects the S1 nerve root because the L5 nerve roots exit lateral to the protrusion.

Less frequent causes of radiculopathy include neoplastic, autoimmune, infectious, and traumatic etiologic factors. Metastatic tumors (eg, lymphoma, melanoma, and breast, lung, prostate, and colon carcinoma) can invade adjacent structures and compress or infiltrate nerve roots. This is more common than intrinsic nerve root tumors, such as schwannomas or neurofibromas or other less common tumors, including meningiomas, ependymomas, paragangliomas, and primitive neuroectodermal tumors. Patients with acquired polyradiculopathies can initially present with injury to a single nerve root; this is most commonly seen in the inflammatory diabetic neuropathies. Herpes zoster (caused by reactivation of latent varicella zoster virus) often affects a single nerve root with an accompanying painful dermatomal rash, which is occasionally associated with paresis in a similar distribution. Traumatic injury can cause root avulsion; with a pure root avulsion, sensory nerve action potentials remain intact because the injury is proximal to the dorsal root ganglion.

Treatment is determined by the cause and severity of the radiculopathy. Medications such as tricyclic antidepressants and anticonvulsants such as gabapentin can be useful for neuropathic pain. Epidural injections of anesthetics and anti-inflammatory medications, as well as surgical intervention with laminectomy, diskectomy, and foraminotomy, can be considered depending on the clinical scenario.

- The most common nerve roots affected by intervertebral disk extrusions include C5, C6, and C7 in the cervical spine and L5 and S1 in the lumbar spine and sacrum.

Spinal Stenosis

Spinal stenosis is a slowly progressive condition caused by a combination of compressive lesions, including disk herniation and degenerative spine disease (hypertrophy of the ligamentum flavum and facet arthropathy). Lumbar stenosis is characterized by neurogenic claudication and chronic back and leg pain that worsens with walking or prolonged standing. Sitting or leaning forward alleviates the symptoms. In contrast, vascular claudication is exacerbated by exercise and relieved by standing, not by leaning forward.

Patients with cervical stenosis often present with radicular arm pain consistent with nerve root compression. Lower motor neuron findings are identified at the level of the lesion, and upper motor neuron findings are identified below the area of compression. For example, cervical stenosis at the C7 level could cause hyporeflexia and weakness at the triceps with spasticity and hyperreflexia in the lower extremities (see Chapter 38, "Myelopathies," for further discussion of myelopathies).

Patients with cauda equina syndrome may initially present with radicular pain in the distribution of the affected lumbosacral spinal roots. As cauda equina syndrome becomes more severe, flaccid asymmetric weakness, saddle anesthesia, and sphincter changes occur.

- Lumbar stenosis is characterized by neurogenic claudication and chronic back and leg pain that worsens with walking or prolonged standing.
- Patients with cauda equina syndrome may initially present with radicular pain in the distribution of the affected lumbosacral spinal roots.

41 Neuromuscular Junction Disorders[a]

BRENT P. GOODMAN, MD

Introduction

The neuromuscular junction (NMJ) is a critical component of the motor unit that is made up of the distal, unmyelinated nerve terminal, synaptic space, and end-plate region of the muscle fiber. Generation of muscle fiber contraction involves a coordinated series of steps that ultimately generates an action potential at the muscle endplate (also known as an end-plate potential). The end-plate potential normally substantially exceeds the threshold necessary to trigger an action potential in the muscle fiber, and this difference is termed the *safety factor of neuromuscular transmission*. Disorders that affect the NMJ reduce this safety factor, a change that results in fatigable weakness.

Anatomy

Review of the events involved in the generation of a muscle fiber action potential at the level of the NMJ facilitates greater understanding of NMJ disorders and the rationale for diagnosing them electrodiagnostically. The steps involved in the generation of a muscle fiber action potential can be summarized as follows: 1) an action potential travels down the postsynaptic nerve terminal; 2) calcium channels open, leading to calcium influx into the nerve terminal; 3) synaptic vesicles fuse with the presynaptic membrane of the nerve terminal, releasing acetylcholine (ACh) into the synaptic space; 4) ACh binds with ACh receptors (AChRs) on the motor end plate; 5) channels in AChRs open leading to 6) sodium influx and 7) generation of an end-plate potential; and 8) muscle contraction results, and ACh is degraded by acetylcholinesterase (Figure 41.1).

The NMJ disorders can be characterized on the basis of the component of the NMJ affected—presynaptic, synaptic, and postsynaptic—and can be acquired or hereditary. Patients with NMJ disorders present with fatigable weakness, which should be demonstrable on neurologic examination. Pain and sensory loss are not associated with the NMJ disorders.

Myasthenia Gravis

Epidemiology

Myasthenia gravis (MG) is an acquired, autoimmune NMJ disorder that results from T-cell–dependent, antibody-mediated attack of the postsynaptic muscle membrane. With appropriate diagnostic testing and treatment, a normal life expectancy is expected, although many patients with MG report persistent, residual symptoms and limitations, reduction in quality of life, and the potential for treatment-related complications.

The prevalence of MG ranges from 77 to 150 per million, with an estimated incidence of 5 to 15 per million per year. Incidence increases with advancing age, and incidence distribution is bimodal, with a higher proportion of females in younger age groups and male predominance in older age groups.

[a] Portions of the "Botulism" section previously published in Goodman BP, Benarroch EE. Autonomic manifestations of systemic disease. In: Lewis SL, editor. Neurological disorders due to systemic disease. Oxford (United Kingdom): Wiley-Blackwell; c2013. p. 239–60. Used with permission.

Abbreviations: ACh, acetylcholine; AChR, acetylcholine receptor; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis; MuSK, muscle-specific kinase; NMJ, neuromuscular junction

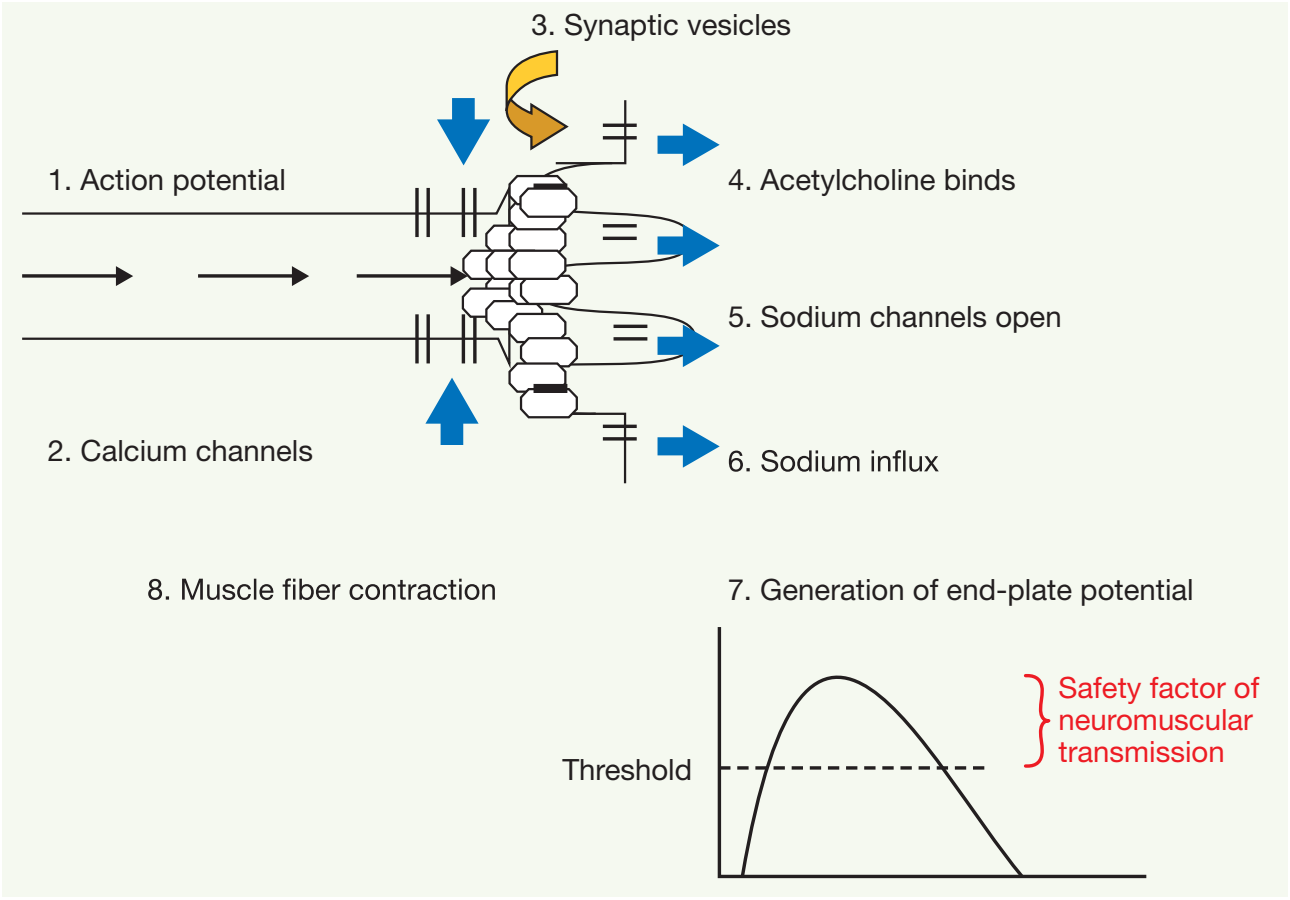


Figure 41.1 *Events of Neuromuscular Transmission.*

Clinical Features

Patients with MG present with fluctuating, fatigable weakness that may involve ocular and other bulbar muscles, limb muscles, and paraspinal muscles. Most patients with MG have ocular signs and symptoms at some point during their course, and in some, the disease remains confined to ocular muscles (ocular MG). Weakness of other bulbar, limb, and paraspinal muscles can occur in patients with generalized MG and, when severe and progressive, can lead to myasthenic crisis.

Diagnosis

The diagnostic evaluation of patients in whom MG is suspected involves laboratory, radiologic, and electrodiagnostic testing. All patients with MG require chest computed tomography to rule out thymoma. Laboratory studies are performed to assess autoantibody status. Antibodies to the AChR are present in 80% to 90% of patients with generalized MG but in only 30% to 50% of patients with ocular MG. In patients without AChR antibodies, antibodies to muscle-specific kinase (MuSK) are found in 40% to 50% of patients. Approximately 5% of patients with generalized MG will not have antibodies to AChR or MuSK.

Electrodiagnostic testing, including repetitive nerve stimulation and single-fiber electromyography, is necessary to confirm the presence and type of NMJ disorder and to exclude other neuromuscular conditions. Repetitive nerve stimulation is particularly important when results of serologic tests for MG are negative. Results of repetitive nerve stimulation are abnormal in approximately 75% of patients with MG, but they are abnormal in less than 30% of patients with ocular MG. Single-fiber electromyography is performed when MG is suspected but findings on repetitive nerve stimulation are normal. Single-fiber electromyography is less specific than repetitive nerve stimulation and can have abnormal results in other conditions such as motor neuron disease, myopathy, radiculopathy, or peripheral neuropathy. Single-fiber electromyography is, however, the most sensitive diagnostic test used in the evaluation of MG, with a sensitivity that approaches 90%.

Edrophonium (Tensilon) testing lacks sensitivity and specificity, is not widely available, and has little role in the modern diagnostic evaluation of suspected NMJ disorders.

Treatment

The successful treatment of MG requires a thoughtful, tailored approach that considers multiple factors, including

age of the patient, distribution and severity of disease, antibody type, and other medical comorbidities. For example, management in an elderly patient with mild ocular MG is much different than that in a patient with severe, generalized MG. The treatment options in MG include surgical (thymectomy), symptomatic (pyridostigmine), and immune-modulating medications or treatments.

Successful treatment of acute exacerbations, including myasthenic crisis, requires prompt recognition, urgent evaluation, and immediate treatment (see also Chapter 8, "Neuromuscular Disease in the Neuroscience Intensive Care Unit").

Myasthenic crisis refers to an acute exacerbation of MG that compromises respiratory function and necessitates ventilatory assistance. Severe exacerbations with bulbar and respiratory involvement require hospitalization and careful monitoring in the intensive care unit. Progressive NMJ failure can lead to life-threatening hypoventilation, necessitating the use of continuous pulse oximetry, frequent pulmonary function tests with maximal inspiratory and inspiratory pressures, occasional measurement of arterial blood gases, and frequent clinical assessments. The 20–30–40 rule may be helpful as a general guideline to indicate when intubation may be necessary (vital capacity <20 mL/kg, peak inspiratory pressure >−30 cm H_2O, peak expiratory pressure <40 cm H_2O). The use of noninvasive ventilation may be considered in some patients. Both plasma exchange and intravenous immunoglobulin may be considered in the treatment of acute MG exacerbations; recent clinical trials suggest equal efficacy.

Acetylcholinesterase inhibitors, such as pyridostigmine, increase the availability of ACh in the NMJ and may provide symptomatic benefit in some patients with MG. These medications are used in most patients with MG, given that they are safe and generally well tolerated and may provide benefits within 30 minutes of taking the medication. Patients with mild ocular or generalized MG may benefit from pyridostigmine alone and may not need additional immune-modulating therapy. Some MG patients with MuSK antibodies may not tolerate pyridostigmine, a clinical feature that may prompt MuSK antibody testing in MG patients with unknown antibody status. In patients undergoing electromyographic testing for MG, use of pyridostigmine should be stopped 12 hours before the testing (if safe to do so).

Immunomodulating pharmacotherapy is necessary in most patients with MG. Prednisone remains a first-line therapy for MG, with potential for benefit within weeks of starting use of the medication. A minority of patients in whom use of prednisone is initiated may have an initial exacerbation of symptoms that necessitates the use of plasma exchange or intravenous immunoglobulin before or concomitant with initiation of prednisone therapy. Once a sustained benefit or remission is achieved, a gradual taper to every-other-day administration is recommended. Other immunomodulating medications such as azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, and rituximab are often used in combination with prednisone as steroid-sparing agents to enhance the beneficial effects of and limit the dose (and adverse effects) of prednisone. Azathioprine and mycophenolate mofetil are typically used as first-line agents but can take as long as 6 to 12 months to benefit patients with MG.

Thymectomy should be performed in patients with thymoma and should be considered in young patients with MG (<50 years of age), even in the absence of thymoma or thymic hyperplasia. There is no role for thymectomy in ocular MG, and thymectomy is not performed in older patients (>50 years of age) without thymoma. Patients with MG should be stable before thymectomy is performed. Plasma exchange or intravenous immunoglobulin can be considered preoperatively in patients with considerable symptoms to minimize potential perioperative or postoperative complications. Video-assisted thoracoscopy and transsternal surgical approaches are considered equally effective.

- Incidence of myasthenia gravis (MG) increases with advancing age, and incidence distribution is bimodal, with a higher proportion of females in younger age groups and male predominance in older age groups.
- Patients with MG present with fluctuating, fatigable weakness that may involve ocular and other bulbar muscles, limb muscles, and paraspinal muscles.
- All patients with MG require chest computed tomography to rule out thymoma. Laboratory studies are performed to assess autoantibody status.
- In patients without AChR antibodies, antibodies to muscle-specific kinase (MuSK) are found in 40% to 50% of patients.
- Repetitive nerve stimulation is particularly important when results of serologic tests for MG are negative. Results of repetitive nerve stimulation are abnormal in approximately 75% of patients with MG, but they are abnormal in less than 30% of patients with ocular MG.
- Acetylcholinesterase inhibitors, such as pyridostigmine, increase the availability of ACh in the NMJ and may provide symptomatic benefit in some patients with MG.
- Patients with mild ocular or generalized MG may benefit from pyridostigmine alone and may not need additional immune-modulating therapy.
- Immunomodulating pharmacotherapy is necessary in most patients with MG.
- Thymectomy should be performed in patients with thymoma and should be considered in young patients with MG (<50 years of age), even in the absence of thymoma or thymic hyperplasia.

Lambert-Eaton Myasthenic Syndrome

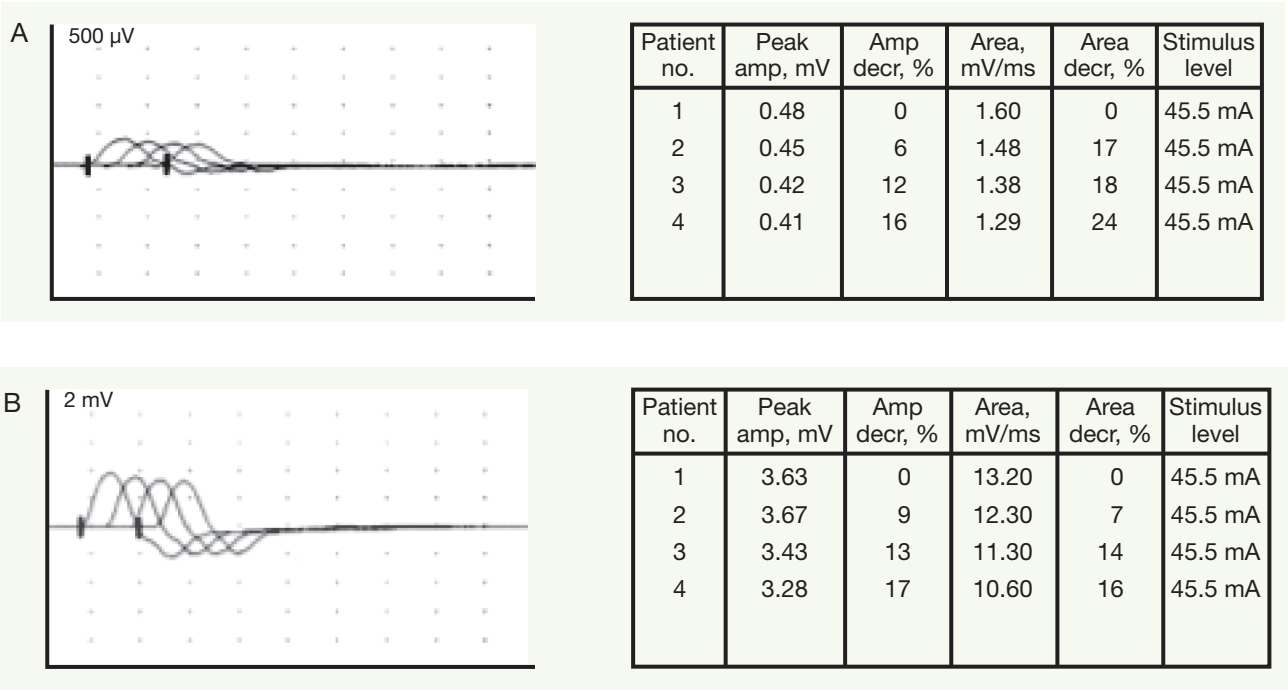
Clinical Features

Lambert-Eaton myasthenic syndrome (LEMS) is a rare, presynaptic NMJ disorder. Antibodies to P/Q-type voltage-gated calcium channels on the presynaptic nerve terminal result in a reduction of ACh release into the NMJ, reducing the safety factor of neuromuscular transmission. Patients with LEMS characteristically present with symptoms of proximal limb weakness, frequently have autonomic symptoms, and on clinical examination are hyporeflexic or areflexic. Facilitation or improvement in muscle strength and muscle stretch reflexes can occur in some patients with LEMS and can be assessed by asking the patient to contract the muscle to be tested for 10 seconds (brief exercise) and then immediately testing muscle strength and (when possible) the muscle stretch reflex. Ocular signs and symptoms are much less common in LEMS than in MG.

Diagnosis

LEMS is associated with cancer, particularly small cell lung carcinoma, although other types of cancer such as non–small cell lung, breast, gastric, and renal can occur. LEMS can occur in patients with established malignancy or can precede the diagnosis of cancer. A diagnosis of LEMS should prompt a thorough initial investigation for malignancy, which may include computed tomography of the chest, abdomen, and pelvis, bronchoscopy (particularly in patients with a smoking history), gynecologic and mammographic screening examinations in women, upper and lower endoscopies, and whole-body positron emission tomography. If results of initial malignancy screening are negative, ongoing periodic screening is necessary. Cancer is ultimately diagnosed in 40% of patients with LEMS, within 2 years in most, and the malignancy will have "declared itself" within 4 years.

As indicated, P/Q-type calcium channel antibodies should be checked when LEMS is suspected, and results are abnormal in 75% to 100% of patients with LEMS and small cell lung carcinoma and in 50% to 90% of patients with LEMS who are without cancer. Repetitive nerve stimulation characteristically shows a low-amplitude motor response (compound muscle action potential) with decrement at low rates of stimulation. With brief exercise or high-frequency stimulation, a facilitation or increment in the amplitude of the motor response occurs and the decrement repairs (Figure 41.2). This effect is an electrophysiologic correlate to the facilitation in muscle strength or reflexes after brief exercise described above.



Patient no.	Peak amp, mV	Amp decr, %	Area, mV/ms	Area decr, %	Stimulus level
1	0.48	0	1.60	0	45.5 mA
2	0.45	6	1.48	17	45.5 mA
3	0.42	12	1.38	18	45.5 mA
4	0.41	16	1.29	24	45.5 mA

Patient no.	Peak amp, mV	Amp decr, %	Area, mV/ms	Area decr, %	Stimulus level
1	3.63	0	13.20	0	45.5 mA
2	3.67	9	12.30	7	45.5 mA
3	3.43	13	11.30	14	45.5 mA
4	3.28	17	10.60	16	45.5 mA

Figure 41.2 *Repetitive Nerve Stimulation in Lambert-Eaton Myasthenic Syndrome.*
Repetitive nerve stimulation, 2 Hz, of median motor nerve recording over abductor pollicis brevis before (A) and immediately after brief exercise (B). Note the low-amplitude compound muscle action potential at rest, with decrement in amplitude (Amp) and area, and increment in amplitude and area after brief exercise. These electrodiagnostic findings are typical of those found in Lambert-Eaton myasthenic syndrome.

Treatment

The treatment approach in patients with LEMS is based on the severity of disease and cancer status. In the patient with LEMS who has cancer, therapy is focused primarily on the underlying malignancy. Acetylcholinesterase inhibitors such as pyridostigmine can be modestly beneficial in some patients, although this symptomatic therapy does not affect the presynaptic defect of impaired vesicular release of ACh into the synaptic space. 3,4-Diaminopyridine is the most useful symptomatic therapy in patients with LEMS, acting to improve the safety factor of neuromuscular transmission by blocking presynaptic potassium channels, which normally act as delayed rectifiers to close calcium channels. 3,4-Diaminopyridine then prolongs the open time of presynaptic calcium channels, an effect that improves the vesicular release of ACh. Immune-modulating therapy can be considered in those LEMS patients without cancer who are not responding to symptomatic therapy.

- Lambert-Eaton myasthenic syndrome (LEMS) is a rare, presynaptic NMJ disorder.
- Patients with LEMS characteristically present with symptoms of proximal limb weakness, frequently have autonomic symptoms, and on clinical examination are hyporeflexic or areflexic.
- LEMS is associated with cancer, particularly small cell lung carcinoma, although other types of cancer such as non–small cell lung, breast, gastric, and renal can occur.
- Cancer is ultimately diagnosed in 40% of patients with LEMS, within 2 years in most, and the malignancy will have "declared itself" within 4 years.
- With brief exercise or high-frequency stimulation, a facilitation or increment in the amplitude of the motor response occurs and the decrement repairs.
- In the patient with LEMS who has cancer, therapy is focused primarily on the underlying malignancy.
- 3,4-Diaminopyridine is the most useful symptomatic therapy in patients with LEMS.

Table 41.1 • Congenital Myasthenic Syndromes

Disorder	Genetic Defect	Distinguishing Clinical Feature
Choline acetyltransferase deficiency	Chromosome 10	Episodic apnea
Paucity of synaptic vesicles		
Congenital LEMS		
End-plate AChE deficiency	*COLQ* gene Chronosome 3	Repetitive CMAP No response to pyridostigmine
β2 Laminin deficiency	*LAMB2* gene Chromosome 3	Nephrotic syndrome Ocular abnormalities
Primary AChR deficiency	Chromosome 17	
Rapsyn deficiency	Chromosome 11	Joint contractures Weakness precipitated by infection
Sodium channel defect	*SCN4A* gene Chromosome 17	
Plectin deficiency	*PLEC* gene Chromosome 8	Epidermolysis bullosa simplex
Dok-7 myasthenia	*DOK7* gene Chromosome 4	Limb-girdle weakness Worse after pyridostigmine
CMS in centronuclear myopathy		Distinctive histopathologic findings on muscle biopsy
GFPT1 myasthenia	*GFPT1* gene Chromosome 2	Tubular aggregates on muscle biopsy Limb-girdle weakness
Slow channel	Multiple genes	Cervical, wrist, digit extensor weakness Repetitive CMAP Responds to quinine, quinidine, fluoxetine
Fast channel	Multiple genes	

Abbreviations: AChE, acetylcholinesterase; AChR, acetylcholine receptor; CMAP, compound muscle action potential; CMS, congenital myasthenic syndrome; LEMS, Lambert-Eaton myasthenic syndrome.

Botulism

Botulism is caused by the anaerobic, spore-forming bacterium *Clostridium botulinum*, which produces a diverse array of neurotoxins with different properties. Human botulism results from types A, B, and E, and 4 clinical forms of botulism are recognized: foodborne botulism, wound botulism, infant botulism, and adult infectious botulism. In the United States, infantile and foodborne botulism (eg, raw honey) are the most common forms. Botulinum toxin binds to presynaptic nerve terminals in the NMJ and in the autonomic nervous system, preventing the release of ACh. Botulism results in a descending pattern of weakness in addition to autonomic features (gastrointestinal symptoms, mydriasis, and orthostatic hypotension). For additional features, diagnosis, and treatment, see Chapter 8, "Neuromuscular Disease in the Neuroscience Intensive Care Unit."

- Botulinum toxin binds to presynaptic nerve terminals in the NMJ and in the autonomic nervous system, preventing the release of ACh.

Congenital Myasthenic Syndromes

Overview

The congenital myasthenic syndromes are a group of rare, clinically heterogeneous disorders that reduce the safety factor of neuromuscular transmission through several different mechanisms. These disorders can be broadly categorized on the basis of localization of the defect within the NMJ as presynaptic, synaptic, and postsynaptic. Genetic testing is commercially available for some of these disorders. Establishing a diagnosis of a congenital myasthenic syndrome requires high clinical suspicion and detailed electrodiagnostic studies, genetic testing, and, in some instances, in vitro physiologic studies.

Clinical Features

Clinical features of congenital myasthenic syndrome are highly variable, although a history of fatigable weakness with onset in infancy or early childhood should prompt consideration. Certain clinical and electrodiagnostic features may provide clues to individual disorders (Table 41.1). For example, patients with end-plate choline acetyltransferase deficiency have recurrent apneic episodes often prompted by fever or vomiting; extensor weakness of cervical, wrist, and digital muscles occurs with slow-channel syndrome; multiple joint contractures with respiratory insufficiency are common in rapsyn deficiency; and epidermolysis bullosa simplex is associated with plectin deficiency.

- Clinical features of congenital myasthenic syndrome are highly variable, although a history of fatigable weakness with onset in infancy or early childhood should prompt consideration.

42 Acquired Muscle Disorders

MARGHERITA MILONE, MD, PHD

Introduction

Muscle diseases consist of various disorders that primarily affect skeletal muscle, but they can also affect cardiac or smooth muscle. The disorders may be inherited, congenital, or acquired (Boxes 42.1 and 42.2). The pathophysiology, clinical manifestations, diagnostic routes, and treatment options are different for each disorder. This chapter reviews common acquired muscle disorders. Chapter 43, "Inherited Muscle Disorders," reviews congenital and inherited muscle disorders.

Inflammatory Myopathies

Overview

Inflammatory myopathies are characterized by muscle weakness, elevated creatine kinase (CK) values, and inflammatory reaction in muscle. They can occur with infections or systemic inflammatory diseases or be idiopathic. On the basis of clinical, histologic, and immunopathologic criteria, idiopathic inflammatory myopathies can be distinguished as dermatomyositis, polymyositis, or inclusion body myositis. When dermatomyositis or polymyositis occurs in association with a connective tissue disease, the disorder is called *overlap syndrome*.

Epidemiology

The prevalence of dermatomyositis is estimated to be approximately 21 per 100,000 people. Polymyositis is uncommon as a stand-alone clinical entity. Inclusion body myositis is the most common muscle disease in patients older than 50 years.

Pathophysiology

Dermatomyositis is the result of a humoral-mediated microangiopathy. Polymyositis is a cell-mediated autoimmune myopathy. Inclusion body myositis is thought to be the result of both inflammation and muscle degeneration.

Clinical Features

Dermatomyositis can manifest at any age with acute or insidiously progressive proximal muscle weakness that is more pronounced than distal weakness. Skin manifestations, in the form of malar rash, heliotropic lid discoloration, Gottron sign, and papule, accompany or precede the onset of the weakness (Figure 42.1). Patients with polymyositis present with proximal muscle weakness and a similar onset often associated with pain but without a skin rash.

Box 42.1 • Overview of Muscle Disorders

- Inherited
  - Muscular dystrophies
  - Congenital myopathies
  - Channelopathies
  - Metabolic myopathies
  - Mitochondrial myopathies
- Acquired
  - Inflammatory: polymyositis, dermatomyositis, inclusion body myositis
  - Infectious
  - Endocrine, metabolic
  - Drugs, toxins
  - Rhabdomyolysis

Abbreviations: CK, creatine kinase; EMG, electromyography; HIV, human immunodeficiency virus

Box 42.2 • Differential Diagnosis of Acquired Muscle Disorders

- Inflammatory
  - Polymyositis, dermatomyositis
  - Inclusion body myositis
  - Connective tissue disorders (lupus, Sjögren syndrome, rheumatoid arthritis, scleroderma)
  - Vasculitis (Wegener syndrome, Churg-Strauss syndrome, polyarteritis nodosa)
  - Sarcoid
  - Eosinophilic myositis, fasciitis, and myalgia syndrome
  - Orbital myositis
- Infectious
  - Viral: human immunodeficiency virus, influenza virus, parainfluenza virus, cytomegalovirus, adenovirus, Epstein-Barr virus, coxsackievirus
  - Bacterial: Lyme disease, pyomyositis, *Clostridium perfringens* (myonecrosis), *Legionella pneumophila*
  - Fungal
  - Parasitic: trichinosis, toxoplasmosis, cysticercosis, trypanosomiasis (Chagas disease)
- Endocrine
  - Hypothyroidism, hyperthyroidism
  - Cushing syndrome
- Metabolic
  - Electrolyte disturbances (potassium, phosphate, calcium, sodium)
- Drugs, toxins
  - Corticosteroids
  - Statins (HMG-CoA reductase inhibitors)
  - Other: Antimalarial medications, zidovudine, penicillamine, colchicine, fibrates
- Rhabdomyolysis
  - Seizures
  - Trauma
  - Malignant hyperthermia
  - Severe dehydration
- Other
  - Critical illness myopathy

Malignancy is associated with dermatomyositis in up to 30% of patients and to a lesser extent in patients with polymyositis. Therefore, screening for underlying malignancy is mandatory. Some patients may have interstitial lung disease, often with Jo-1 antibodies (antisynthetase syndrome).

Inclusion body myositis manifests with weakness of the deep finger flexors and quadriceps (Figure 42.2). The weakness is often asymmetric and insidiously progressive. The deltoids are often spared.

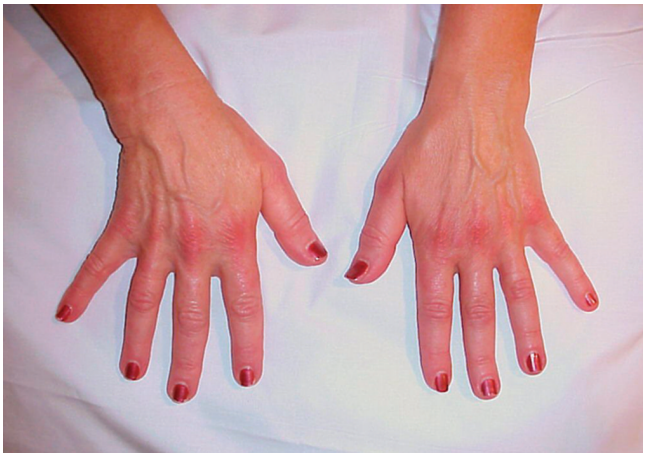


Figure 42.1 *Dermatomyositis.*
Characteristic heliotrope rash involves the extensor surfaces of the fingers of a patient with dermatomyositis.
(Adapted from Mowzoon N. Disorders of muscle. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 885–931. Used with permission of Mayo Foundation for Medical Education and Research.)

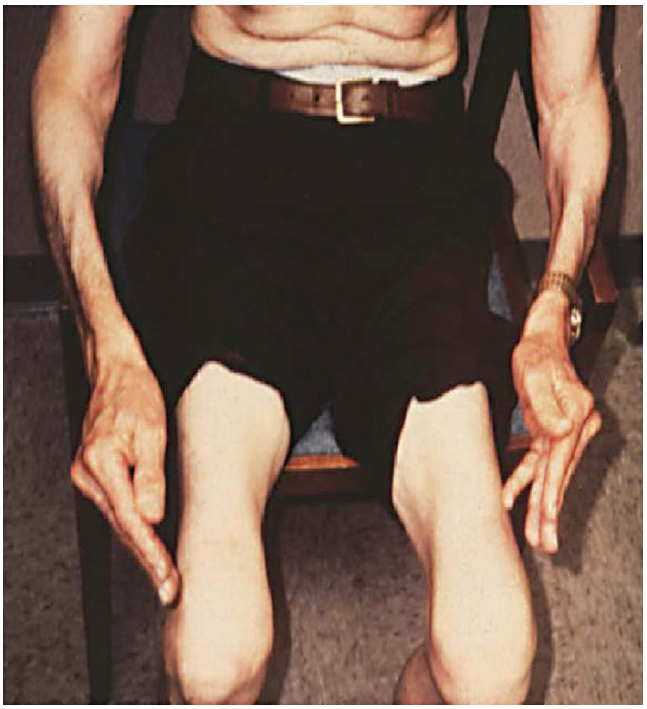


Figure 42.2 *Inclusion Body Myositis.*
Prominent weakness and atrophy of the quadriceps and finger flexors are present in this patient with sporadic inclusion body myositis.
(Adapted from Engel WK, Askanas V. Inclusion-body myositis: clinical, diagnostic, and pathologic aspects. Neurology. 2006 Jan 24;66[2 Suppl 1]:S20–9. Used with permission.)

Dysphagia can occur in dermatomyositis, polymyositis, and inclusion body myositis.

Diagnosis

Clinical history and findings provide important clues for diagnosis. CK values may or may not be elevated, especially in dermatomyositis and inclusion body myositis. Electromyography (EMG) shows myopathic changes, often with fibrillation potentials in dermatomyositis and polymyositis and with mixed myopathic and neurogenic changes in inclusion body myositis. Muscle biopsy in dermatomyositis shows a perivascular and perimysial inflammatory reaction consisting of B cells, $CD4^+$ cells, and perifascicular structural changes (muscle fiber atrophy, degeneration, regeneration, vacuolar changes, and increased internal nuclei) (Figure 42.3). Typical pathologic features of polymyositis are muscle fiber necrosis and regeneration and endomysial inflammatory reaction, mainly consisting of $CD8^+$ T cells and macrophages invading nonnecrotic muscle fibers. Characteristic pathologic signs of inclusion body myositis are autoaggressive inflammatory exudate, rimmed vacuoles, and intracellular congophilic deposits (Figure 42.4).

Treatment

Dermatomyositis and polymyositis are usually responsive to immunotherapy. Corticosteroids, steroid-sparing immunosuppressive agents (eg, methotrexate, azathioprine, or mycophenolate mofetil), and intravenous immunoglobulin are potential drugs for treatment. Response to pharmacologic treatment should be established on clinical findings because the CK level may not be a reliable indicator of disease activity, especially in dermatomyositis.

Inclusion body myositis is refractory to immunotherapy. Physical therapy helps prevent development of contracture and may improve strength.

- Inflammatory myopathies are characterized by muscle weakness, elevated creatine kinase values, and inflammatory reaction in muscle.
- Inclusion body myositis is the most common muscle disease in patients older than 50 years.
- Patients with dermatomyositis present with proximal muscle weakness. Skin manifestations may accompany or precede the onset of weakness.
- Patients with polymyositis present with proximal muscle weakness often accompanied by pain.
- Malignancy is associated with dermatomyositis in up to 30% of patients and to a lesser extent in patients with polymyositis.
- EMG shows myopathic changes, often with fibrillation potentials in dermatomyositis and polymyositis and with mixed myopathic and neurogenic changes in inclusion body myositis.
- Dermatomyositis and polymyositis are usually responsive to immunotherapy.
- Inclusion body myositis is refractory to immunotherapy.

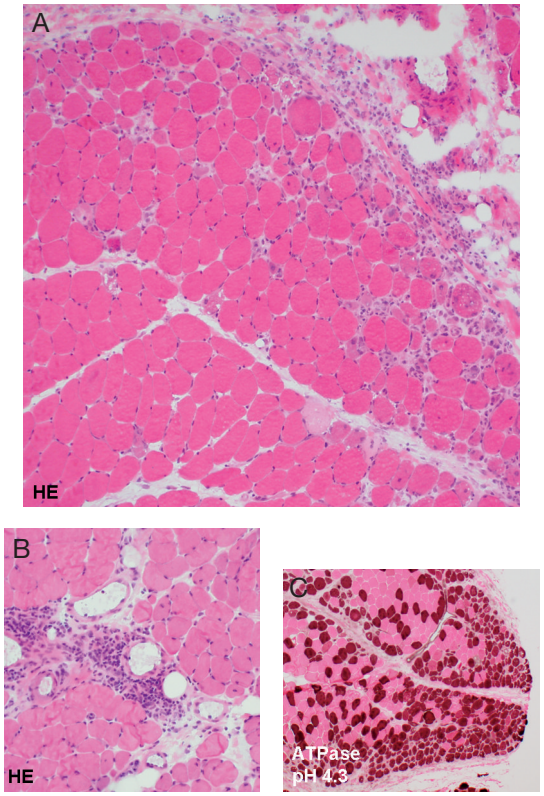


Figure 42.3 *Dermatomyositis Histopathology. A and B, Hematoxylin-eosin (HE)-stained sections show predominant perifascicular structural changes, including muscle fiber atrophy, necrosis, regeneration, basophilia, internal nuclei, vacuolar changes (A), and perivascular inflammatory exudate in the perimysium (B). C, The perifascicular muscle atrophy is also seen in the adenosine triphosphatase (ATPase)-reacted section.*

Endocrine Myopathies

Thyroid Disease

Muscle weakness occurs frequently in dysthyroidism and develops in up to 60% to 80% of patients with thyrotoxicosis. Hypothyroidism and hyperthyroidism affect muscle metabolism; Graves ophthalmopathy is considered an autoimmune disorder.

Hypothyroidism can lead to myopathy with proximal muscle weakness, fatigue, myalgia, myoedema, and mus-

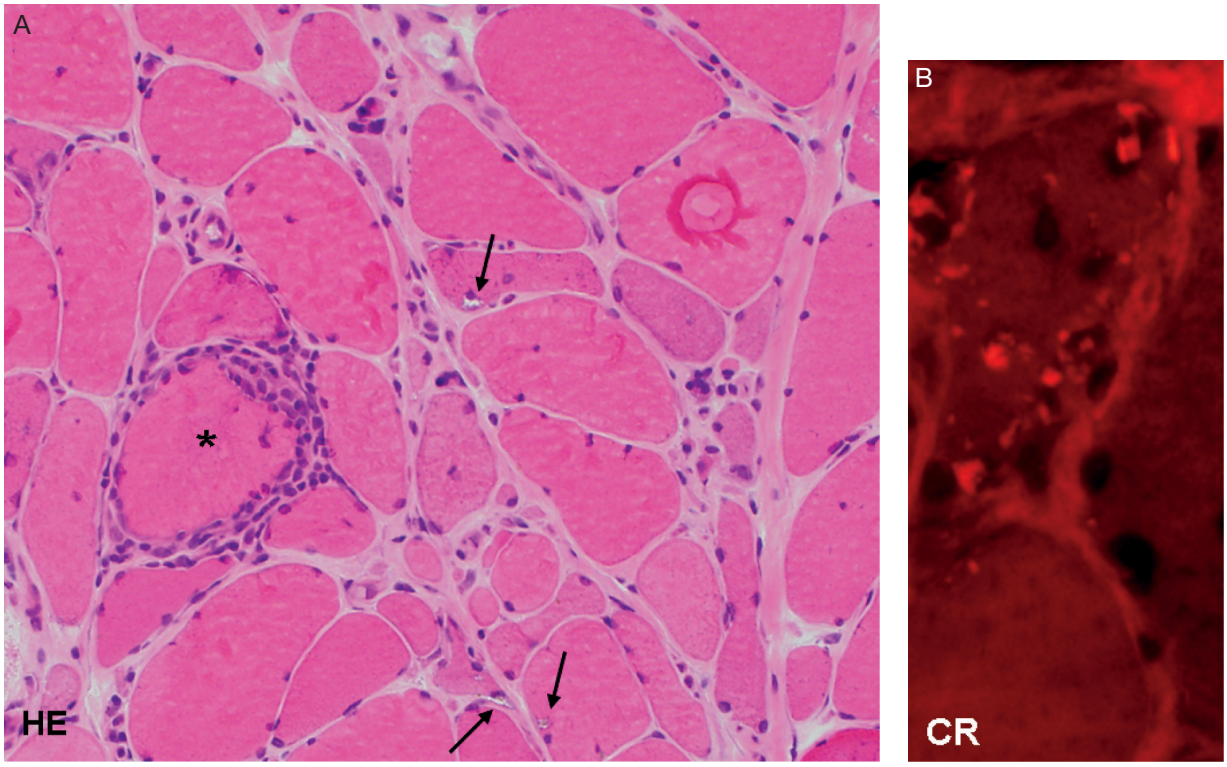


Figure 42.4 *Inclusion Body Myositis Histopathology.*
A, A nonnecrotic muscle fiber (asterisk) is focally invaded by macrophages. The arrows point to rimmed vacuoles (hematoxylin-eosin [HE]). B, Congo red (CR)-stained section of a muscle fiber viewed under rhodamine optics shows small congophilic deposits that appear as dense red dots.

cle enlargement. Hypothyroidism can induce rhabdomyolysis.

Thyrotoxicosis can lead to thyrotoxic myopathy or thyrotoxic periodic paralysis. Thyrotoxic myopathy manifests with predominantly proximal muscle weakness and atrophy, fatigue, and myalgia. Thyrotoxic periodic paralysis is characterized by episodic weakness, hypokalemia, suppressed thyrotropin levels, and elevated thyroid hormone levels. The condition is more frequent in Asian and Latin American males. Triggering factors include carbohydrate-rich meals, rest after intense physical activity, emotional stress, fever, and infection. Up to 33% of patients with thyrotoxic periodic paralysis carry mutations in the skeletal muscle potassium channel Kir2.6.

Graves ophthalmopathy can occur with hyperthyroidism or after treatment of hyperthyroidism when the patient has become hypothyroid. Graves ophthalmopathy manifests with lid retraction, often painful exophthalmos, diplopia, and optic neuropathy due to enlargement of the orbital content.

The CK value is elevated in most patients with hypothyroid myopathy and normal or low in patients with thyrotoxicosis. EMG often shows mild myopathic or normal findings. Myoedema of hypothyroidism is electrically silent. Muscle biopsy may show normal findings, atrophy of type 1 and 2 fibers, or minimal nonspecific abnormalities.

Restoration of the euthyroid state is essential for the treatment of myopathy. Propranolol and antithyroid drugs help prevent paralysis in thyrotoxic periodic paralysis. Prisms, corticosteroids, and muscle recession are effective in Graves ophthalmopathy.

Glucocorticoid Defects

At least 50% of patients who have Addison disease or Cushing disease have muscle weakness. The incidence of myopathy in patients receiving long-term glucocorticoid therapy has been estimated to be between 2% and 20%. The fluorinated corticosteroids are most likely to induce myopathy.

Glucocorticoids impair protein and carbohydrate metabolism in muscle and may affect the sarcoplasmic reticulum function, impairing the excitation-contraction coupling. In primary adrenal insufficiency, the weakness can also result from hyperkalemia.

Adrenal insufficiency may cause generalized muscle weakness, fatigue, and muscle cramping. Endogenous and

iatrogenic excess of glucocorticoids leads to muscle weakness and atrophy.

In patients with adrenal insufficiency, the CK values are normal. EMG findings may be normal or show myopathic motor unit potentials. Muscle biopsy is unremarkable in adrenal insufficiency, but it shows selective type 2 fiber atrophy in corticosteroid-induced myopathy.

The main treatment of corticosteroid-induced myopathy is dose reduction of corticosteroids; alternate-day treatment and transition to nonfluorinated glucocorticoids is beneficial. Providing glucocorticoid therapy and decreasing the serum potassium level, if needed, correct the weakness in primary adrenal insufficiency.

- Hypothyroidism can lead to myopathy with proximal muscle weakness, fatigue, myalgia, myoedema, and muscle enlargement.
- Thyrotoxicosis can lead to thyrotoxic myopathy or thyrotoxic periodic paralysis.
- Graves ophthalmopathy manifests with lid retraction, often painful exophthalmos, diplopia, and optic neuropathy due to enlargement of the orbital content.
- The creatine kinase value is elevated in most patients with hypothyroid myopathy and normal or low in patients with thyrotoxicosis.
- Endogenous and iatrogenic excess of glucocorticoids leads to muscle weakness and atrophy.
- In patients with adrenal insufficiency, the creatine kinase values are normal. EMG findings may be normal or show myopathic motor unit potentials.

Metabolic Disorders

Various electrolyte disorders can result in muscle weakness, fatigue, or periodic paralysis. Electrolyte disorders are covered in more detail in Chapter 77, "Electrolyte Disturbance and Acid-Base Imbalance."

Drugs and Toxins

Statins

Statins (HMG-CoA reductase inhibitors) decrease cholesterol levels and have other pleiotropic effects that are particularly important for vascular disease. A commonly feared side effect is myopathy which affects only about 0.1% to 0.5% of patients. The risk is influenced by several factors (Box 42.3).

The exact mechanism that results in myopathy is not clear, but theories include reduction of coenzyme Q10, elevation of plant sterols in skeletal muscle, and increased expression of atrogin-1.

Box 42.3 • Factors That Increase the Risk of Statin-Induced Myopathy

- Statin selection and dose
  - Pravastatin and fluvastatin may present lower risk
- Preexisting neuromuscular disease
  - Amyotrophic lateral sclerosis
  - Certain inherited metabolic myopathies
  - Mitochondrial myopathy
- Preexisting metabolic or endocrine conditions
  - Hypothyroidism
  - Acute or chronic renal failure
  - Obstructive liver disease
- Concomitant medications
  - Inhibitors and inducers of cytochrome P450 3A4 isozyme (numerous)
  - Calcium channel blockers
  - Grapefruit juice

Zidovudine

Although human immunodeficiency virus (HIV) itself may cause myopathy, some of the medications used to treat HIV may also cause myopathy. Zidovudine (also called AZT) and other HIV nucleoside reverse transcriptase inhibitors can cause myopathy typically manifesting with proximal muscle weakness, myalgias, and tenderness.

CK levels are usually elevated, and EMG shows typical myopathic changes. Muscle biopsy can be helpful in distinguishing between an HIV-related myopathy and a nucleoside reverse transcriptase inhibitor myopathy. Light microscopy shows no inflammation in nucleoside reverse transcriptase inhibitor–related myopathy, which also may have evidence of mitochondrial myopathy because the medication may inhibit mitochondrial DNA synthesis.

Critical Illness Muscle Disorders

Critical Illness Myopathy

Critical illness myopathy and several other neuromuscular disorders that occur in critically ill patients are discussed in Chapter 8, "Neuromuscular Disease in the Neuroscience Intensive Care Unit."

Rhabdomyolysis

Overview

Rhabdomyolysis is a potentially life-threatening condition characterized by muscle destruction. The causes of rhabdomyolysis are varied and include trauma, excess heat

(seizure, amphetamine overdose, and delirium tremens), hypothermia, medications, toxins, severe infections, electrolyte disturbances, metabolic myopathies, and thyroid disease.

Clinical Features

Although a range of severity exists, patients commonly present with severe muscle pain, myoglobinuria, and an elevated CK level. When the condition is severe, additional symptoms can include fever, nausea, vomiting, abdominal pain, and tachycardia. Additional symptoms related to the primary cause may also be present.

Diagnosis and Treatment

Patients with rhabdomyolysis have an elevated CK level that is sometimes as high as 10 times the upper limit of the reference range. The CK elevation usually reaches its maximum level 1 to 3 days after the onset of symptoms. Myoglobin is present in the urine. Patients may have further electrolyte and volume disturbances (hyperkalemia, hyperphosphatemia, hypocalcemia, and hypovolemia) and renal injury.

Treatment involves hydrating the patient, treating the fluid and electrolyte abnormalities, and identifying and eliminating the potential causes.

- Rhabdomyolysis is a potentially life-threatening condition characterized by muscle destruction.
- The causes of rhabdomyolysis are varied and include trauma, excess heat (seizure, amphetamine overdose, and delirium tremens), hypothermia, medications, toxins, severe infections, electrolyte disturbances, metabolic myopathies, and thyroid disease.
- Patients with rhabdomyolysis have an elevated creatine kinase level that is sometimes as high as 10 times the upper limit of the reference range.

43 Inherited Muscle Disorders

MARGHERITA MILONE, MD, PHD

Introduction

Congenital and inherited muscular disorders occur commonly in infants and children, but some also present in adulthood. The differential diagnosis is broad (Box 43.1). These include muscular dystrophies, congenital myopathies, disorders of metabolism, channelopathies, and mitochondrial disorders.

Muscular dystrophies may present at any age, are inherited, and involve progressive degeneration of muscle, often being replaced by connective tissue. Muscular dystrophies result from defects in the dystrophin-associated muscle membrane protein complex (Figure 43.1).

Congenital myopathies are those presenting at birth, often with hypotonia, poor respiratory effort, and reduced feeding ability. The course is often slow or nonprogressive. Orthopedic complications as a result of the weakness are common. Biopsy is key in diagnosing these entities.

Disorders of lipid and glycogen metabolism may result in muscle disease. These may manifest at various ages and often affect exercise performance.

Channelopathies are a group of disorders whose pathophysiologic basis is defects in sodium, calcium, and chloride channels. These diseases manifest at various ages with muscle symptoms and signs and are generally inherited.

Mitochondrial myopathies are those related to defects in mitochondrial metabolism. Mitochondrial disorders are maternally inherited (see Chapter 76, "Mitochondrial

Box 43.1 • Differential Diagnosis of Inherited Myopathies

Muscular Dystrophies	Congenital Myopathies	Metabolic Myopathies	Channelopathies	Mitochondrial Myopathies
Duchenne	Central core	Myophosphorylase deficiency	Myotonia congenita	MERFF
Becker	Nemaline rod	Acid α-glucosidase (acid-maltase) deficiency	Hypokalemic periodic paralysis	MELAS
Emery-Dreifuss	Multicore	Debrancher deficiency (glycogenosis III)	Hyperkalemia periodic paralysis	Kearn-Sayres
Oculopharyngeal	Myotubular	Branching enzyme deficiency (glycogenosis IV)	Paramyotonia congenita	Progressive external ophthalmoplegia
Facioscapulohumeral		Phosphofructokinase deficiency (glycogenosis VII)		MNGIE
Limb-girdle		CPTII deficiency		
Myotonic				
Walker-Warburg				
Fukuyama				
Distal myopathies				

Abbreviations: CPTII, carnitine polymitoyltransferase; MELAS, mitochondrial encephalopathy with lactic acidosis and strokelike episodes; MERFF, myoclonic epilepsy with ragged red fibers; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy.

Abbreviations: BMD, Becker muscular dystrophy; CPTII, carnitine palmitoyltransferase II; DMD, Duchenne muscular dystrophy; DM, myotonic dystrophy (1 and 2); EMD, Emery-Dreifuss muscular dystrophy; GAA, acid α-1,4-glucosidase; hyperKPP, hyperkalemic periodic paralysis; hypoKPP, hypokalemic periodic paralysis; LGMD, limb-girdle muscular dystrophies; PP, periodic paralysis

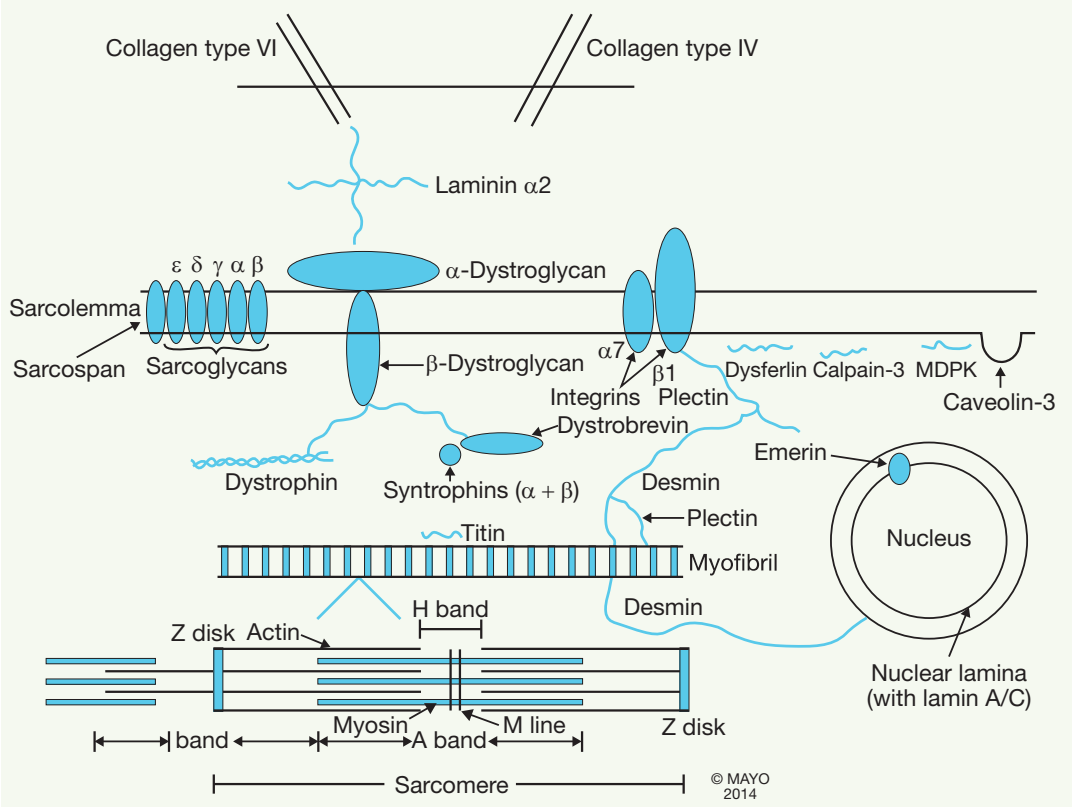


Figure 43.1 *Dystrophin-Associated Muscle Membrane Protein Complex.*
(Adapted from Banwell BL. Muscular dystrophies. In: Noseworthy JH, editor. Neurological therapeutics: principles and practice. Vol 2. London [United Kingdom]: Martin Dunitz; c2003. p. 2312–27. Used with permission of Mayo Foundation for Medical Education and Research.)

Disease") or sporadic. Mitochondrial disorders may result in muscle disease and affect other organ systems. Each mitochondrial disease has unique features.

Muscular Dystrophies

Dystrophinopathies

Overview

Dystrophinopathies are X-linked recessive myopathies presenting with a spectrum of phenotypes, varying from Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), myalgia and rhabdomyolysis, and asymptomatic hyperCKemia. Dystrophinopathies are caused by mutations in the largest human gene, dystrophin (Figure 43.1), located on chromosome Xp21.

Epidemiology

DMD is the most severe dystrophinopathy and the most common muscular dystrophy; its incidence is 1 in 3,500 newborn males. A third of DMD cases result from spontaneous mutations. BMD is less severe and has an incidence of 5 in 100,000.

Pathophysiology

Dystrophin is a sarcolemmal protein and a component of the dystrophin-glycoprotein complex, which links the cytoskeleton to the extracellular matrix stabilizing the sarcolemma and protecting muscle fibers from contraction-induced damage. Mutations in the dystrophin gene result in reduction or absence of dystrophin, leading to mechanical damage of the sarcolemma and muscle fiber degeneration. The amount of residual dystrophin in muscle is an important determinant of the clinical severity of the myopathy. Mutations altering the reading frame of dystrophin result in near loss of dystrophin, often translating in DMD. In-frame mutations result in dystrophin of smaller size and amount, leading to the less severe BMD.

Clinical Features

DMD manifests in childhood with progressive proximal muscle weakness and calf muscle enlargement. The disease affects the cardiac and respiratory muscles. Affected boys lose the ability to ambulate around age 13 years and die of cardiac and respiratory causes in their 20s, if untreated.

BMD has a similar phenotype but a later age at onset (around 12 years). Loss of ambulation occurs around age 40 years, and the degree of reduction in life expectancy is

variable. Up to 70% of patients with BMD develop a cardiomyopathy; this is the primary cause of death in BMD, but its onset and severity are unrelated to the course and severity of the skeletal myopathy.

Milder phenotypes include myalgia and rhabdomyolysis, asymptomatic hyperCKemia, or dilated cardiomyopathy. A small percentage of female carriers can have mild proximal weakness or cardiomyopathy.

Diagnosis

Clinical features and increased creatine kinase level (50–100 times normal) help establish the diagnosis of dystrophinopathies. Molecular analysis shows deletions in the dystrophin gene in approximatively 70% of patients, duplications in 7% to 10%, and point mutations in 20%. Most deletions occur between exons 44 and 55 of the dystrophin gene. Muscle histologic studies show signs of an active and chronic myopathy (increase in internal nuclei, muscle fiber splitting, muscle fiber necrosis and regeneration, and increased endomysial connective tissue) (Figure 43.2). Immunocytochemical studies show no dystrophin in DMD and reduced sarcolemmal dystrophin in BMD. Normal creatine kinase values do not exclude the carrier state in a female.

Treatment

Corticosteroids prolong ambulation, maintain pulmonary function, and delay ventricular dysfunction in DMD. Effective treatments are prednisone 0.75 mg/kg a day or deflazacort 0.9 mg/kg a day. Treatment is usually initiated between the ages of 4 and 6 years. In patients with DMD, the continuation of corticosteroid therapy after the ability to ambulate is lost, with the goal of preserving arm strength and slowing respiratory and cardiac impairment, remains controversial. Potential long-term adverse effects from corticosteroid treatment include reduction in height, weight gain, vertebral fractures, behavior changes, arterial hypertension, and delayed puberty. Treatment with an angiotensin-converting enzyme inhibitor or an angiotensin-converting enzyme inhibitor plus a β-blocker can delay progression of the cardiomyopathy. Noninvasive ventilatory support with biphasic positive airway pressure is available for children with respiratory insufficiency. Spinal fusion is offered to children with scoliosis of 35° or more. Gene therapy, such as the delivery of minidystrophin and exon skipping, is promising. In BMD, early cardiac care is essential because the primary cause of death is heart failure.

- Duchenne muscular dystrophy (DMD) is the most severe dystrophinopathy and the most common muscular dystrophy.
- Mutations in the dystrophin gene result in reduction or absence of dystrophin, leading to mechanical damage of the sarcolemma and muscle fiber degeneration. The amount of residual dystrophin in muscle is an important determinant of the clinical severity of the myopathy.
- DMD manifests in childhood with progressive proximal muscle weakness and calf muscle

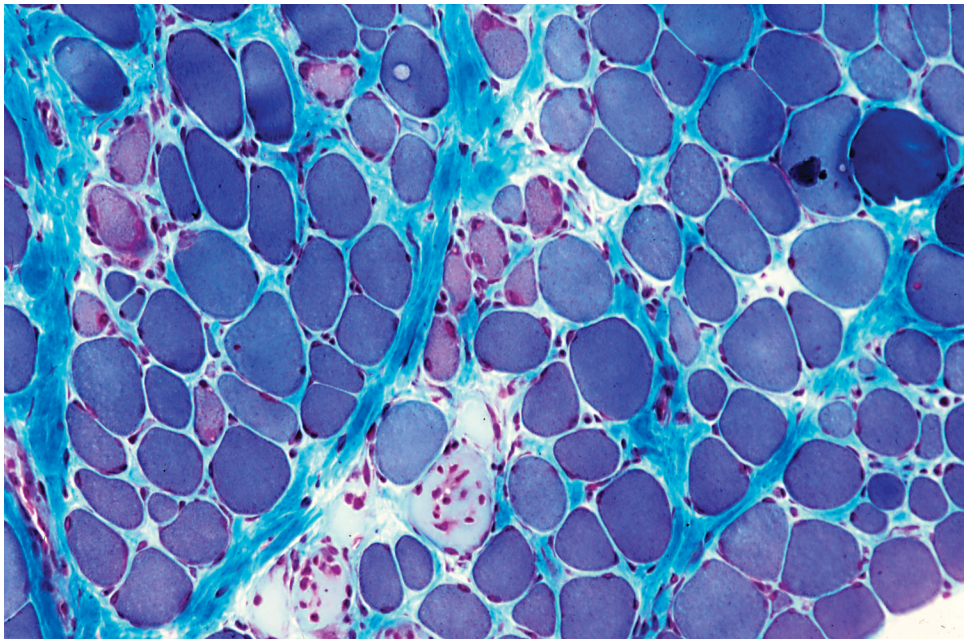


Figure 43.2 *Muscle Histopathologic Features of Duchenne Dystrophy.*
Photomicrograph shows endomysial and perimysial macrophage invasion of necrotic fibers undergoing phagocytosis, hypercontracted (opaque) fibers, mild endomysial fibrosis, and central fiber necrosis (trichrome stain).
(Courtesy of Andrew G. Engel, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

enlargement. The disease affects the cardiac and respiratory muscles.
- Becker muscular dystrophy (BMD) has a similar phenotype to DMD but a later age at onset (around 12 years). Loss of ambulation occurs around age 40 years, and the degree of reduction in life expectancy is variable.
- Clinical features and increased creatine kinase level (50–100 times normal) help establish the diagnosis of dystrophinopathies.
- Corticosteroids prolong ambulation, maintain pulmonary function, and delay ventricular dysfunction in DMD.

Facioscapulohumeral Muscular Dystrophy

Overview

Facioscapulohumeral muscular dystrophy is a myopathy with autosomal dominant inheritance. Mutations are de novo in 10% to 30% of cases.

Epidemiology

It is the third most common muscular dystrophy, with an incidence of 1 in 15,000 to 20,000. The disease usually manifests in the second decade of life, but the age at onset varies between early childhood and late life. A severe congenital form is very rare.

Pathophysiology

More than 95% of patients carry a contraction of D4Z4 repeats (normal subjects have 11–100 repeats) array on chromosome 4q35, resulting in DNA hypomethylation and chromatin relaxation. The remaining 5% of patients lack the D4Z4 repeat contraction but still show chromatin relaxation. In either case, there is an incomplete suppression of the DUX4 retrogene in skeletal muscle, which in turn leads to release of inappropriate gene expression in muscle.

Clinical Features

Asymmetric weakness of the facial muscles and scapular stabilizer muscles, often resulting in scapular winging, is typical. The weakness may progress to involve the tibialis anterior, the axial, or pelvic muscles. Sparing of the facial muscles can occur; rare subjects may present with focal weakness resulting in monomelic amyotrophy. The weakness is slowly progressive, sometimes in a stepwise fashion. About 20% of patients will need to use a wheelchair. Life expectancy is normal.

Extramuscular manifestations include high-frequency hearing loss, asymptomatic retinal telangiectasias seldom resulting in retinal exudates and detachment (Coats disease), and, in very rare cases, atrial arrhythmias.

Diagnosis

The clinical phenotype often suggests facioscapulohumeral muscular dystrophy. The diagnosis is confirmed by genetic testing. Creatine kinase values may be normal to moderately increased. A muscle biopsy is often not needed for diagnosis and may show inflammatory changes.

Treatment

Treatment is supportive with physical therapy. Surgical stabilization of the scapula may be considered when patients are unable to raise the arm above the head because of muscle weakness. Subjects with footdrop benefit from ankle-foot orthotics.

- Facioscapulohumeral muscular dystrophy is a myopathy with autosomal dominant inheritance.
- In facioscapulohumeral muscular dystrophy, symmetric weakness of the facial muscles and scapular stabilizer muscles, often resulting in scapular winging, is typical.

Limb-Girdle Muscular Dystrophies

Overview

Limb-girdle muscular dystrophies (LGMDs) are genetically heterogeneous progressive myopathies characterized by predominantly proximal muscle weakness. LGMD1 refers to LGMDs with autosomal dominant inheritance (Table 43.1), and LGMD2 refers to autosomal recessive inheritance (Table 43.2).

Epidemiology

The estimated prevalence for all forms of LGMD is 1 in 14,500 to 123,000, but the incidence of each specific LGMD is unknown.

Pathophysiology

Sarcolemmal, sarcomeric, cytosolic, and nuclear envelope protein defects can be responsible for LGMD.

Clinical Features

LGMDs present with predominantly proximal weakness and may manifest from childhood to adulthood; the progression and severity of the weakness vary in different subjects and genetic types. Bulbar and extraocular muscles are usually spared. Cardiomyopathy or cardiac conduction defects can accompany several forms of LGMD. Therefore, screening for underlying cardiac involvement is mandatory. In addition, mutations in the same gene can result not only in LGMD but also in distal myopathy or other phenotypes (Tables 43.1 and 43.2).

Diagnosis

Creatine kinase values are often increased. Muscle biopsies show signs of muscle degeneration and regeneration. Immunohistochemical studies and immunoblot can be diagnostic for some subtypes of LGMD (eg, dysferlinopathy). Gene analysis may be necessary for other subtypes (eg, anoctaminopathy or laminopathy).

Table 43.1 • Autosomal Dominant Limb-Girdle Muscular Dystrophies

LGMD	Gene	Protein	Other Phenotypes
1A	*MYOT*	Myotilin	Myofibrillar myopathy Predominant distal myopathy
1B	*LMNA*	Lamin A/C	AD or AR Emery-Dreifuss muscular dystrophy Congenital muscular dystrophy Dilated cardiomyopathy Partial lipodystrophy CMT2A Hutchinson-Gilford progeria syndrome Mandibuloacral dysplasia
1C	*CAV3*	Caveolin 3	Rippling muscle disease HyperCKemia ± myalgia Distal myopathy Dilated cardiomyopathy
1D/1E	*DNAJB6*	DnaJ homolog, subfamily B, member 6	
1E	Unknown		
1F	Unknown		
1G	Unknown		
1H	Unknown		

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; LGMD, limb-girdle muscular dystrophy.

Table 43.2 • Autosomal Recessive Limb-Girdle Muscular Dystrophies

LGMD	Gene	Protein	Other Phenotypes
2A	*CAPN3*	Calpain 3	
2B	*DYSF*	Dysferlin	Distal myopathy affecting calf muscles (Miyoshi myopathy)
2C	*SGCG*	Sarcoglycan γ	
2D	*SGCA*	Sarcoglycan α	
2E	*SGCB*	Sarcoglycan β	
2F	*SGCD*	Sarcoglycan δ	Familial cardiomyopathy, AD
2G	*TCAP*	Telethonin	
2H	*TRIM32*	Tripartite motif containing 32	
2I	*FKRP*	Fukutin-related protein	Congenital muscular dystrophy
2J	*TTN*	Titin	Tibial muscular dystrophy, AD Familial hypertrophic cardiomyopathy
2K	*POMT1*	Protein-O-mannosyltransferase 1	Congenital muscular dystrophy
2L	*ANO5*	Anoctamin 5	Distal myopathy
2M	*FKTN*	Fukutin	Congenital muscular dystrophy
2N	*POMT2*	Protein-O-mannosyltransferase 2	Congenital muscular dystrophy
2O	*POMGNT1*	Protein-O-linked mannose beta 1, 2 acetylglucosaminyltransferase	Congenital muscular dystrophy
2P	*DAG1*	Dystroglycan 1	
2Q	*PLEC1*	Plectin	Epidermolysis bullosa simplex

Abbreviations: AD, autosomal dominant; LGMD, limb-girdle muscular dystrophy.

Treatment

No definitive treatment is available. Physical therapy is helpful for avoiding development of contractures. Mechanical aids, such as cane or orthotics, improve functionality. Respiratory support and treatment of the cardiac disease are important.

- Limb-girdle muscular dystrophies (LGMDs) are genetically heterogeneous progressive myopathies characterized by predominantly proximal muscle weakness.
- LGMDs present with predominantly proximal weakness and may manifest from childhood to adulthood.
- Cardiomyopathy or cardiac conduction defects can accompany several forms of LGMD. Therefore, screening for underlying cardiac involvement is mandatory.

Congenital Muscular Dystrophies

Overview

Congenital muscular dystrophies are a group of genetically heterogeneous myopathies characterized by perinatal onset.

Pathophysiology

Extracellular matrix proteins, membrane receptors for extracellular matrix, and endoplasmic reticulum proteins can be responsible for congenital muscular dystrophy. The most common congenital muscular dystrophy is due to recessive mutations in merosin, an extracellular matrix protein.

Clinical Features

Merosin-deficient congenital muscular dystrophy manifests with facial and limb weakness and often contractures. Extensive brain white-matter disease accompanies the weakness. Structural brain abnormalities such as pachygyria and peripheral neuropathy can occur.

Diagnosis

The serum creatine kinase value is increased. Muscle histochemical studies show dystrophic changes. Muscle or skin immunostain for merosin shows total or partial merosin deficiency. Gene analysis confirms the diagnosis.

Treatment

Treatment is supportive.

- Congenital muscular dystrophies are a group of genetically heterogeneous myopathies characterized by perinatal onset.
- The serum creatine kinase value is increased in congenital muscular dystrophies.

Emery-Dreifuss Muscular Dystrophy

Overview

There are 2 types of Emery-Dreifuss muscular dystrophy (EMD). EMD-1 is caused by a mutation of the *STA* gene on chromosome Xq28, which encodes the nuclear membrane protein emerin. EMD-2 is due to a mutation of the *LMNA* gene on chromosome 1q21.23, which encodes nuclear envelope proteins lamins A and C. It is inherited in an autosomal dominant or recessive manner.

Clinical Features

EMD presents in early to middle childhood with predominant scapulohumeroperoneal (limb-girdle) distribution. In EMD-1, there is early onset of joint contractures (common at ankle, elbows, cervical spine), often before weakness. In EMD-2, contractures follow the onset of weakness. Cardiomyopathy with conduction abnormalities can occur in the 20s to 30s.

Diagnosis and Treatment

Muscle biopsy shows a dystrophic pattern with variation in muscle fiber size and increased connective tissue. Reduced or absent emerin immunostaining in muscle or skin biopsy can be found in EMD-1.

Treatment is aimed at physical therapy and prevention of complications (screening for cardiac abnormalities).

- Emery-Dreifuss muscular dystrophy (EMD) presents in early to middle childhood with predominant scapulohumeroperoneal (limb-girdle) distribution.
- In EMD-1, there is early onset of joint contractures (common at ankle, elbows, cervical spine), often before weakness.
- Reduced or absent emerin immunostaining in muscle or skin biopsy can be found in EMD-1.

Oculopharyngeal Dystrophy

Overview

Oculopharyngeal dystrophy is most commonly inherited in an autosomal dominant pattern and results in difficulty with ptosis and swallowing. There is an expanded GCG repeat in the *PABPN1* gene on chromosome 14.

Clinical Features

Symptoms begin in the fifth to sixth decade of life, and patients present with progressive ptosis and dysphagia. Extraocular muscle involvement occurs late. Proximal muscle weakness may also occur.

Diagnosis and Treatment

The creatine kinase level is usually normal. Electromyography shows typical myopathic motor units. Muscle biopsy shows dystrophic changes and rimmed vaculoes and intranuclear inclusions.

Treatment is aimed at preventing medical complications (nutritional issues with dysphagia; surgery for ptosis).

- Oculopharyngeal dystrophy is most commonly inherited in an autosomal dominant pattern and results in difficulty with ptosis and swallowing.

Myotonic Muscular Dystrophies

Overview

Myotonic dystrophy type 1 (DM1) and type 2 (DM2) are multisystem disorders inherited in an autosomal dominant pattern. DM1 is also known as Steinert disease, and DM2 is also known as proximal myotonic myopathy.

Epidemiology

DM1 is the second most common muscular dystrophy after dystrophinopathy and the most common adult-onset muscular dystrophy. DM1 has an incidence of 13.5 per 100,000 live births. The incidence of DM2 is unknown; its prevalence varies in different populations and is higher in Germany and Poland and in subjects with German or Polish ancestry.

Pathophysiology

DM1 is caused by heterozygous expansion of unstable CTG trinucleotide repeats in the 3′ untranslated region of the dystrophia myotonica protein kinase (*DMPK*) gene on chromosome 19q13.2. Longer CTG repeats are associated with more severe and earlier disease onset. The size of the repeats expands from one generation to the next, resulting in anticipation (earlier onset and more severe disease) in the successive generations.

DM2 is due to heterozygous expansion of the CCTG tetranucleotide repeats within the first introns of the zinc finger protein 9 (*ZNF9*) gene on chromosome 3q21. Unlike DM1, the size of the repeat expansion does not correlate with age at onset or disease severity in DM2. Although genetically distinct, DM1 and DM2 share the same pathogenic mechanism, which is thought to be mediated by the mutant RNA transcripts containing expanded repeats, leading to protein sequestration and abnormal splicing of many gene transcripts.

Clinical Features

DM1 can present at any age. When present at birth, the disease is called congenital myotonic dystrophy. Congenital DM1 has a high mortality due to respiratory failure and is accompanied by learning difficulty. Myotonia is usually not evident during infancy. A child with congenital DM1 almost always inherits the mutant allele from the mother.

The main symptoms of DM1 are distal muscle weakness and myotonia. These are prominent in the hands. Ptosis, facial muscle weakness, and temporalis muscle wasting are common.

DM2 manifests in the third decade of life and is characterized by proximal muscle weakness, myalgia, and less prominent myotonia, sometimes detectable only by electromyography. Anticipation is less evident clinically in DM2 than in DM1, and a congenital form of DM2 has not been reported.

Additional manifestations of DM include frontal baldness, posterior subcapsular cataracts, cardiac conduction defects, and, less frequently, cardiomyopathy, smooth muscle involvement resulting in dysphagia and pseudo-obstructions, central sleep apnea and daytime hypersomnolence, endocrinopathies (insulin resistance, primary gonadal failure), and cognitive dysfunction. The extramuscular manifestations are more common and more prominent in DM1. The disease is slowly progressive. Life expectancy is reduced in DM1, mainly because of cardiac complications.

Diagnosis

Genetic testing confirms the diagnosis of DM1 or DM2. Electromyography shows myotonic discharges. Creatine kinase values can be normal or mildly increased. Prenatal diagnosis is possible by amniocentesis or chorionic villous biopsy. Pre-implantation diagnosis is available.

Treatment

There is no treatment for the muscle weakness. Mexiletine 150 to 200 mg 3 times daily is an effective and safe antimyotonia treatment in DM1 and might be beneficial in DM2. Patients should be closely followed for development of cardiac and endocrine complications. In particular, severe electrocardiographic abnormality and diagnosis of atrial tachyarrhythmia in DM1 predict sudden death, and prophylactic permanent pacing lowers the incidence of sudden death in such cases.

- Myotonic dystrophy type 1 (DM1) is the most common adult-onset muscular dystrophy.
- DM1 is caused by heterozygous expansion of unstable CTG trinucleotide repeats.
- The main symptoms of DM1 are distal muscle weakness and myotonia.
- Life expectancy is reduced in DM1, mainly because of cardiac complications.
- Genetic testing confirms the diagnosis of DM1 or Myotonic dystrophy type 2 (DM2).

Congenital Myopathies

Congenital myopathies present early. Prenatally, fetal movements may be reduced. Postnatally, infants may have hypotonia, poor respiratory effort, inability to feed, and weakness. Unlike muscular dystrophies, the course is slow or nonprogressive. However, respiratory and orthopedic complications often develop because of weakness.

Several subtypes exist: central core, multicore, nemaline rod, and myotubular myopathy. Distinction can be made on biopsy. Treatment is supportive.

Inherited Metabolic Muscle Disorders

Overview

Defects in glycolysis and glycogen synthesis and disorders of lipid metabolism may result in muscle disorders. Glycogenoses include defects of the lysosomal and nonlysosomal glycogenolysis, and defects of glycolysis and of glycogen synthesis. Glycogenoses can affect skeletal muscle alone or in association with other tissues. Examples include acid α-glucosidase deficiency (Pompe disease) and myophosphorylase deficiency (McArdle disease). Fatty acid oxidation is a process that metabolizes fats to generate energy and occurs in the mitochondria. Carnitine palmitoyltransferase deficiency 2 is an example of a disorder of lipid metabolism resulting in muscle disease. These disorders are reviewed below and compared in Table 43.3.

Acid α-Glucosidase Deficiency (Pompe Disease)

Epidemiology

Deficiency of acid α-1,4-glucosidase (GAA), also called acid maltase, is a lysosomal storage disease inherited with autosomal recessive trait. It is also called Pompe disease or glycogen storage disease type II. The reported prevalence of the disease varies from 1 in 35,000 to 1 in 138,000 for the early-onset form and is approximately 1 in 57,000 for the adult-onset form.

Pathophysiology

GAA is a lysosomal enzyme that catalyzes the breakdown of glycogen into glucose. Its deficiency results in glycogen accumulation and autophagic vacuoles.

Clinical Features

The clinical spectrum includes 1) the infantile form characterized by hypotonia, cardiomegaly, macroglossia, possible hepatomegaly, and death due to cardiopulmonary failure occurring before age 2 years; 2) the juvenile form presenting in the first decade of life with predominant muscle weakness; and 3) the adult forms manifesting in the third or fourth decade of life with proximal muscle weakness. Respiratory muscle weakness is frequent also in the juvenile and adult forms and can be the presenting symptom. Heart involvement is infrequent in the infantile form and usually does not occur in the adult form. The residual GAA enzyme activity does not always explain the difference in phenotype.

Diagnosis

Creatine kinase values are increased. Electromyography shows myopathic motor unit potentials, fibrillation potentials, myotonic discharges, and often complex repetitive discharges. The GAA deficiency can be found in dried blood spot, muscle tissue, and skin fibroblasts. Muscle biopsy shows vacuoles containing glycogen and overreactive for acid phosphatase because of their lysosomal origin (Figure 43.3).

Treatment

Enzyme replacement therapy with alglucosidase alfa before age 6 months and before the need for ventilatory assistance improves survival and ventilator-independent survival and acquisition of motor skills and reduces cardiac mass compared with untreated controls. Enzyme replacement therapy attenuates the progression of late-onset acid α-glucosidase deficiency in most patients, but further data are required in this regard.

Myophosphorylase Deficiency (McArdle Disease)

Epidemiology

Myophosphorylase deficiency is the most common nonlysosomal glycogenosis (glycogenosis type V); its prevalence is 1 in 100,000. It is transmitted with autosomal recessive inheritance.

Table 43.3 • A Comparison of Selected Metabolic Myopathies

Myopathy	Type	Defect	Clinical Feature	Other
McArdle disease	CHO Glycogenoses	Myophosphorylase deficiency	Exercise intolerance; improves with rest Myalgia Normal strength	CK: increased Ischemic exercise test fails to show increase in lactate
Pompe disease	CHO Glycogenoses	Acid α-glucosidase (acid maltase)	Infantile: severe hypotonia and early death Juvenile and adult: proximal muscle and respiratory weakness	EMG: denervation of paraspinals Treatment: recombinant α-glucosidase
CPT deficiency 2	Lipid	CPT	Myoglobinuria and increased CK after exercise	Triggered by cold, medications, general anesthesia EMG normal between events

Abbreviations: CHO, carbohydrate; CK, creatine kinase; CPT, carnitine palmitoyltransferase; EMG, electromyogram.

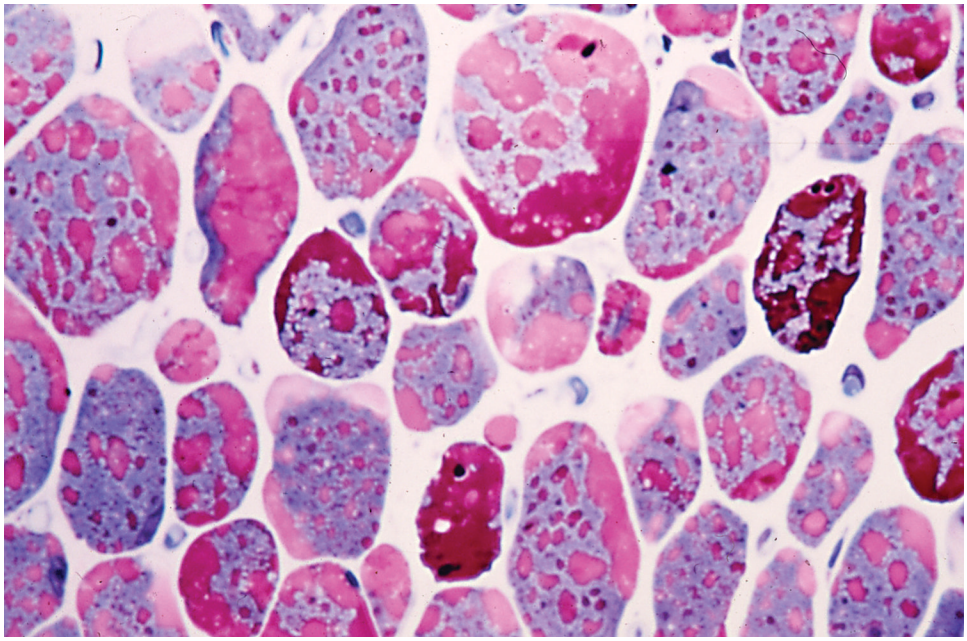


Figure 43.3 *Muscle Histopathologic Features of Infantile Acid Maltase Deficiency.*
PAS–methylene blue staining shows glycogen accumulation in skeletal muscle fibers. Note vacuoles of various sizes and shapes and filled with PAS–positive material.
(Courtesy of Andrew G. Engel, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

Pathophysiology
The deficient enzyme results in a block of muscle glycogen breakdown.

Clinical Features
Typical symptoms are exercise intolerance with premature exertional fatigue and myalgia, exercise-induced muscle contractures, and myoglobinuria. The symptoms are commonly triggered by brief exertion with isometric contractions. Many patients experience the second-wind phenomenon, which consists of ability to resume exercising with improved endurance if patients briefly rest after development of the myalgia and fatigue. Muscle strength is usually normal.

Diagnosis
The serum creatine kinase value is increased at rest in the majority of patients. The forearm ischemic exercise test causes no increase in lactate and a normal increase in ammonia (an increase in both lactate and ammonia occurs in normal muscles). Electromyography results are often normal between attacks of myoglobinuria or may show mild myopathic changes. Muscle contractures are electrically silent. Muscle biopsy confirms the diagnosis by showing the lack of phosphorylase by histochemical or biochemical studies. Subsarcolemmal glycogen deposits may be present. Analysis of the *PYGM* gene encoding myophosphorylase is available and shows homozygous or compound heterozygous mutations.

Treatment
Maximal aerobic and isometric exercise should be avoided. A high-protein and low-carbohydrate diet has been reported to be beneficial. Creatine monohydrate may improve symptoms. Oral glucose or fructose before exercise and vitamin B_6 might be beneficial.

Carnitine Palmitoyltransferase Deficiency 2

Epidemiology
The myopathic form of carnitine palmitoyltransferase II (CPTII) deficiency is the most common disorder of lipid metabolism involving the skeletal muscle. Its prevalence is unknown, and the disease may be underdiagnosed because of its mildness in some persons.

Pathophysiology
CPTII is essential for the transport of acylcarnitine across the inner mitochondrial membrane; therefore, its deficiency compromises mitochondrial fatty oxidation.

Clinical Features
CPTII deficiency has 3 clinical phenotypes: 1) lethal neonatal form, 2) severe infantile hepatocardiomuscular

form, and 3) myopathic form. The myopathic form manifests in the first or second decade of life with myalgia and paroxysmal myoglobinuria on prolonged exercise. Fasting, infections, fever, high fat intake, general anesthesia, or drugs, such as diazepam or valproic acid, can trigger rhabdomyolysis.

Diagnosis

Serum creatine kinase levels are markedly increased during an attack and normal between attacks. Electromyography findings are also normal between attacks. Plasma acylcarnitine profile is a screening tool for CPTII deficiency and often shows increase of the long-chain acylcarnitine fractions (C12 to C18), suggesting a defect in the mitochondrial β-oxidation. CPTII deficiency is usually diagnosed with enzyme assay in muscle tissue. Muscle biopsy often shows normal histologic findings or a mild increase in lipid droplets. Identification of 2 mutations in the CPTII gene confirms the diagnosis.

Treatment

A high-carbohydrate and low-fat diet provides substrate for glycolysis and ameliorates symptoms; carnitine might also be beneficial. Administration of glucose in the setting of infections, frequent meals, and avoidance of fasting and prolonged exercise can prevent the attacks of myoglobinuria. Hydration is necessary during rhabdomyolysis to prevent renal failure. Valproic acid, general anesthesia, and diazepam in high doses should be avoided, when possible.

- The juvenile and adult forms of acid α-glucosidase deficiency present with proximal muscle weakness. Respiratory muscle weakness is frequent also in the juvenile and adult forms and can be the presenting symptom.
- Enzyme replacement therapy attenuates the progression of late-onset acid α-glucosidase deficiency in most patients, but further data are required in this regard.
- Typical symptoms of myophosphorylase deficiency are exercise intolerance with premature exertional fatigue and myalgia, exercise-induced muscle contractures, and myoglobinuria.
- In myophosphorylase deficiency, the forearm ischemic exercise test causes no increase in lactate and a normal increase in ammonia (an increase in both lactate and ammonia occurs in normal muscles).
- The myopathic form of carnitine palmitoyltransferase II (CPTII) manifests in the first or second decade of life with myalgia and paroxysmal myoglobinuria on prolonged exercise.

Channelopathies

Overview

Channelopathies are disorders affecting the chloride, calcium, or sodium channels. These disorders manifest with variable neurologic symptoms. Select channelopathies are reviewed here.

Myotonia Congenita

Overview

Myotonia congenita is a nondystrophic skeletal muscle disorder due to abnormal muscle excitability; it can be inherited as an autosomal dominant (Thomsen myotonia) or recessive (Becker myotonia) trait. It is considered a channelopathy.

Epidemiology

Thomsen myotonia has a prevalence of approximately 1 in 400,000, whereas Becker myotonia is more common, with a prevalence of 1 in 25,000.

Pathophysiology

Mutations in muscle chloride channel (*CLCN1*) can lead to autosomal dominant or recessive myotonia congenita. Mutations in the alpha subunit of the skeletal muscle sodium channel (*SCN4A*) can result in sodium channel myotonia (also called potassium-aggravated myotonia) but also in paramyotonia congenita (paradoxical myotonia) or overlapping phenotypes.

Clinical Features

Myotonia congenita manifests with muscle stiffness and inability of the muscle to relax after voluntary contraction, warm-up phenomenon, muscle hypertrophy, and exacerbation of the symptoms with cold. Muscle weakness often accompanies the recessive form.

Diagnosis

Creatine kinase values are normal or mildly increased. Electromyography shows myotonic discharges. Genetic testing confirms the diagnosis.

Treatment

Mexiletine prevents involuntary repetitive firing of muscle action potentials and alleviates the symptoms. However, most patients do not require pharmacologic treatment.

Familial Periodic Paralysis

Overview

Periodic paralysis (PP) is characterized by attacks of flaccid weakness associated with reduced serum potassium level (hypokalemic PP, hypoKPP) or increased serum potassium levels (hyperkalemic PP, hyperKPP). PP can occur also in the setting of normal potassium levels (normokalemic PP).

Epidemiology

The prevalence of disease is estimated to be 1 in 100,000 for hypoKPP and 1 in 200,000 for hyperKPP.

Pathophysiology

HypoKPP is caused by mutations in the alpha 1 subunit of the skeletal muscle calcium channel (*CACNA1S*) or less frequently the alpha subunit of the skeletal muscle sodium channel (*SCN4A*). HyperKPP is caused by mutations in the *SCN4A* gene. Mutations in *SCN4A* can result also in myotonia congenita and paramyotonia congenita. Mutations in the inwardly rectifying potassium channel (*KCNJ2*) are responsible for Andersen-Tawil syndrome (see below). Familial PPs are autosomal dominant, although penetrance may vary.

Clinical Features

In hypoKPP, the paralytic attacks manifest in the first 2 decades of life; rest after exercise and carbohydrate-rich meals trigger the attacks. In hyperKPP, the paralytic attacks manifest in the first decade of life, and their duration is shorter (usually less than 2 hours). The frequency of the attacks often decreases after age 35 years; fixed weakness develops in some patients.

Andersen-Tawil syndrome is characterized by periodic paralysis (hypo-, normo-, or hyperkalemic), cardiac arrhythmias (such as long QT and ventricular arrhythmias), and dysmorphic features (eg, hypertelorism, low-set ears, micrognathia).

Diagnosis

The clinical history, measurement of potassium level during the attack, and genetic testing allow the diagnosis. Other considerations in the differential diagnosis of PP are presented in Box 43.2.

Creatine kinase values can be normal or mildly increased. Muscle biopsy may show vacuoles or tubular aggregates. Myotonic discharges may be present in *SCN4A*-associated hyperKPP. Compound muscle action potential amplitude may decrease during an attack or in response to short exercise.

Box 43.2 • Differential Diagnosis of Periodic Paralysis

Calcium abnormalities other than channelopathies
Potassium abnormalities other than channelopathies
Hypophosphatemia
Hypermagnesemia
Thyrotoxicosis
Rhabdomyolysis
Myasthenia gravis
Lambert-Eaton myasthenic syndrome

Adapted from Mowzoon N. Disorders of muscle. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 885–931. Used with permission of Mayo Foundation for Medical Education and Research.

Treatment

A high-carbohydrate diet and preventive fasting and acetazolamide and dichlorphenamide may reduce the frequency and severity of the paralytic attacks in hyperKPP.

Avoidance of high-carbohydrate food and intense exertion, potassium salts, acetazolamide, and dichlorphenamide may reduce the frequency and severity of the paralytic attacks in hypoKPP. However, acetazolamide may worsen hypoKPP because of *SCN4A* mutations.

Patients with *CACNA1S*-associated hypoKPP have an increased risk for malignant hyperthermia; therefore, preventive measures are necessary in this regard. Antiarrhythmics or pacemaker implantation and acetazolamide are the main treatment of Andersen-Tawil syndrome.

- Myotonia congenita can be inherited as an autosomal dominant (Thomsen myotonia) or recessive (Becker myotonia) trait.
- Periodic paralysis (PP) is characterized by attacks of flaccid weakness associated with reduced serum potassium level (hypokalemic PP, hypoKPP) or increased serum potassium levels (hyperkalemic PP, hyperKPP).
- The clinical history, measurement of potassium level during the attack, and genetic testing allow the diagnosis of PP.
- Patients with *CACNA1S*-associated hypoKPP have an increased risk for malignant hyperthermia; therefore, preventive measures are necessary in this regard.

Mitochondrial Myopathies

Mitochondrial myopathies are generally maternally inherited or sporadic mutations. They may be variable in phenotypic expression. Diagnosis can be made from characteristic clinical features, muscle biopsy, and genetic testing.

Common pathologic findings among mitochondrial myopathies include evidence of ragged red fibers (Figure 43.4). Abnormal mitochondria seen with modified Gomori trichrome staining show subsarcolemmal accumulation of abnormal mitochondria that appear ragged and red. On cytochrome oxidase staining, unstained muscle fibers indicate mitochondrial disease. Succinate dehydrogenase stain results in dark staining of muscle fibers with mitochondrial accumulation (ragged blue

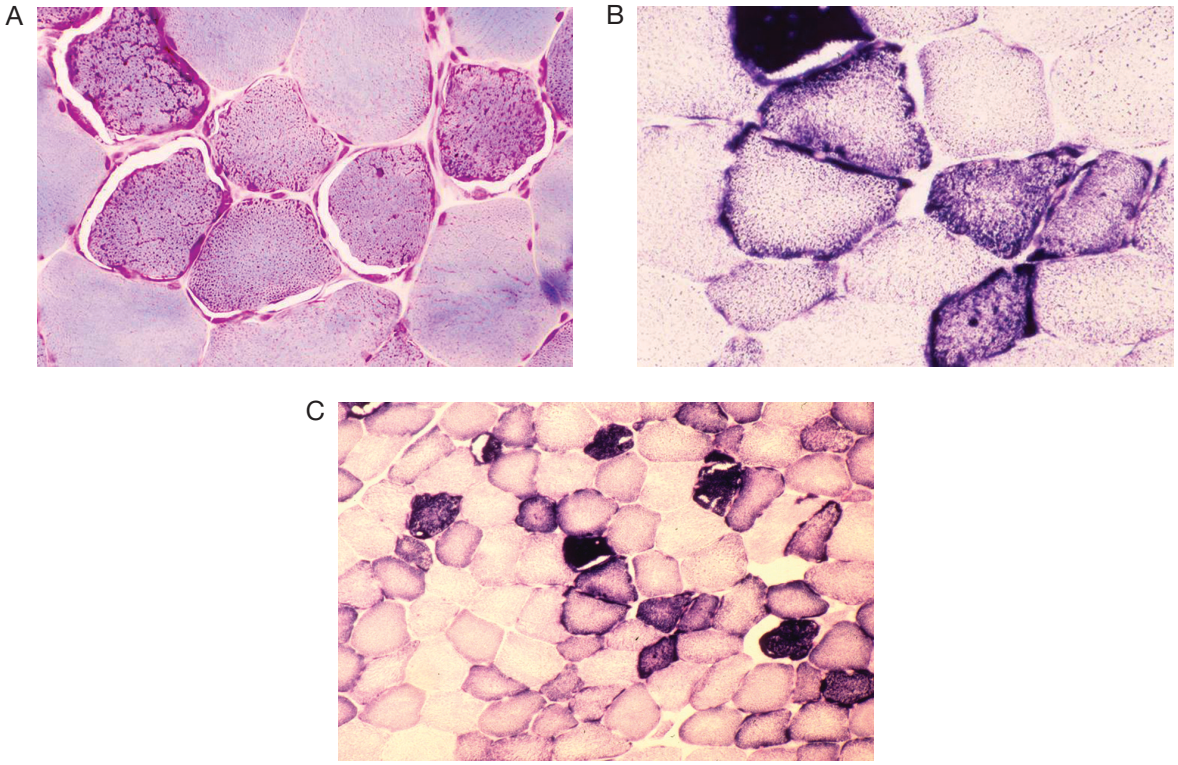


Figure 43.4 *Mitochondrial Encephalomyopathy, Lactic Acidosis, and Strokelike (MELAS) Episodes. A, Muscle biopsy shows ragged red fibers and mitochondrial aggregates with ragged red appearance on modified Gomori trichrome staining. B and C, With SDH staining, the aggregates in B appear as ragged blue fibers.*
(Courtesy of Andrew G. Engel, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

fibers). Genetic testing can be performed on muscle and serum.

Clinical characteristics and muscle characteristics of various mitochondrial diseases with muscle manifestations are discussed in Chapter 76, "Mitochondrial Disease."

- Common pathologic findings among mitochondrial myopathies include evidence of ragged red fibers.

44 Autonomic Disorders

WOLFGANG SINGER, MD

Introduction

A **practical but arbitrary** classification of autonomic disorders is used at Mayo Clinic. In modified and abbreviated form in this chapter, that classification serves to organize and provide an overview of autonomic disorders (Box 44.1). It is organized by anatomical systems and levels, although some syndromes and disorders do not fit neatly into this organization and therefore are assigned their own category. This classification quickly shows how abundant and interspersed autonomic dysfunction is among various categories of neurologic disease. Therefore, the role of this chapter is not to describe every disorder that can be associated with autonomic dysfunction. Rather, the chapter focuses on disorders with autonomic dysfunction as a predominant or important feature and thereby covers what are generally referred to as autonomic disorders.

Multiple System Atrophy

Overview

Multiple system atrophy (MSA) comprises a spectrum of sporadic, adult-onset, chronic degenerative disorders, characterized by parkinsonism, cerebellar ataxia, and autonomic failure. The term *MSA* encompasses disorders previously known as striatonigral degeneration, sporadic olivopontocerebellar atrophy, and Shy-Drager syndrome (see also Chapter 23, "Atypical Parkinsonian Syndromes"). Autonomic failure is a core feature of this disorder, and diagnostic consensus criteria require the presence of autonomic impairment for a diagnosis of MSA.

Pathology

MSA is characterized neuropathologically by glial cytoplasmic inclusions with positive synuclein staining and neuronal loss in the brainstem, cerebellum, basal ganglia, cortex, and spinal cord (Figure 44.1).

Clinical Features

Two main phenotypes of MSA are recognized: parkinsonian (MSA-P) and cerebellar (MSA-C). MSA-P is characterized by progressive, poorly levodopa-responsive bradykinesia, rigidity, and postural instability, along with a characteristic dysarthria with quivering, high-pitched speech. Tremor, if present, is typically postural, not resting. MSA-C is characterized by progressive gait and limb ataxia, ataxic speech, and cerebellar oculomotor findings. Phenotypic overlap increases as the disease progresses, and both phenotypes often develop pyramidal signs in the disease course.

Severe autonomic failure is a prominent and early finding in both phenotypes of MSA and is clinically apparent as orthostatic hypotension, supine hypertension, urinary incontinence, and erectile dysfunction in males. Formal autonomic testing is characterized by severe cardiovascular adrenergic and cardiovagal dysfunction and by characteristic preganglionic sudomotor failure with evidence of widespread anhidrosis with thermoregulatory stimuli but relatively preserved postganglionic sudomotor function. Because the postsynaptic neurons remain largely intact, baseline (supine) norepinephrine is often normal, but there is an inadequate increase with orthostatic challenge. In contrast to patients with Parkinson disease, most

Abbreviations: AAG, autoimmune autonomic ganglionopathy; DAN, diabetic autonomic neuropathy; HSAN, hereditary sensory and autonomic neuropathy; ^{123}I-MIBG-SPECT, iodine-123 meta-iodobenzylguanidine single-photon emission computed tomography; MSA, multiple system atrophy; MSA-C, cerebellar phenotype of multiple system atrophy; MSA-P, parkinsonian phenotype of multiple system atrophy; PAF, pure autonomic failure; POTS, postural orthostatic tachycardia syndrome; TTR, transthyretin

Box 44.1 • Classification of Disorders Associated With Autonomic Dysfunction

1. Autonomic disorders with brain involvement

I. Neurodegenerative disorders

A. Autonomic failure clinically prominent

Multiple system atrophy (MSA)

Lewy body disorders (Parkinson disease, dementia with Lewy bodies)

B. Autonomic failure occasionally associated

Fragile X–associated tremor/ataxia syndrome

Inherited olivopontocerebellar atrophy

Machado-Joseph disease

Progressive supranuclear palsy

Corticobasal degeneration

II. Focal CNS disorders

A. Disorders affecting cortical autonomic areas

Medial frontal lesions, insular stroke, temporal seizures

B. Disorders affecting subcortical autonomic areas

Diencephalic syndrome, limbic encephalitis, Morvan syndrome, fatal familial insomnia, hypothalamic lesions

C. Disorders affecting brainstem and cerebellum

Wallenberg syndrome, brainstem encephalitis, tumors

2. Autonomic disorders with spinal cord involvement

Traumatic tetraplegia, syringomyelia, multiple sclerosis, tumors

3. Autonomic neuropathies

I. Acute or subacute autonomic neuropathies

Autoimmune autonomic ganglionopathy

Paraneoplastic autonomic ganglionopathy

Guillain-Barré syndrome

Toxic or metabolic etiologies (botulism, porphyria, others)

II. Chronic autonomic neuropathies

A. Distal small-fiber neuropathies

B. Pure cholinergic neuropathies

Lambert-Eaton myasthenic syndrome

Chronic idiopathic anhidrosis

Adie syndrome

Chagas disease

C. Pure adrenergic neuropathies

D. Combined sympathetic and parasympathetic impairment

Amyloid neuropathy

Diabetic autonomic neuropathy

Chronic autoimmune or paraneoplastic neuropathy or ganglionopathy

Sensory neuronopathy with autonomic failure

Hereditary neuropathies (HSAN categories, Fabry disease)

Sjögren syndrome, etc

4. Disorders of reduced orthostatic tolerance

Postural orthostatic tachycardia syndrome (POTS)

Neurally mediated syncope (vasovagal, vasodepressor)

Orthostatic intolerance related to bed rest

Chronic fatigue syndrome

5. Paroxysmal vasomotor or sudomotor disorders

Paroxysmal hyperhidrosis, Raynaud disease, erythromelalgia

6. Genetic disorders of autonomic neurotransmission

Dopamine β-hydroxylase or tyrosine hydroxylase deficiency

7. Drug-induced autonomic disorders

Neuroleptic malignant syndrome, serotonin syndrome

Stimulant intoxication, sedative withdrawal

Vasoconstrictors, vasodilators, anticholinergics, diuretics, β-blockers

8. Pure autonomic failure

Abbreviations: CNS, central nervous system; HSAN, hereditary sensory and autonomic neuropathy.

Adapted from Low PA, Sandroni P, Benarroch EE. Clinical autonomic disorders: classification and clinical evaluation. In: Low PA, Benarroch EE, editors. Clinical autonomic disorders. 3rd ed. Philadelphia (PA): Wolters Kluwer Health/Lippincott Williams & Wilkins; c2008. p. 1–16. Used with permission.

patients with MSA have spared peripheral cardiac sympathetic innervation, as assessed by iodine-123 meta-iodobenzylguanidine single-photon emission computed tomography (^{123}I-MIBG-SPECT). Magnetic resonance imaging findings include putaminal atrophy and T2 hypointensity and atrophy of the pons (at times, with the characteristic "hot cross bun" sign), middle cerebellar peduncles, and cerebellum.

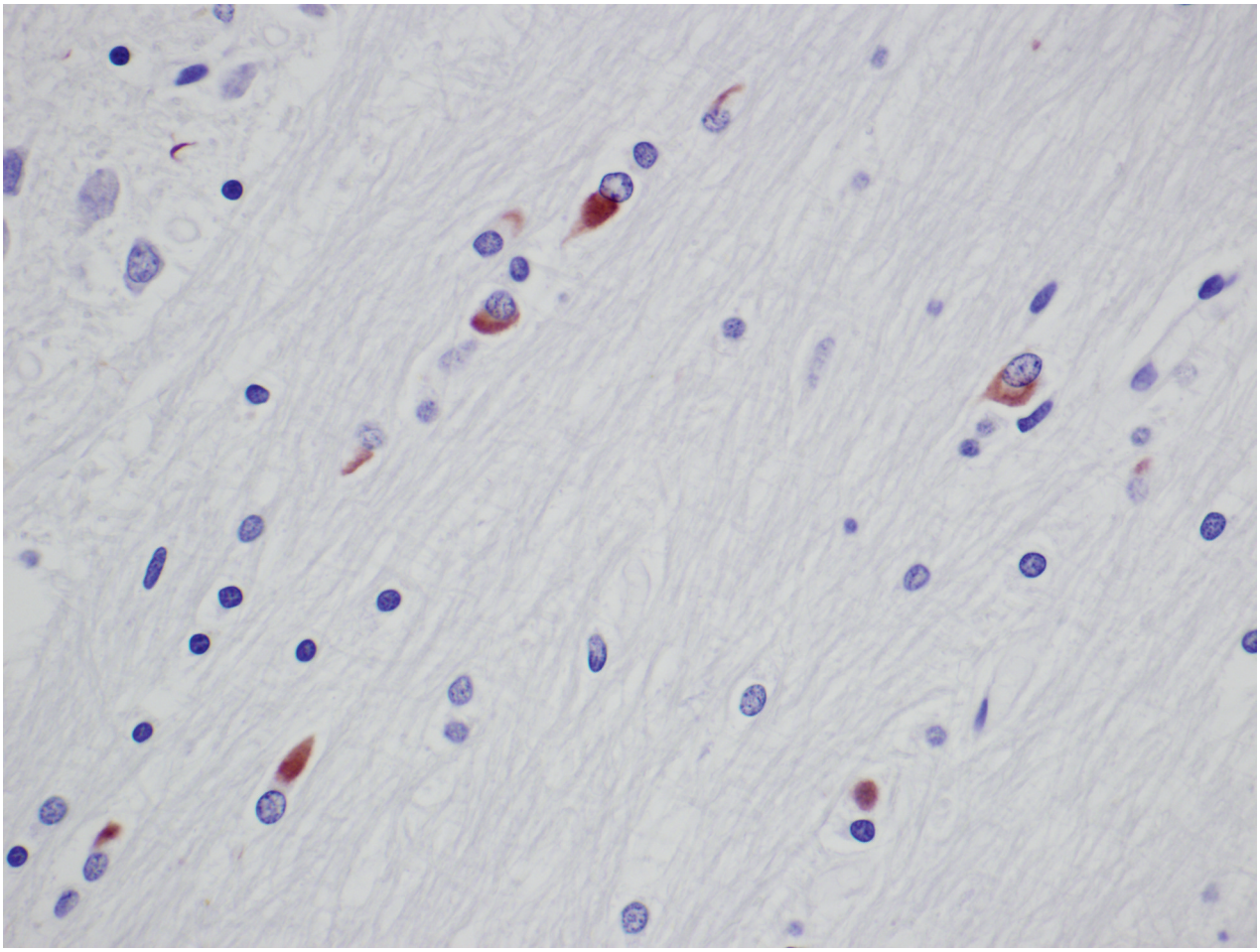


Figure 44.1 *Multiple System Atrophy (MSA).*
Synuclein-immunostained section of the pons from a patient with MSA shows glial cytoplasmic inclusions (original magnification × 600).
(Courtesy of Joseph E. Parisi, MD, Mayo Clinic, Rochester, Minnesota.)

Overlapping clinical features with other parkinsonian or cerebellar syndromes can result in diagnostic challenges. Although other synucleinopathies can also be associated with autonomic failure, the degree of autonomic impairment in Parkinson disease and dementia with Lewy bodies is almost invariably less severe (Table 44.1). Other extrapyramidal syndromes are rarely associated with notable autonomic failure.

Table 44.1 • Clinical and Pathologic Characteristics of the Synucleinopathies

Feature	MSA	PD	DLB	PAF
Autonomic failure	+++	+	++	+++
Movement disorder	+++	++	+	–
Cognitive impairment	+ or –	+	+++	–
Lewy bodies	–	+	+	+
Glial cytoplasmic inclusions	+	–	–	–

Abbreviations and symbols: DLB, diffuse Lewy body disease; MSA, multiple system atrophy; PAF, pure autonomic failure; PD, Parkinson disease; –, absent; +, ++, and +++, present to various degrees.
Adapted from Norcliffe-Kaufmann L, Kaufman H. Autonomic dysfunction. In: Kompoliti K, Verhagen L, editors-in-chief. The encyclopedia of movement disorders. Vol 1. San Diego (CA): Academic Press; c2010. p. 103–12. Used with permission.

Treatment of MSA is symptomatic. Adequate management of orthostatic hypotension and supine hypertension (Box 44.2), gastrointestinal dysmotility, and urinary dysfunction (including self-catheterization) is crucial to improve the patient's quality of life and prevent complications. Respiratory dysfunction is common and should be evaluated. Laryngeal stridor, sleep apnea, and respiratory dysrhythmia are common and can be life-threatening. MSA progresses relentlessly; patients have a mean survival of 8 to 9 years.

Box 44.2 • Symptomatic Treatment of Orthostatic Hypotension

Nonpharmacologic measures

1. Adequate fluid and salt intake
   - 6–8 glasses (about 240 mL each) of water or other fluid daily
   - Total sodium intake 150–250 mmol (10–20 g salt) daily
2. Compressive garments
   - Elastic abdominal binder and waist- or thigh-high compression stockings (to decrease venous capacitance and increase peripheral resistance)
3. Sleep in reverse Trendelenburg position
   - Head of the bed elevated 10 cm higher than the foot of the bed (to decrease supine hypertension and nocturnal diuresis)
4. Water bolus treatment
   - Drinking 1–2 glasses of water temporarily increases orthostatic blood pressure (by about 20 mm Hg for 2 h)
5. Physical counter maneuvers
   - Maneuvers involving isometric muscle contraction below the waist (toe-raising, leg-crossing, thigh contractions, etc) can help improve orthostatic blood pressure
6. Exercise
   - Modest aerobic and resistance training help orthostatic tolerance

Pharmacologic measures

1. Eliminate use of medications known to cause or exacerbate orthostatic hypotension
2. Midodrine
   - 5–10 mg 3 times daily (last dose in mid to late afternoon)
   - A vasopressor—it may exacerbate supine hypertension
3. Fludrocortisone
   - 0.1–0.2 mg once daily
   - A mineralocorticoid—it may exacerbate supine hypertension
   - Monitor and supplement potassium
4. Pyridostigmine
   - 30–60 mg 3 times daily
   - A cholinesterase inhibitor—it improves ganglionic neurotransmission
   - Does not affect supine blood pressure
   - Only modest efficacy

- Multiple system atrophy (MSA) is characterized neuropathologically by glial cytoplasmic inclusions with positive synuclein staining and neuronal loss in the brainstem, cerebellum, basal ganglia, cortex, and spinal cord.
- Severe autonomic failure is a prominent and early finding in both phenotypes of MSA and is clinically apparent as orthostatic hypotension, supine hypertension, urinary incontinence, and erectile dysfunction in males.
- Treatment of MSA is symptomatic. Adequate management of orthostatic hypotension and supine hypertension, gastrointestinal dysmotility, and urinary dysfunction (including self-catheterization) is crucial to improve the patient's quality of life and prevent complications.

Pure Autonomic Failure

Pure autonomic failure (PAF) is also a sporadic, adult-onset, chronic degenerative disorder, previously referred to as Bradbury-Eggleston syndrome or asympathicotonic hypotension. Clinical manifestations of PAF are limited to those of autonomic failure, with a characteristic lack of clinical involvement of other neurologic systems such as motor or sensory symptoms. Its precise prevalence is unknown but lower than that of MSA.

Autopsies of cases of PAF report Lewy bodies in autonomic ganglia and nerves with a marked postganglionic loss of autonomic neurons.

Clinically, the dysautonomia in PAF is characterized by progressive orthostatic hypotension. Males almost invariably report early erectile dysfunction. Symptoms of hypohidrosis, sicca symptoms, and bowel or bladder dysfunction also occur. Autonomic testing of patients with PAF generally shows widespread autonomic denervation, typically with a peripheral pattern. Supine and orthostatic norepinephrine levels are markedly decreased. In most patients, ^{123}I-MIBG-SPECT shows severely reduced cardiac sympathetic nerve terminals.

The diagnosis of PAF is one of exclusion. Chronic peripheral neuropathies with predominant autonomic involvement can mimic PAF. Some patients present with a clinical picture suggestive of PAF but years later have symptoms of parkinsonism, cerebellar ataxia, or dementia and receive a diagnosis of MSA or dementia with Lewy bodies.

Treatment of PAF is symptomatic and is generally focused on treating orthostatic hypotension and supine hypertension. PAF has a much more favorable prognosis than MSA, and life expectancy can be close to normal with proper management.

- Clinical manifestations of pure autonomic failure (PAF) are limited to those of autonomic failure, with a characteristic lack of clinical involvement of other neurologic systems such as motor or sensory symptoms.
- Autonomic testing of patients with PAF generally shows widespread autonomic denervation, typically with a peripheral pattern.

Autonomic Neuropathies

A long list of peripheral neuropathies can be associated with autonomic impairment (Box 44.1). Among those, only a few are characterized by frequent and severe autonomic dysfunction. The arguably most important of these are discussed below in more detail.

Hereditary Sensory and Autonomic Neuropathy

Hereditary sensory and autonomic neuropathy (HSAN) is a heterogeneous group of peripheral neuropathies characterized by prominent involvement of sensory and autonomic neurons. They are associated with a range of clinical presentations and molecular genetic abnormalities. The dominantly inherited forms (HSAN type 1) are characterized by a length-dependent process of the lower limbs with an onset later in life, characterized by neuropathic pain or sensory loss especially of pain and temperature.

The recessively inherited forms, which often have a congenital onset, show more generalized involvement. Among those, HSAN type 3 (also called familial dysautonomia or Riley-Day syndrome), seen predominantly in Ashkenazi Jewish infants and children, deserves special emphasis. Characteristic features are alacrima, absence of fungiform tongue papillae, kyphoscoliosis, delayed development, decreased pain sensation, corneal abrasions, orthostatic hypotension, gastrointestinal dysmotility, and autonomic crises with vomiting, hypertension, fever, and blotching of the skin. Autonomic testing shows an absence of the histamine-induced axon flare response and afferent baroreflex failure. Several causative mutations within the *IKBKAP* gene on chromosome 9 have been identified, and genetic testing (including carrier and prenatal) is available.

Treatment is supportive and includes the use of diazepam and clonidine for autonomic crises. Life expectancy is decreased owing to primarily respiratory, but also cardiac and renal, complications.

Autoimmune Autonomic Ganglionopathy

Autoimmune autonomic ganglionopathy (AAG), previously referred to as acute pandysautonomia, is an acquired autoimmune disorder that selectively affects the peripheral autonomic nervous system, typically acutely or subacutely. Patients are usually young or middle-aged adults. The clinical presentation is often dramatic and characterized by widespread autonomic failure affecting parasympathetic, sympathetic, and enteric autonomic functions. Patients with AAG have several signs and symptoms that typically emerge over days to weeks in a monophasic fashion: a combination of orthostatic hypotension, gastrointestinal dysmotility (vomiting, diarrhea, pseudo-obstruction), anhidrosis, sicca symptoms, and impaired pupillary responses and also urinary and sexual dysfunction.

Apart from the time course, the prominent gastrointestinal symptoms and pupillary abnormalities distinguish these patients from those with other neurodegenerative disorders discussed above (Table 44.2). High titers of an antibody directed against nicotinic ganglionic acetylcholine receptors are found in about 50% of patients with AAG. These antibodies have been shown to be directly pathogenetic, but seronegative patients may present with virtually identical symptoms and findings. Autonomic testing shows widespread autonomic failure; plasma norepinephrine is typically decreased with a blunted orthostatic increase. Electromyographic findings are normal.

The natural history of AAG includes a slow, incomplete recovery. Various immunosuppressive and immunomodulatory treatments, including intravenous immunoglobulin, have been reported as beneficial, but controlled trials are lacking. When patients have AAG with an insidious onset and chronic time course, it can be difficult to discern from PAF but is nevertheless important to recognize because these patients are reported to respond to immunomodulatory therapy.

Amyloid Neuropathy

Amyloid refers to fibrillary material (protein and glycosaminoglycans) deposited in various tissues with a characteristic staining pattern and a property of birefringence. Among the different types of amyloidosis, only some have been associated with amyloid neuropathy. Among those, the most common type is primary (also called AL) amyloidosis, usually consisting of monoclonal light chains. A less common type is familial amyloidosis, with precursor proteins that are most often variants of the transthyretin (TTR) molecule (thus, TTR amyloidosis is the most common familial type).

Amyloid neuropathy is a sensorimotor peripheral neuropathy, or polyradiculoneuropathy, with loss of pain and temperature sensation, paresthesias, neuropathic pain, weakness, and characteristically prominent autonomic dysfunction. The most common autonomic symptoms are

Table 44.2 • Differential Characteristics of the Classic Autonomic Disorders

Feature	MSA	PAF	AAG
Onset	Insidious	Insidious	Acute or subacute
Primary autonomic symptom	OH or urinary incontinence (or both)	OH	Multiple
Upper gastrointestinal symptoms	– or +	–	+++
Movement disorder	+++	–	–
Course	Relentless progression	Slow progression	Usually monophasic
Prognosis	Poor	Good	Good
Lesion site	Mainly preganglionic or central	Mainly postganglionic	Mainly ganglionic
Supine plasma norepinephrine	Normal	Decreased	Decreased

Abbreviations and symbols: AAG, autoimmune autonomic ganglionopathy; MSA, multiple system atrophy; OH, orthostatic hypotension; PAF, pure autonomic failure; –, absent; + and +++, present to various degrees.

orthostatic intolerance and gastrointestinal symptoms. Patients commonly have associated fatigue and weight loss. A fat aspirate may be diagnostic for amyloid, and nerve biopsy may show axonal degeneration and the characteristic deposits of homogenous, amorphous material. Autonomic function testing shows a moderately severe to severe autonomic failure in all domains, with cardiovagal function most severely affected. Electromyographic findings are characteristically those of an axonal neuropathy. Genetic testing is available for TTR amyloidosis.

The prominent somatic fiber involvement helps to differentiate this condition from other autonomic disorders discussed above. Treatment options include the following: 1) for AL amyloidosis, the use of alkylating agents, such as melphalan, and peripheral stem cell transplant and 2) for TTR amyloidosis, liver transplant and (more recently) the use of agents that inhibit conformational changes in TTR (by stabilizing the TTR tetramer), such as tafamidis, flufenamic acid, and diflunisal. Unless the patient is a suitable candidate for stem cell or liver transplant, the disease is relentlessly progressive and the prognosis is poor, particularly for patients with AL amyloidosis.

Diabetic Autonomic Neuropathy

Autonomic impairment is common among patients with diabetes mellitus. Population-based studies suggest a clinical prevalence of 14% to 18% among diabetic patients, although formal autonomic testing findings are abnormal in more than 50% of patients. Among the various types of diabetic autonomic neuropathy (DAN), 4 types are associated with a more significant degree of dysautonomia: diabetic distal sensory or sensorimotor neuropathy, diabetic distal small-fiber neuropathy, diabetic autoimmune ganglionopathy, and diabetic lumbosacral radiculoplexus neuropathy. Clinical autonomic involvement varies among these 4 types. It typically occurs in only advanced cases of distal sensorimotor neuropathy; it is clinically prominent but limited in distribution in distal small-fiber neuropathy; and it is clinically prominent with widespread abnormalities of typically subacute onset in autoimmune ganglionopathy and lumbosacral radiculoplexus neuropathy.

Symptoms of DAN range from orthostasis and regional vasomotor abnormalities to sweat loss, erectile dysfunction, and symptoms of neurogenic bowel and bladder, including gastroparesis, diarrhea, constipation, urinary hesitancy, frequency, and urgency. DAN is clearly associated with not only significant morbidity but also increased mortality, and recent data suggest that DAN is an independent mortality risk factor. Treatment approaches include prevention of progression with adequate glycemic control (although strict glycemic control appears to be associated with increased mortality), optimal treatment of other associated vascular risk factors, aerobic exercise, symptomatic treatment, and prevention and treatment of complications. Diabetic autoimmune ganglionopathy and radiculoplexus neuropathy seem amenable to immunomodulatory treatment approaches, although controlled studies are lacking.

- Hereditary sensory and autonomic neuropathy (HSAN) is a heterogeneous group of peripheral neuropathies characterized by prominent involvement of sensory and autonomic neurons.
- Autoimmune autonomic ganglionopathy (AAG), previously referred to as acute pandysautonomia, is an acquired autoimmune disorder that selectively affects the peripheral autonomic nervous system, typically acutely or subacutely.
- Patients with AAG have several signs and symptoms that typically emerge over days to weeks in a monophasic fashion: a combination of orthostatic hypotension, gastrointestinal dysmotility (vomiting, diarrhea, pseudo-obstruction), anhidrosis, sicca symptoms, and impaired pupillary responses and also urinary and sexual dysfunction.

- High titers of an antibody directed against nicotinic ganglionic acetylcholine receptors are found in about 50% of patients with AAG.
- Amyloid neuropathy is a sensorimotor peripheral neuropathy, or polyradiculoneuropathy, with loss of pain and temperature sensation, paresthesias, neuropathic pain, weakness, and characteristically prominent autonomic dysfunction.
- A fat aspirate may be diagnostic for amyloid.
- Symptoms of diabetic autonomic neuropathy range from orthostasis and regional vasomotor abnormalities to sweat loss, erectile dysfunction, and symptoms of neurogenic bowel and bladder, including gastroparesis, diarrhea, constipation, urinary hesitancy, frequency, and urgency.

Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome (POTS) affects a heterogeneous group of typically young or middle-aged, usually female patients with chronic symptoms of orthostatic intolerance (light-headedness, faintness, palpitations, and tremulousness) associated with excessive tachycardia in the upright position but without orthostatic hypotension. A diagnosis of POTS is confirmed with an autonomic study that increases the orthostatic heart rate by more than 30 beats per minute and reproduces the symptoms of orthostatic intolerance. Patients frequently have associated nonorthostatic symptoms, including fatigue, migraines, and various gastroenterologic symptoms.

The pathophysiology of POTS is poorly understood but is likely heterogeneous. The proposed underlying mechanisms include limited forms of autonomic neuropathies, an idiopathic hyperadrenergic state, physical deconditioning, and dehydration.

Treatment of POTS emphasizes physical reconditioning with aerobic activity and strengthening of the lower extremity and abdominal muscles, increased fluid and salt intake, and the use of compressive garments (stockings and an abdominal binder). Pharmacologic approaches include the use of a gentle β-blockade, vasoconstrictors (midodrine), and mineralocorticoids. The long-term prognosis is generally favorable, with about 60% of patients having normal function at 4 years of follow-up.

- A diagnosis of postural orthostatic tachycardia syndrome (POTS) is confirmed with an autonomic study that increases the orthostatic heart rate by more than 30 beats per minute and reproduces the symptoms of orthostatic intolerance.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

VII.1. Where do alpha motor neurons originate?
- a. Dorsal columns of the spinal cord
- b. Lateral white matter of the spinal cord
- c. Anterior gray matter of the spinal cord
- d. Frontal lobe gray matter of the brain
- e. Lateral gray matter of the spinal cord (intermediolateral cell column)

VII.2. Where are large and small peripheral nerve fibers most immediately contained?
- a. Myelin
- b. Endoneurium
- c. Perineurium
- d. Epineurium
- e. Neuropil

VII.3. In the peripheral autonomic nervous system, what is acetylcholine the primary neurotransmitter of?
- a. All preganglionic synapses and parasympathetic postganglionic synapses
- b. Sympathetic preganglionic synapses and postganglionic synapses
- c. Parasympathetic preganglionic synapses and postganglionic synapses
- d. Parasympathetic preganglionic synapses and all postganglionic synapses
- e. All preganglionic synapses and all postganglionic synapses

VII.4. What lesion is compatible with loss of pain and temperature sensation on the right side below the level of the umbilicus, left leg weakness, and loss of proprioception in the left leg?
- a. Anterior spinal artery occlusion with a ventral cord syndrome at the T10 level
- b. Central cord syndrome in the cervical spine
- c. Cauda equina syndrome
- d. Subacute combined degeneration of the spinal cord
- e. Left T10 hemicord syndrome (Brown-Séquard syndrome)

VII.5. Short-segment intramedullary T2-weighted hyperintensity in the cervical cord is most consistent with which of the following?
- a. Multiple sclerosis
- b. Neuromyelitis optica
- c. Paraneoplastic myelopathy
- d. Sarcoidosis
- e. Spinal dural arteriovenous fistula

VII.6. Increased T2-weighted signal in the dorsal columns is most typical of which of the following?
- a. Zinc deficiency
- b. Copper toxicity
- c. Vitamin B_1 deficiency
- d. Vitamin E toxicity
- e. Nitrous oxide toxicity

VII.7. The most common mutation associated with familial amyotrophic lateral sclerosis involves which gene?
- a. *SOD1*
- b. *FUS*
- c. *ALS2*
- d. *C9orf72*
- e. *TARDP*

VII.8. A patient with amyotrophic lateral sclerosis begins to have difficulty with memory and executive dysfunction. What is the most likely diagnosis?
- a. Pseudobulbar affect
- b. Depression
- c. Frontotemporal dementia
- d. Dementia with Lewy bodies
- e. Alzheimer dementia

VII.9. In patients with amyotrophic lateral sclerosis, what has riluzole been shown to do?
- a. Stabilize progression
- b. Extend mean survival by 3 to 4 months
- c. Produce a modest but significant improvement in functional status
- d. Have no benefit
- e. Extend time of independence with activities of daily living by 12 to 15 months

VII.10. The most common mutation causing axonal hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease) involves which gene?
- a. *PMP22*
- b. *MPZ*
- c. *MFN2*
- d. *GJB1*
- e. *TTR*

VII.11. Liver transplant is a treatment option for polyneuropathy associated with which of the following?
- a. Gelsolin gene mutation
- b. Apoprotein A gene mutation
- c. α-Galactosidase deficiency
- d. Transthyretin gene mutation
- e. *ABCA1* mutation

VII.12. A 25-year-old man presents with a painful sensory neuropathy with distal hypohidrosis affecting the hands and feet. His grandfather had similar symptoms, including chronic renal insufficiency and heart failure, and died after a large ischemic stroke. On examination you note purple maculopapular raised lesions in the inguinal region. Testing for a mutation in which gene is most likely to be abnormal?
a. α-Galactosidase
b. *ABCA1*
c. Phytanoyl-CoA hydroxylase
d. *PMP22*
e. Transthyretin

VII.13. What is the most sensitive test in the confirmation of the diagnosis of ocular myasthenia gravis?
a. Acetylcholine receptor binding antibody titer
b. 2-Hz repetitive nerve stimulation of the facial motor nerve
c. Edrophonium testing
d. Anti-MuSK antibody titer
e. Single-fiber electromyography (EMG) of the orbicularis oculi muscle

VII.14. A 45-year-old man presents with limb weakness (proximal muscles of the legs more than the arms). He has noticed recently that he becomes extremely light-headed upon standing. On examination, he has weakness in the proximal muscles of the limbs and is areflexic, although this seems to improve somewhat on repeated testing. On EMG, he has very low-amplitude compound muscle action potentials (CMAPs) (<50% of normal). There is abnormal decrement of the CMAP on 2-Hz repetitive nerve stimulation of the spinal accessory motor nerve, although after the patient exercises for 10 seconds, the CMAP amplitude increases by more than double. Which confirmatory test should be performed?
a. Acetylcholine receptor binding antibody titer
b. P/Q-type calcium channel antibody titer
c. Edrophonium testing
d. Anti-MuSK antibody titer
e. Single-fiber EMG of the orbicularis oculi muscle

VII.15. The mechanism of action of 3,4-diaminopyridine (3,4-DAP) includes which of the following?
a. Inhibition of the enzymatic degradation of acetylcholine
b. Enhanced cross-linking and stabilization of postsynaptic acetylcholine receptor complexes
c. Prolongation of the open time of presynaptic calcium channels
d. Enhanced clearance of P/Q-type calcium channel antibodies
e. Postsynaptic end plate potential stabilization

VII.16. The use of corticosteroids in Duchenne muscular dystrophy is supported by evidence that they do which of the following?
a. Independently and significantly prolong survival time
b. Delay respiratory and cardiac impairment
c. Have no significant long-term side effects
d. Prevent scoliosis and the need for spinal fusion
e. Enhance the delivery of gene therapy

VII.17. The most common congenital muscular dystrophy is associated with mutations in which of the following genes?
a. Fukutin
b. Collagen VI
c. Emerin
d. Merosin
e. Fukutin-related protein (*FKRP*)

VII.18. A 35-year-old woman presents with weakness of the proximal muscles of the legs and shortness of breath. EMG shows fibrillation potentials and myotonic discharges in paraspinal muscles with myopathic motor unit potentials in proximal muscles. Muscle biopsy shows vacuoles containing glycogen that overreact for acid phosphatase. What does the available treatment include?
a. Corticosteroids
b. Intravenous immunoglobulin (IVIG)
c. Alglucosidase alpha enzyme replacement therapy
d. Physical and occupational therapy without disease-specific treatment
e. Dysferlin gene therapy

VII.19. A 75-year-old man presents with a 2-year history of progressive orthostatic intolerance, urinary incontinence, and erectile dysfunction. On examination, he has a postural tremor without resting tremor, bradykinesia, and "shaky" slurred speech. He has increased tone in the limbs. The pull test is abnormal 3 out of 3 times. What results are expected on autonomic testing?
a. Widespread anhidrosis with preserved sudomotor function
b. Reduced supine norepinephrine levels with no response to orthostatic challenge
c. Normal cardiovascular adrenergic and cardiovagal function
d. Normal tilt-table testing
e. Abnormal peripheral cardiac sympathetic innervation on single-photon emission computed tomography (SPECT)

VII.20. A 37-year-old man presents with acute onset of syncope on standing, episodic vomiting, diarrhea and pseudo-obstruction, diffuse lack of sweating, dry eyes and dry mouth, sensitivity to light with sluggish pupillary reactivity, and erectile dysfunction and bladder dysfunction. What would further testing show?
a. A chromosome 9 *IKBKAP* mutation
b. "Hot cross bun" sign in the pons on magnetic resonance imaging of the brain
c. Normal levels of supine plasma norepinephrine with no response to orthostatic challenge
d. Intraneural amorphous material showing apple-green birefringence on nerve biopsy
e. Elevated titers of nicotinic ganglionic acetylcholine receptor antibody

VII.21. On postmortem examination, a case of severe pandysautonomia has Lewy bodies in autonomic ganglia. No glial cytoplasmic inclusions were found. There was no history of cognitive impairment or bradykinesia, rigidity, tremor, or ataxia. These findings are consistent with which diagnosis?
a. Cerebellar phenotype of multiple system atrophy (MSA-C)
b. Parkinsonian phenotype of multiple system atrophy (MSA-P)
c. Parkinson disease
d. Pure autonomic failure
e. Dementia with Lewy bodies

Answers

VII.1. Answer c.
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VII.2. Answer b.
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VII.4. Answer e.
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VII.14. Answer b.
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VII.15. Answer c.
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Section
VIII

Clinical Disorders of the Cranial Nerves and Brainstem

Carrie E. Robertson, MD, *editor*

45 Neuro-ophthalmology: Visual Fields

JACQUELINE A. LEAVITT, MD

Introduction

Visual field testing is an important part of the assessment of the afferent visual system. This chapter reviews the clinical process of visual field evaluation and the localization of lesions that affect the visual system. The anatomy of the afferent visual system is reviewed in Volume 1, Chapter 13, "Cranial Nerves I and II."

Visual Field Definition and Testing

The visual field can be thought of as an island with an outer edge, beyond which one cannot see, and an elevated center. The normal extent of the peripheral field of vision from the center is 90° to 100° temporally, 75° inferiorly, and 60° nasally and superiorly (Figure 45.1). Visual fields are subjective and should be considered only 1 part of the examination of the visual pathways.

Visual Field Testing Terminology

Kinetic describes the target moving from the unseen to the seen area of the field. *Static* refers to light increasing in intensity but not moving. Moving targets are more readily seen than stationary targets.

Informal Visual Fields

Confrontation visual field testing is quick and easy (finger counting in each quadrant; each eye is tested individually). Unfortunately, confrontation visual field results are not very sensitive; defects identified with confrontation visual field tests are usually present, but defects may not be identified. A more sensitive test may be the use of a red object to determine whether there is relative desaturation in the visual fields (temporal vs nasal, inferior vs superior).

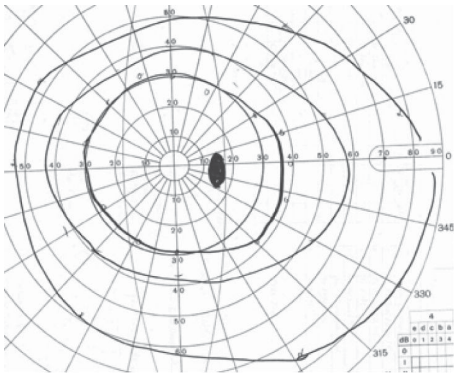

Figure 45.1 *Goldmann Visual Field, Right Eye. This normal visual field shows the extent of the periphery in all quadrants with 3 isopters, 3 different sizes of targets, and the normal blind spot.*

Formal Visual Field Testing

Kinetic visual field tests (eg, Goldmann perimetry, tangent screen testing) involve a moving target that delineates the extent of the peripheral vision. The outer edge at which an object is seen is noted. Goldmann perimetry, performed with the technician moving a lighted spot, can test the peripheral extremes (Figure 45.1). The tangent screen test is performed with the patient sitting 1 m away from the test target while the technician moves white or colored disks of various sizes from the unseen field into the area in which the patient can see the field, which the patient notes aloud (Figure 45.2). (This test measures the central 30° of the visual field.)

Automated (computerized) visual field tests are simple in concept but difficult to perform. They are typically static visual field tests involving light sources of increasing brightness that randomly appear at various points in the periphery. Constant straight-ahead fixation is necessary. Results of a static visual field show multiple data points that register

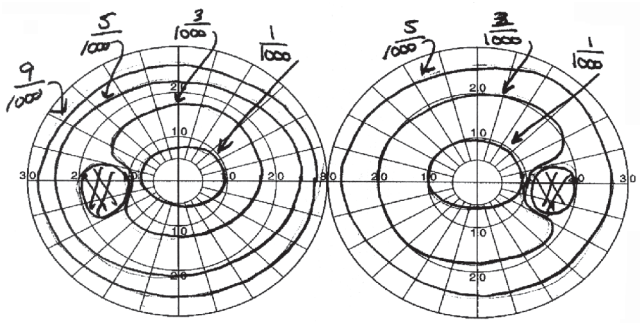

Figure 45.2 *Tangent Screen With Different Target Size Isopters.*

as normal or abnormal, with a level of abnormality noted. The computer generates the patient's responses and determines the level of abnormality by comparison with age-matched normative data. Automated visual fields have several parameters that are helpful in determining reliability of the visual field performance (test time, fixation losses, and false-positive and false-negative results).

Visual Field Pathologic Terminology

The anatomy of the visual pathway is reviewed in detail in Volume 1, Chapter 13, "Cranial Nerves I and II." Figure 45.3 relates visual field defects to the anatomy of the visual system. When dysfunction of this pathway occurs, specific terminology is used to describe the defects.

A *scotoma* is an area of missing visual field with surrounding intact visual field. The optic disc has no photoreceptors and is represented by the normal blind spot (Figure 45.1).

Incongruous fields are dissimilar between the 2 eyes. *Congruous fields* are more similar between the 2 eyes. In general, the more congruous the visual field defect, the more posteriorly the pathology is located.

Hemianopia describes half the visual field missing in each eye, and *quadrantanopia* describes one-fourth of the visual field missing. *Homonymous* means that the visual field defect is in the same right-and-left orientation in both eyes—for example, a visual field defect involving the left half of each eye's visual field is called a left homonymous hemianopia (Figure 45.4). With an *altitudinal defect*, the inferior or superior half of a visual field is missing (Figure 45.5).

Visual Field Abnormalities by Location

General Constriction or Depression of the Visual Field

Refractive error, cataract, dry surface, or corneal disease may cause general constriction or depression of the visual field.

External

Eyelid lesions or a drooping upper eyelid (*blepharoptosis*) may block some of the superior portion of the visual field.

Retina

Retinal dysfunction from photoreceptor diseases (retinal detachment, scarring, myelinated nerve fiber, etc) can cause visual field defects that correspond to the affected retinal area. These defects would not necessarily be limited to 1 side of the vertical or horizontal meridians. A ring scotoma affecting the middle of the visual field is characteristic of retinal diseases such as autoimmune retinopathy or retinitis pigmentosa (Figure 45.6). The central retinal artery divides into superior and inferior retinal branches. Therefore, vascular disease of the retina may produce altitudinal defects (Figure 45.5).

Optic Nerve

Optic neuritis and compressive lesions tend to be associated with monocular central visual field defects, such as central scotomas (Figure 45.7) or cecocentral scotomas. Ischemic optic neuropathy and optic neuritis may be associated with altitudinal defects. An arcuate scotoma (Figure 45.8) is a comma-shaped defect often associated with glaucoma, but it may also occur with optic neuritis, anterior ischemic optic neuropathy, optic nerve drusen, and branch retinal artery or vein occlusions. These entities may also cause nasal visual field loss. An enlarged blind spot (Figure 45.9) may be associated with optic disc swelling.

Chiasm Defect

Visual field information crosses within the chiasm so that the right side of the brain sees to the left and vice versa. Bitemporal field defects can occur from chiasmal compression or infiltration because the crossing fibers are affected (Figure 45.10). A classic example would be compression of the optic chiasm inferiorly by a pituitary mass. The inferior nasal fibers of 1 optic nerve cross ventrally into the contralateral optic nerve, known as the Wilbrand knee (Figure 45.3). Occasionally, compression anterior to the chiasm affects the optic nerve of 1 eye (causing ipsilateral central scotoma) and the crossing inferior nasal fibers of the other optic nerve (causing contralateral superior temporal visual field defect). This is known as junctional syndrome (Figure 45.11). At the chiasm and beyond, visual field defects do not cross the vertical meridian.

Optic Tracts

Lesions in the optic tracts produce homonymous visual field defects on the contralateral side.

Lateral Geniculate Body

The lateral geniculate body has 6 layers and a dual blood supply that includes the anterior choroidal artery (a branch

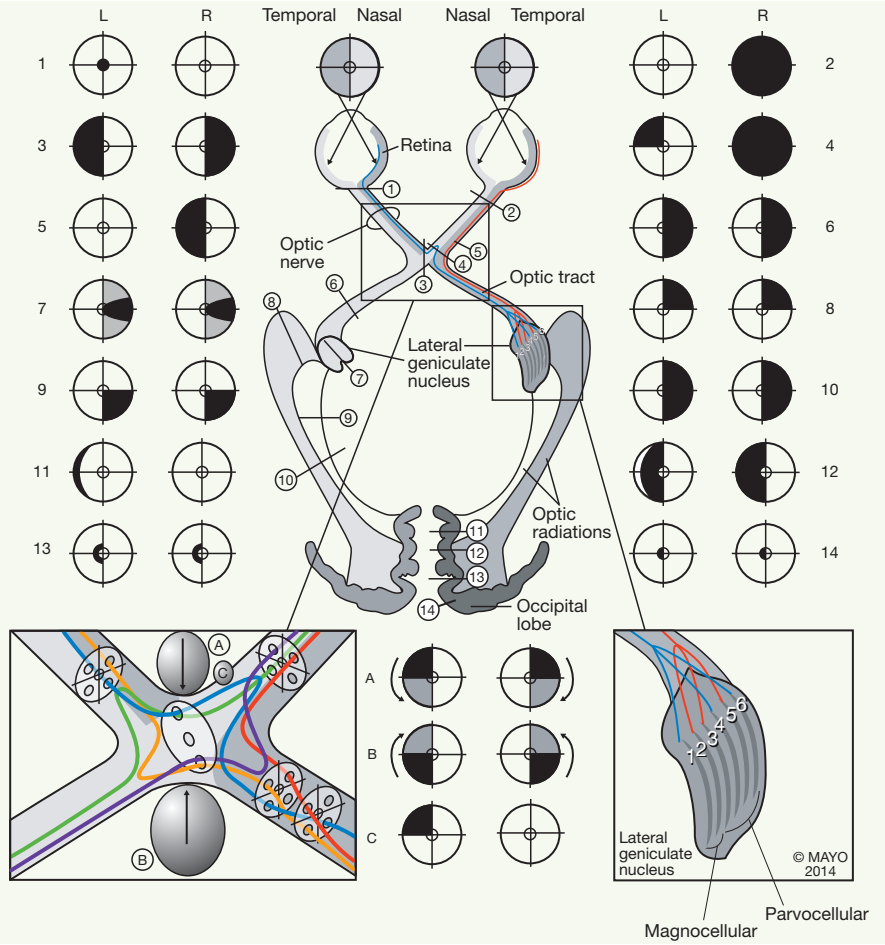

Figure 45.3 *Anatomy of the Visual System and the Associated Visual Field Defects.*
1, Central scotoma from optic neuropathy. 2, Unilateral blindness due to optic nerve transection. 3, Bitemporal hemianopia from optic chiasmal lesion, which may or may not be macular splitting. Left lower inset and lower center: A, Lesion anterior to chiasm, with a more prominent defect in the bitemporal upper quadrants early on and eventually evolving to a full bitemporal field defect; B, lesion posterior to the chiasm, with a more prominent defect in the bitemporal lower quadrants early on and eventually evolving to a full bitemporal field defect. 4, Anterior chiasm or junctional syndrome is characterized by an ipsilateral optic nerve defect and a contralateral superior temporal field defect due to a posterior optic nerve lesion involving the ipsilateral optic nerve and contralateral crossing fibers of the Wilbrand knee (contralateral lower nasal fibers represent the upper temporal field); this is to be differentiated from the junctional syndrome of Traquair, represented in lesions C in the left lower inset and lower center. 5, Unilateral nasal field defect due to an ipsilateral lateral optic nerve lesion. 6, Macular-splitting homonymous hemianopia from a complete optic tract lesion. 7, Complete (gray and black) homonymous hemianopia and incomplete (black only or gray only) field defects due to lateral geniculate body lesions. Gray represents quadruple sectoranopia *due to vascular lesions in the distribution of the anterior choroidal artery; black represents a* horizontal homonymous sector defect *due to vascular lesions in the distribution of the posterior lateral choroidal artery. 8, Right superior homonymous quadrantanopia (pie-in-the-sky) deficits from a left temporal lesion affecting underlying optic radiations (lower bundle is called the Meyer loop as fibers pass lateral to the temporal horn of the lateral ventricle). 9, Right inferior homonymous quadrantic (pie-on-the-floor) deficits from a left parietal lesion affecting the underlying optic radiations (upper bundle). 10, Macular-splitting homonymous hemianopia from a lesion affecting both superior and inferior optic radiations (usually large hemispheric insults). 11, Temporal crescent (half-moon) syndrome due to a lesion at the anterior tip of the striate cortex. 12, Macular-sparing homonymous hemianopia due to a lesion involving the entire medial occipital lobe, sparing the anterior tip (representing the contralateral temporal crescent). 13, Partial macular-sparing homonymous hemianopia affecting the most posterior portion of the medial occipital lobe, sparing the posterior poles (macular representation). 14, Macular-splitting homonymous field defect limited to the macular distribution and no involvement of peripheral visual fields (could be due to a lesion of the unilateral posterior occipital pole). Right lower inset: 1–6, Layers of the lateral geniculate nucleus. L indicates left; R, right.*
(Adapted from Freeman WD, Mowzoon N. Neuro-ophthalmology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 83–126. Used with permission of Mayo Foundation for Medical Education and Research.)

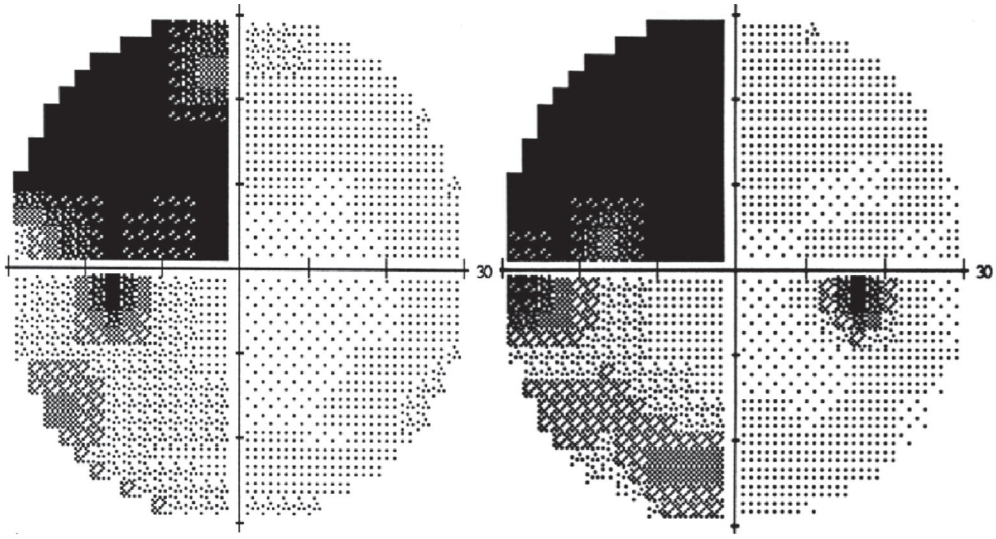

Figure 45.4 *Left Incomplete Homonymous Hemianopia.*
A pie-in-the-sky visual defect in the temporal lobe is depicted.

from the internal carotid artery) and the lateral choroidal artery (a branch from the posterior cerebral artery). Arterial occlusions can produce rather interesting visual field defects. An occlusion of the posterior choroidal artery produces a homonymous hemianopia of the horizontal sectors only, appearing wedge-shaped or triangular. Occlusion of the anterior choroidal artery may produce a *quadruple sectoranopia*, which is a homonymous defect sparing these same horizontal wedge-shaped areas (Figure 45.12).

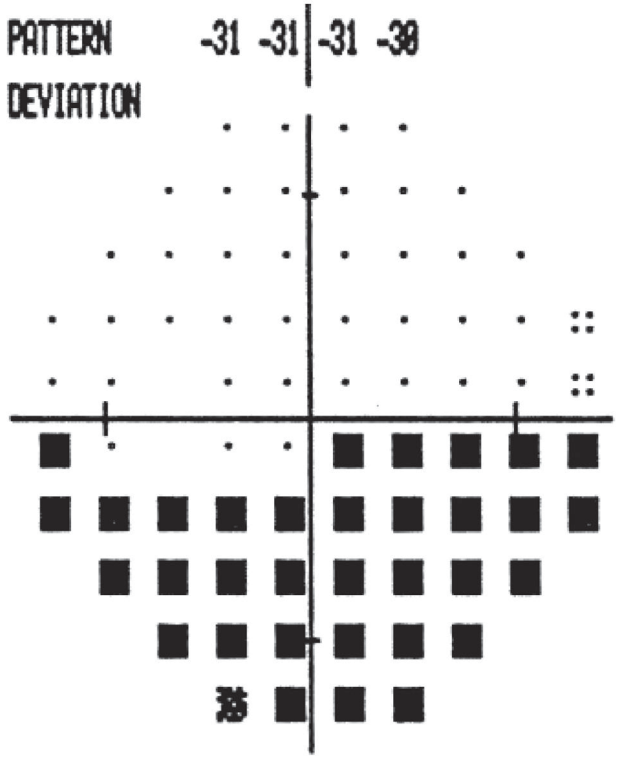

Figure 45.5 *Inferior Altitudinal Defect.*
Associations include ischemic optic neuropathy, retinal vascular occlusion, and optic neuritis.

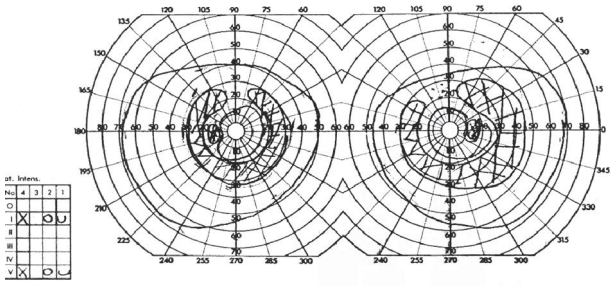

Figure 45.6 *Ring Scotoma in Both Eyes From Retinopathy.*

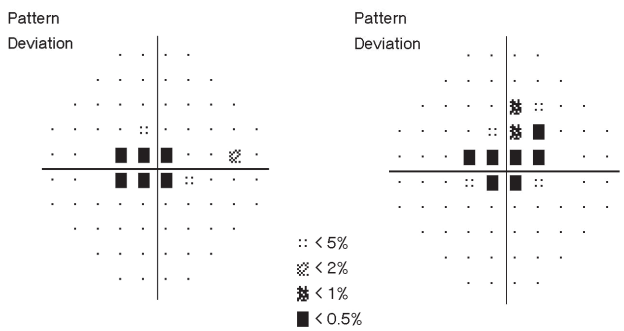

Figure 45.7 *Central Scotoma in Both Eyes.*
Associations include optic neuropathy and maculopathy.

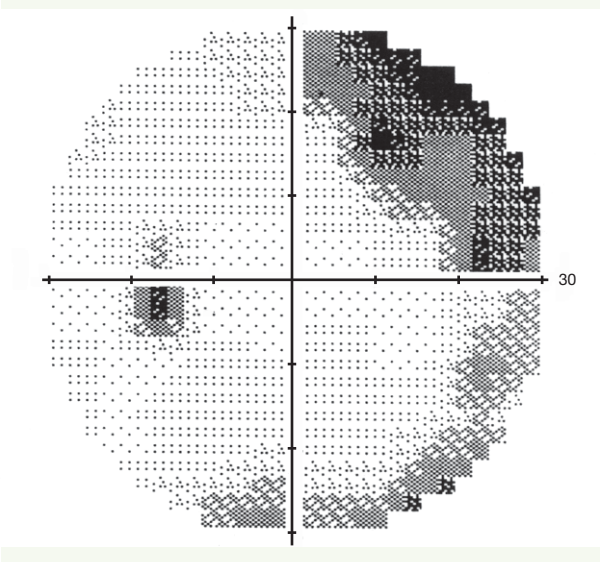

Figure 45.8 *Arcuate Scotoma in Left Eye. Associations include glaucoma and optic neuropathy.*

Optic Radiations

Fibers from the lateral geniculate separate so that fibers representing the superior visual field (Meyer loop) pass through the temporal lobe and project to the occipital lobe just inferior to the calcarine fissure. Lesions here cause a contralateral homonymous quadrantanopia or pie-in-the-sky deficit (Figure 45.4). Inferior visual field fibers travel in the inferior optic radiations through the parietal lobe to the occipital lobe superior to the calcarine fissure. Lesions of these fibers would cause a contralateral inferior homonymous quadrantanopia.

Occipital Lobe

The anatomy of the occipital lobe is organized with the more posterior portion corresponding to the more central portion of the visual field, and the more anterior portion of the occipital lobe corresponds to the more peripheral portion of the field (Figure 45.3). An occipital lesion affecting only the anterior portion of the primary visual cortex could create a temporal crescent visual field defect in the contralateral eye (Figure 45.3; defect 11), and a lesion of the primary visual cortex sparing this anterior portion may result in homonymous hemianopia sparing this temporal crescent (Figure 45.3; defect 12). The principal source of arterial blood supply to the primary visual cortex is the posterior cerebral artery; however, the middle cerebral artery overlaps with the macular representation of the visual cortex. Therefore, occlusion of 1 posterior cerebral artery may result in contralateral homonymous hemianopia with or without macular sparing (Figure 45.13). Occlusion of the tip of the basilar artery could affect both occipital lobes, causing complete cortical blindness. In *Anton syndrome*, cortical blindness is associated with denial of the neurologic impairment.

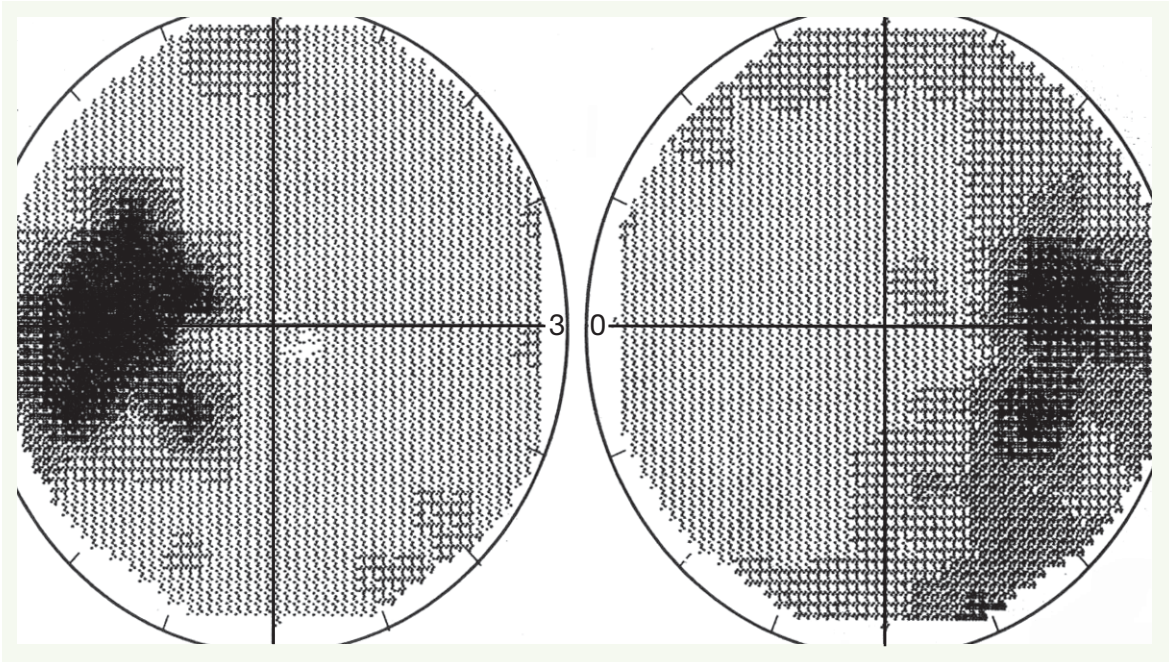

Figure 45.9 *Enlarged Blind Spots in Both Eyes. Associations include optic disc swelling.*

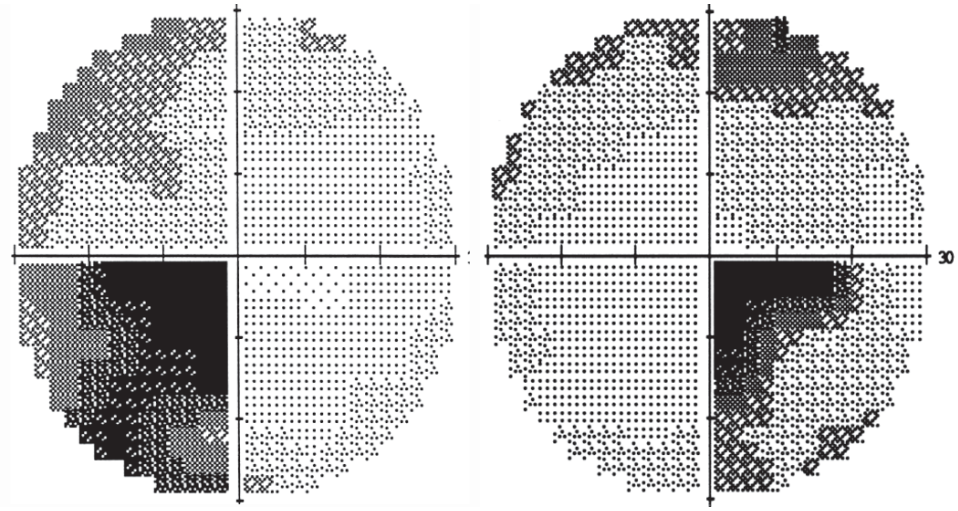

Figure 45.10 *Bitemporal Field Defects That Are Denser Inferiorly. Associations include superior chiasm lesions.*

Nonorganic Fields

Fields that are inconsistent from examination type to examination type or from time to time may be nonorganic. Tangent screen testing in which the visual field does not expand when the test distance increases from 1 m to 2 m is nonorganic. Testing saccades with objects presented outside the "field of view" may distract the patient from the field nature of the test; if patients accurately look to the object within the area that they claim not to see, this is nonorganic. Observation of walking can also give clues to visual field defects. People with true visual field defects are more likely to have searching head or eye movements to avoid bumping into objects.

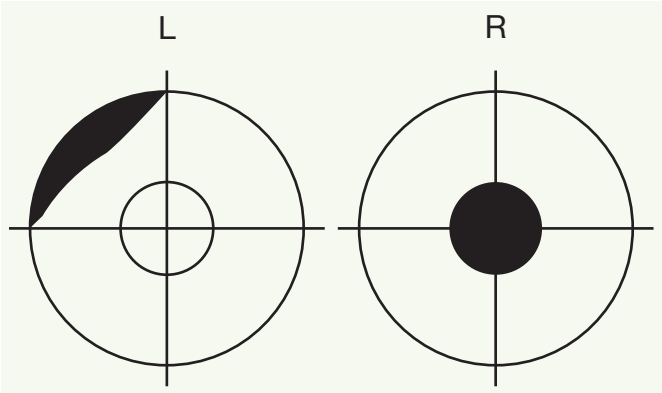

Figure 45.11 *Junctional Syndrome. L indicates left; R, right.*
(Adapted from Freeman WD, Mowzoon N. Neuro-ophthalmology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 83–126. Used with permission of Mayo Foundation for Medical Education and Research.)

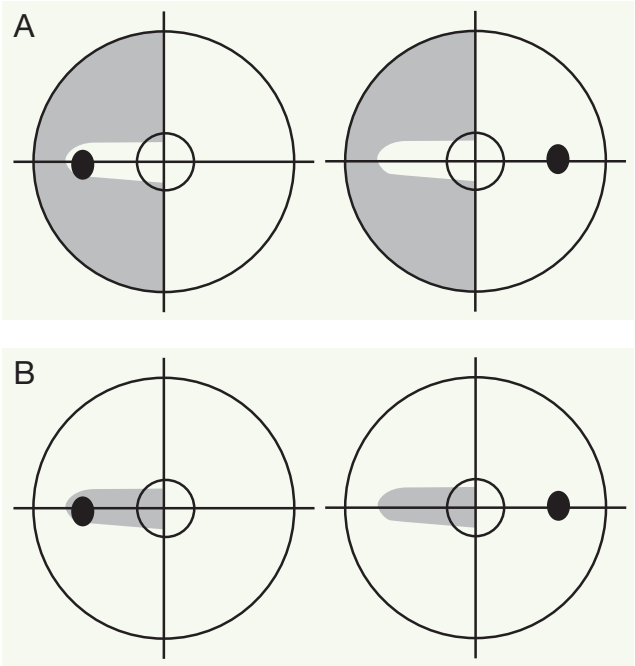

Figure 45.12 *Quadruple Sectoranopia. A, This left quadruple sectoranopia resulted from a lateral geniculate body infarction caused by occlusion of the right anterior choroidal artery. B, This horizontal homonymous sector defect resulted from occlusion of the right posterior lateral choroidal artery. The black dots represent the physiologic blind spots. The circles represent the fovea.*
(Adapted from Freeman WD, Mowzoon N. Neuro-ophthalmology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 83–126. Used with permission of Mayo Foundation for Medical Education and Research.)

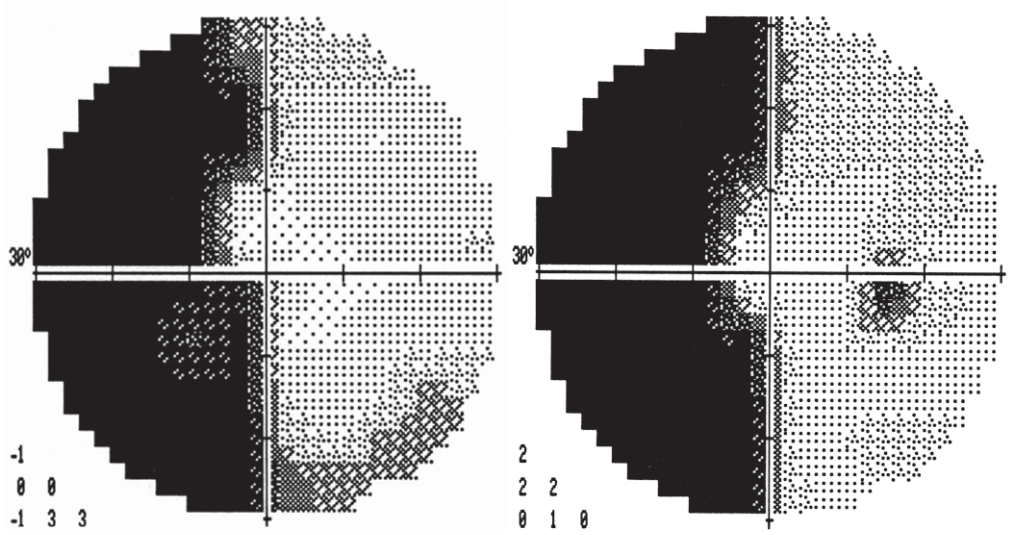

Figure 45.13 *Left Homonymous Hemianopia With Macular Sparing. Associations include posterior occipital lesions.*

- Retinal dysfunction from photoreceptor diseases can cause visual field defects that correspond to the affected retinal area. These defects would not necessarily be limited to 1 side of the vertical or horizontal meridians.
- Optic neuritis and compressive lesions tend to be associated with monocular central visual field defects, such as central scotomas or cecocentral scotomas.
- Bitemporal field defects can occur from chiasmal compression or infiltration because the crossing fibers are affected.
- The inferior nasal fibers of 1 optic nerve cross ventrally into the contralateral optic nerve, known as the Wilbrand knee.
- The lateral geniculate body has 6 layers and a dual blood supply that includes the anterior choroidal artery (a branch from the internal carotid artery) and the lateral choroidal artery (a branch from the posterior cerebral artery).
- The principal source of arterial blood supply to the primary visual cortex is the posterior cerebral artery; however, the middle cerebral artery overlaps with the macular representation of the visual cortex. Therefore, occlusion of 1 posterior cerebral artery may result in contralateral homonymous hemianopia with or without macular sparing.

46 Neuro-ophthalmology: Disorders of Visual Perception, Pupils, and Eyelids

KELLY D. FLEMMING, MD

Introduction

Visual loss may develop acutely, subacutely, or insidiously. The course may be transient, static, or progressive. This chapter reviews the causes, diagnosis, and treatment of various disorders resulting in visual loss or abnormal visual perception. In addition, the chapter reviews clinical disorders of the eyelids and pupils.

Disorders of Visual Perception

General Approach to Patients With Complaints About Visual Perception

Disorders of visual perception involve visual acuity, color perception, visual field defects, and other visual changes. Historic information and physical findings on examination can help to localize the problem and define the cause.

When patients complain of visual loss, it is important to determine the problem's duration (acute, subacute, or chronic) and course (transient, static, or progressive) and whether it is unilateral or bilateral. The investigation should include questions about provoking factors (bright light, positional changes, and heat) and relevant past medical history (migraines, multiple sclerosis, vascular risk factors, and medications). Some patients may also complain of positive visual phenomena (Table 46.1). The differential diagnoses for transient and persistent visual loss are listed in Tables 46.2 and Box 46.1. The examination can further help to determine the source of the problem and to localize it (Table 46.3).

Selected disorders resulting in visual perception difficulty are described below. Defects in visual fields are described in Chapter 45, "Neuro-ophthalmology: Visual Fields." Disorders of cortical visual function are described in Volume 1, Chapter 23, "Focal Cognitive Syndromes."

Disorders With Transient Visual Loss

Amaurosis Fugax

Amaurosis fugax is a common cause of transient monocular blindness. Patients may complain of the classic altitudinal shade of darkness blocking the vision in 1 eye. More subtly, patients may have photogenic claudication (also known as Whisnant phenomena), in which graying of the vision occurs when the patient is subjected to bright light. The shade of darkness and Whisnant phenomena are most commonly due to high-grade ipsilateral internal carotid artery stenosis. Amaurosis fugax may be due to hypoperfusion related to carotid stenosis or artery-to-artery embolism. Photogenic claudication is almost always due to ipsilateral critical stenosis with hypoperfusion. In some instances, amaurosis may be due to a cardiac source or vasculitis (giant cell arteritis or Takayasu arteritis). Funduscopic examination may show nothing abnormal, or it may show a Hollenhorst plaque (Figure 46.1). Amaurosis fugax due to atherosclerotic disease is painless. However, if the history includes temporal region pain or new-onset headache, giant cell arteritis is an important consideration.

Abbreviations: BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; ODEMS, optic disc edema with a macular star

Table 46.1 • Positive Visual Phenomena

Disturbance	Definition	Association
Hallucinations	A perception in the absence of a stimulus; can be simple (geometric shapes or simple patterns) or complex (well-formed perception)	Migraine Seizure Poor visual sensory input Medications or illicit drugs Alcohol withdrawal Delirium Psychosis Brainstem lesions (midbrain or thalamus—stroke or Lewy body dementia)
Hypnagogic or hypnopompic hallucinations	Visual hallucinations occurring immediately before falling asleep (hypnagogic) or on awakening (hypnopompic)	Sleep deprivation or narcolepsy
Charles Bonnet hallucinations	Well-formed hallucinations due to deprivation of sensory input	Occipitotemporal lesion Severe bilateral cataracts or glaucoma
Palinopsia	Persistence of an image after the stimulus has been removed	Occipitotemporal lesion Seizure
Polyopia	Persistence of an object in space	Migraine
Metamorphopsia, micropsia, and macropsia	Distortion of an image in time and space as a distortion of straight lines or grids into wavy ones (metamorphopsia), as objects appearing smaller than reality (micropsia), or as objects appearing larger than reality (macropsia)	Retinal distortions, migraine, and seizure Illicit drug use

Gaze-Evoked Amaurosis

Gaze-evoked amaurosis is fairly rare but may occur with tumors near the optic nerve or orbital disease. With a change in gaze, patients temporarily lose vision because of traction on the optic nerve.

Uthoff Phenomena

Uthoff phenomena refers to a transient loss of vision that generally occurs with increased body temperature and demyelinating disease. Symptoms typically last only seconds, and patients often have a past history of opticneuritis.

Patients may have transient visual loss associated with migraine. They may have retinal migraine with monocular visual loss or have migraine aura followed by visual loss in 1 visual field. For more details, see Chapter 51, "Primary Headache Disorders: Migraine, Tension-Type, and Chronic Daily Headaches."

Table 46.2 • Causes of Persistent Visual Loss

Category of Cause	Disorder
Ocular	Keratitis, corneal edema, glaucoma, retinal detachment, uveitis, hyphema, lens abnormality, vitreous hemorrhage
Vascular	Anterior ischemic optic neuropathy (arteritic and nonarteritic), posterior ischemic optic neuropathy, central retinal artery occlusion, central retinal vein occlusion, bilateral posterior cerebral artery ischemic stroke
Inflammatory or infectious	Optic neuritis, autoimmune disease, neuroretinitis (viral infection [West Nile virus infection], toxoplasmosis, *Bartonella* infection [cat-scratch disease]), syphilis, Lyme disease, meningitis, sarcoidosis; paraneoplastic, parainfectious, or postvaccination disorder
Neoplastic	Pituitary lesion, optic glioma, meningioma, metastases, lymphoma
Toxic, metabolic, or nutritional	Vitamin B_1 or B_{12} deficiency, folate deficiency, tobacco-alcohol amblyopia
Trauma or radiation	. . .
Genetic	Leber hereditary optic neuropathy, Kjer autosomal dominant optic atrophy
Compression	Papilledema (pseudotumor), orbital pseudotumor, thyroid ophthalmopathy, carotid-ophthalmic artery aneurysm, abscess
Psychogenic	. . .

Box 46.1 • Causes of Transient Visual Loss

- Monocular
  - Amaurosis fugax
  - Uthoff phenomena
  - Retinal migraine
  - Gaze-evoked amaurosis
  - Unilateral orbital pseudotumor with transient visual obscuration
- Binocular
  - Transient visual obscurations (increased intracranial pressure)
  - Hypotension
  - TIA affecting posterior cerebral artery bilaterally (top of the basilar artery)
  - Migraine

Abbreviation: TIA, transient ischemic attack.

Transient Visual Obscurations

Patients with papilledema may complain of brief periods (seconds) of loss of vision or graying of vision. These transient visual obscurations are typically bilateral unless the patient has a unilateral orbital pseudotumor. Symptoms are often precipitated by positional changes or straining.

- Amaurosis fugax is a common cause of transient monocular blindness.
- In amaurosis fugax, the shade of darkness and Whisnant phenomena are most commonly due to high-grade ipsilateral internal carotid artery stenosis.
- *Uthoff phenomena* refers to a transient loss of vision that generally occurs with increased body temperature and demyelinating disease.

Table 46.3 • Localization of Visual Perception Problems According to History and Examination

Location	Visual Acuity	Color	Visual Field	Other	Funduscopic Examination	Light Reflex
Retina	Normal Impaired (macula involved)	Distortion of blue	Central, cecocentral, or arcuate scotomas Altitudinal	Micropsia Metamorphopsia	Retinal changes	Normal
Optic nerve	Decreased	Distortion of red	Monocular Altitudinal	Gaze-evoked amaurosis	Papilledema (later atrophy)	Afferent defect
Optic chiasm	Decreased (bilateral if medial lesion)	Distortion of red	Bitemporal (if anterior: ipsilateral temporal or contralateral upper temporal defect)	. . .	Nerve fiber layer atrophy with "bow tie" configuration	Afferent defect
Optic tract	Normal (if unilateral)	Distortion of red	Contralateral homonymous hemianopia	. . .	Bilateral segmental optic atrophy and nerve fiber layer atrophy	Afferent defect (contralateral eye)
Lateral geniculate body	Normal	Distortion of red in affected field	Contralateral homonymous hemianopia	. . .	Bilateral segmental optic atrophy and nerve fiber layer atrophy	Normal
Optic radiations	Normal	Distortion of red in affected field	Contralateral homonymous hemianopia or quadrantanopia	. . .	Normal	Normal
Nondominant infracalcarine occipital gyri (fusiform and lingual gyri)	Normal	Unable to distinguish colors (cerebral achromatopsia)	Superior quadrantanopia	. . .	Normal	Normal

Adapted from Visual pathways. In: Brazis PW, Masdeu JC, Biller J, editors. Localization in clinical neurology. 6th ed. Philadelphia (PA): Wolters Kluwer Health/Lippincott Williams & Wilkins; c2011. p. 133–72. Used with permission.

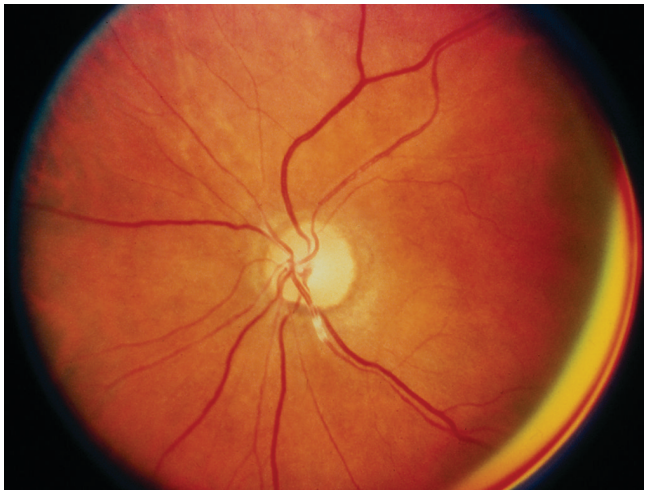

Figure 46.1 *Hollenhorst Plaque.*
(Adapted from Freeman WD, Mowzoon N. Neuro-ophthalmology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 83–126. Used with permission of Mayo Foundation for Medical Education and Research.)

Disorders With Visual Perception Change and Optic Disc Swelling or Atrophy

Reduced visual acuity with findings of optic disc swelling or atrophy may be due to a number of causes (Table 46.4). Optic nerve lesions may result in unilateral or bilateral visual loss. Unilateral visual loss may result from an afferent pupillary defect. Central visual loss, swollen optic disc, and eventual optic atrophy are common findings.

Papilledema

Swelling of the optic disc due to increased intracranial pressure is often referred to as papilledema. Patients with papilledema may present with headache, transient visual obscurations (temporary unilateral or bilateral graying of the vision that lasts for seconds and is often associated with postural changes or straining), enlarged blind spots, and visual field loss (usually beginning nasally) if chronic. The examination typically shows swollen discs (blurred disc margins) and absent venous pulsations, and it may show splinter hemorrhages, exudates, and cotton-wool spots (Figure 46.2). True papilledema should be distinguished from pseudopapilledema, which shows optic disc elevation but generally no hyperemia of the optic disc and no hemorrhages, exudates, or cotton-wool spots. Recognition of these clinical findings should prompt cerebral imaging to assess for an intracranial mass. If the imaging findings are not helpful, other causes of elevated intracranial pressure should be sought. (See Chapter 53, "Secondary Headache Disorders.")

Table 46.4 • Causes of Optic Disc Swelling or Atrophy

Category of Cause	Disorder
Vascular	Nonarteritic ischemic optic neuropathy (NAION) Arteritic ischemic optic neuropathy (AION) Carotid ophthalmic artery aneurysm
Infectious	Neuroretinitis: viral infection, toxoplasmosis, *Bartonella* infection Syphilis Lyme disease
Inflammatory	Optic neuritis Neuroretinitis: sarcoid, autoimmune disease Papillophlebitis Parainfectious Orbital abscess with compression
Neoplastic or paraneoplastic	Orbital tumor: meningioma, glioma, retrobulbar mass, sheath cysts, metastases Infiltrative lymphoma Mass lesion with increased intracranial pressure Paraneoplastic
Toxic or metabolic	Anemia Hypoxemia Radiation Proliferative retinopathies Thyroid disease (thyroid ophthalmopathy) Diabetes mellitus Tobacco-alcohol amblyopia Nutritional deficiency (vitamin B_1 or B_{12}, folate) Drugs (ethambutol, isoniazid, amiodarone, infliximab, bevacizumab, sildenafil)
Genetic	Leber hereditary optic neuropathy Kjer autosomal dominant optic atrophy
Other	Elevated intracranial pressure (intracranial mass or pseudotumor) Ocular disease: uveitis, vein occlusion, orbital pseudotumor Trauma

Ischemic Optic Neuropathy

Ischemic optic neuropathy is another common cause of swollen optic discs. It is often described as either anterior or posterior (retrobulbar) and as either arteritic or nonarteritic. Patients with nonarteritic anterior ischemic optic neuropathy are often older than 50 years and have common vascular risk factors. Patients with arteritic ischemic optic neuropathy may be older also and have systemic symptoms of giant cell arteritis or an elevated sedimentation rate (or both). No matter the cause, patients typically complain of painless acute visual loss unilaterally, although bilateral cases have been reported.

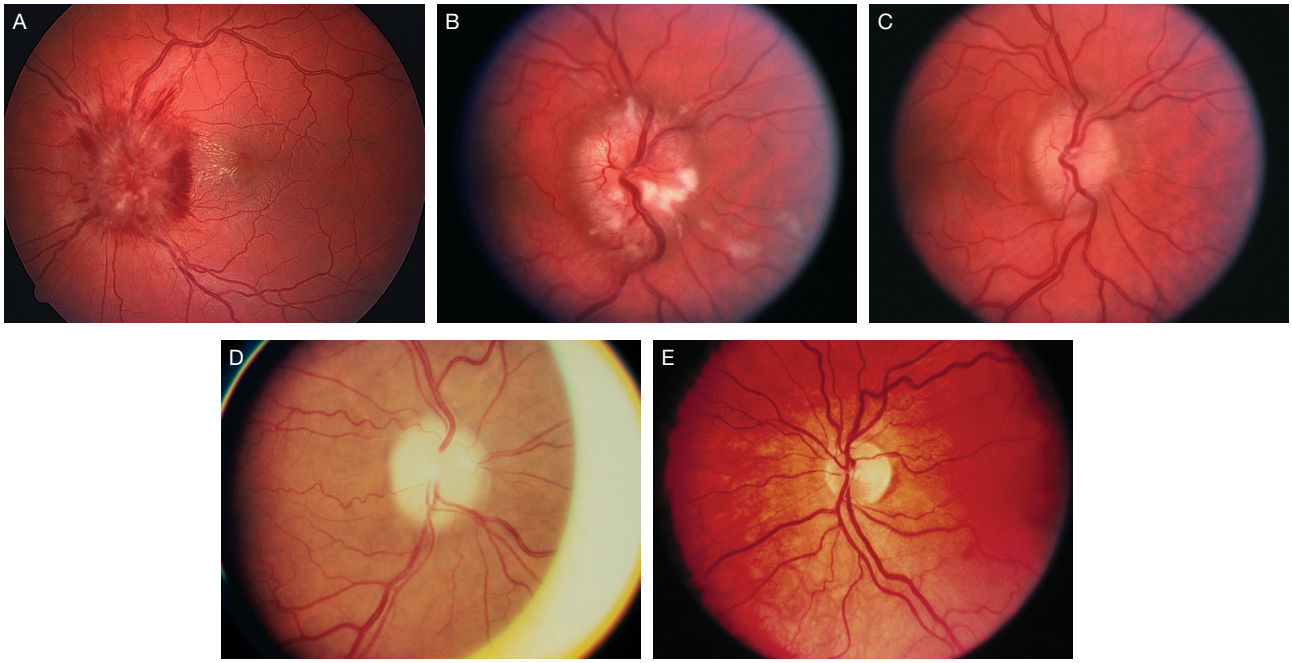

Figure 46.2 *Stages of Papilledema.*
A, Severe acute (fully developed) papilledema. The optic disc appears hyperemic, with blurred margins, splinter hemorrhages, and engorged, dilated surrounding veins. There is early development of tiny hard exudates tracking along the maculopapular bundle. B, In the chronic stage, the optic disc has a pale appearance. There is persistence of optic disc edema and cotton-wool spots, continued dilatation of the venous structures and capillaries, and the appearance of neovascularization and the disappearance of hemorrhages. C, Less severe papilledema in a patient with pseudotumor cerebri. D, End-stage papilledema is characterized by optic disc pallor due to optic atrophy and gliosis (atrophic papilledema); the optic disc margins remain indistinct. E, In contrast, the optic disc margins remain sharp and distinct in the chronic optic disc pallor seen with traumatic transection of the optic nerve. (The margins are sharp and distinct also in retrobulbar optic neuritis.)
(A-C, Courtesy of Brian R. Younge, MD, Mayo Clinic, Rochester, Minnesota. Used with permission. D and E, Courtesy of Shelley A. Cross, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

Examination shows reduced visual acuity, and patients may have an altitudinal field defect. In patients with anterior ischemic optic neuropathy, funduscopic examination shows optic disc swelling (Figure 46.3). It may also show branch retinal artery occlusion (BRAO), central retinal artery occlusion (CRAO), or cotton-wool spots. Causes of anterior ischemic optic neuropathy are listed in Table 46.5. In posterior (retrobulbar) ischemic optic neuropathy, the examination findings are normal (a common saying is "the patient can't see and neither can you [see the pathology]"). The normal findings should increase suspicion for arteritis, but they are not exclusively due to arteritis. Any suspicion for arteritic optic neuropathy should prompt treatment, and temporal artery biopsy should not be delayed since one-third of patients may have binocular involvement soon. (Giant cell arteritis is reviewed in Chapter 53, "Secondary Headache Disorders.") Posterior ischemic optic neuropathies may also occur with prolonged surgical procedures (eg, spinal and cardiac procedures), although they are rare. Prognosis for recovery is poor, but the risk of recurrence is low.

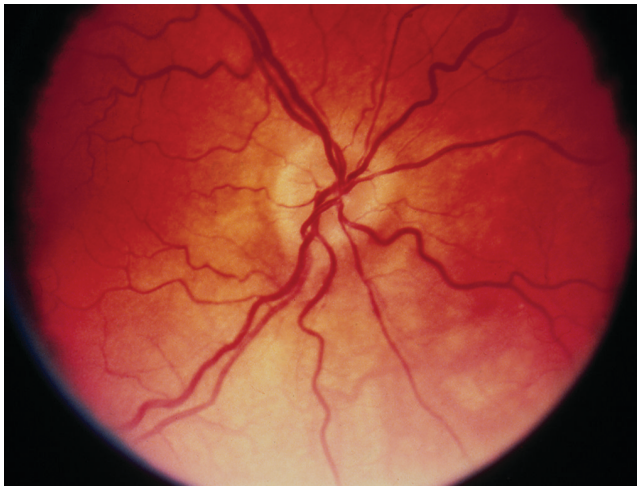

Figure 46.3 *Arteritic Anterior Ischemic Optic Neuropathy. Characteristic features are optic disc edema and associated retinal pallor.*
(Courtesy of Shelley A. Cross, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

Table 46.5 • Causes of Anterior Ischemic Optic Neuropathy (AION)

Cause	Clue to Diagnosis
Atherosclerosis	Vascular risk factors
Arteritis	Systemic symptoms: headache, weakness, weight loss, polymyalgia, jaw claudication Elevated sedimentation rate
Hypotension or hypovolemia	Recent blood loss or dehydration Prolonged hypotension Poor cardiac function Severe anemia
Cataract surgery	Surgical and medical history

Retinal Artery Occlusion

Patients with CRAO or BRAO may present with painless monocular visual loss. They typically have vascular risk factors (hypertension, diabetes mellitus, tobacco use, older than 50 years). Causes can include carotid atherosclerosis (most common in patients older than 50 years), arteritis, and, less likely, cardiac embolism (more common in patients younger than 40 years). Rarely hematologic causes, dissection, and other diseases have been implicated. In patients with CRAO, examination generally shows profound visual loss and an afferent pupillary defect. Funduscopic examination may show a cherry-red spot and occasional retinal emboli. The cherry-red spot is distinct because the surrounding retina is ischemic and white, and the macula appears red because the cilioretinal arteries to this area are preserved (Figure 46.4). The diagnosis can be confirmed by history and examination. Further diagnostic tests for elucidating a cause may include a complete blood cell count, erythrocyte sedimentation rate, C-reactive protein level, carotid artery study, electrocardiogram, and echocardiogram (for select patients). Secondary prevention of further vascular events is dependent on the cause. Experimental data show that the retina may have permanent ischemic damage by 90 to 100 minutes after symptom onset. The prognosis for patients with nonarteritic CRAO is poor; however, most patients with BRAO recover normal vision.

Given the poor prognosis for patients with nonarteritic CRAO, various conservative and aggressive treatments have been tried: ocular massage, anterior chamber paracentesis or medications to reduce intraocular pressure, vasodilation medications, and hyperbaric oxygen. Retrospective studies of intravenous and intra-arterial tissue plasminogen activator for CRAO have produced data that are mixed and conflicting.

Neuroretinitis

Neuroretinitis affects children and adults. Symptoms may be unilateral or bilateral and are typical of optic nerve injury (reduced visual acuity and change in color vision). About half of patients have a recent history of viral infection. Clinical examination shows optic disc edema with inflammatory peripapillary and macular hard exudates that appear in a star pattern ("macular star") (Figure 46.5). The idiopathic form is often referred to as optic disc edema with a macular star (ODEMS). Secondary forms may be due to infectious or inflammatory causes, including cat-scratch disease (*Bartonella henselae* infection), Lyme disease, syphilis, toxoplasmosis, tuberculosis, viral

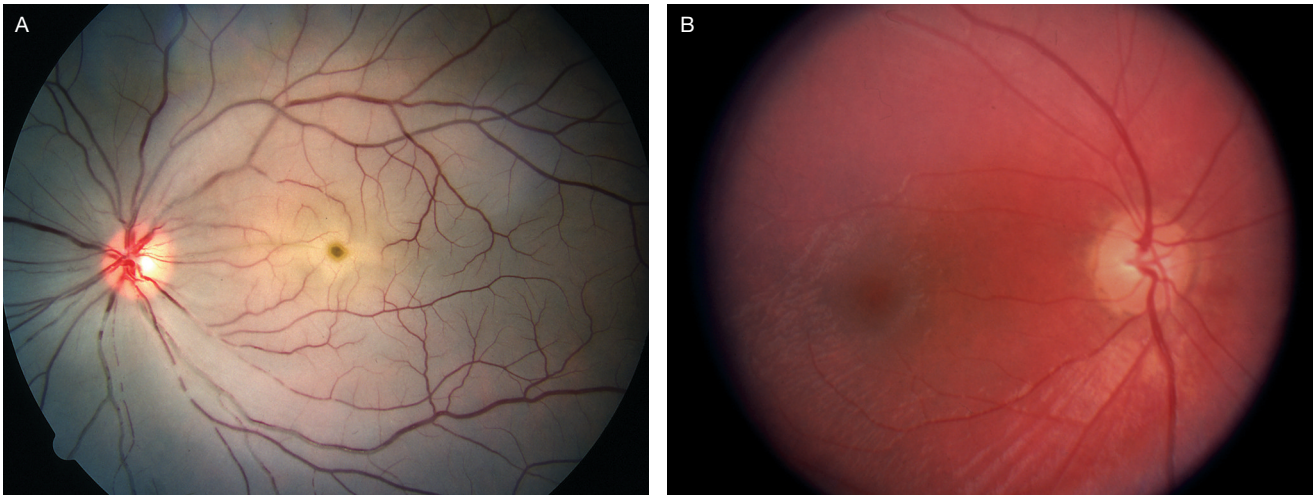

Figure 46.4 *Cherry-Red Spot in Central Retinal Artery Occlusion.*
A, Whitening of the retina and relative preservation of the fovea produce the appearance of a cherry-red spot. B, In contrast, the cherry-red spot in Tay-Sachs disease is not surrounded by retinal whitening or pallor.
(Courtesy of Brian R. Younge, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

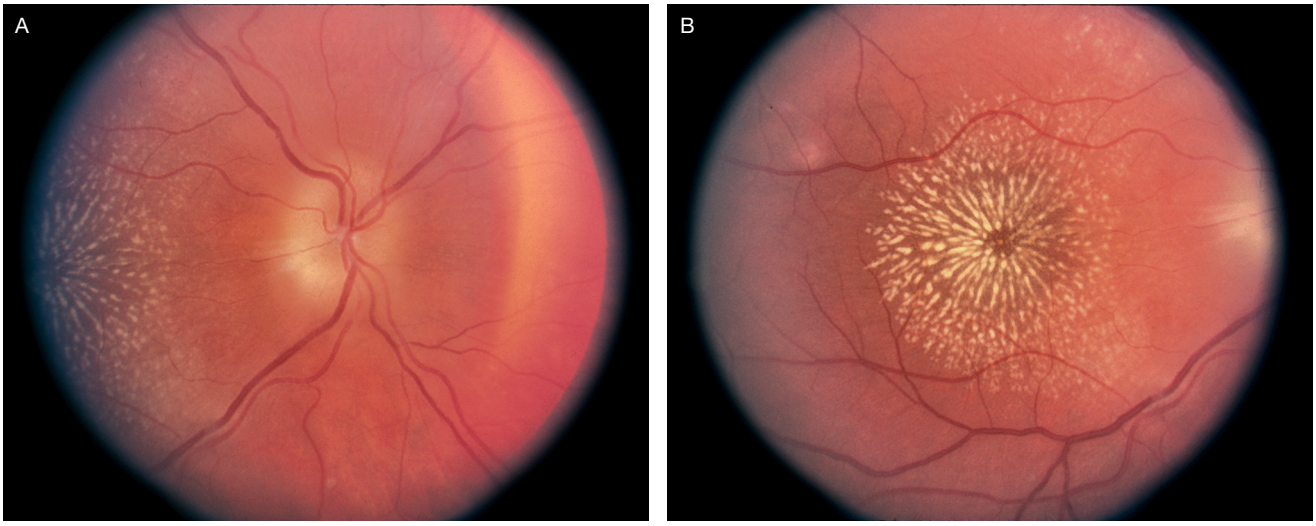

Figure 46.5 *Neuroretinitis.*
A, Optic nerve edema. B, Macular star.
(Courtesy of Brian R. Younge, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

infection (Epstein-Barr virus infection, hepatitis B, and herpes zoster), sarcoid, and systemic lupus erythematosus. Evaluation includes ophthalmologic examination and tests to rule out the infectious and inflammatory causes. Treatment is aimed at the identified cause.

Optic Neuritis

Optic neuritis (papillitis) is inflammation of the optic nerve. One-third of cases are intraocular; two-thirds are retrobulbar. Patients are usually 18 to 40 years old. Typically, patients with optic neuritis present with acute to subacute (2–3 days) visual loss that is usually unilateral but may be bilateral. Pain can be associated with the visual loss, especially with eye movement. The examination may show an afferent pupillary defect, a swollen optic disc (with intraocular disease but not retrobulbar), and possibly a central scotoma. Magnetic resonance imaging of the brain with a contrast agent often shows enhancement of the optic nerve. Most patients have improvement over 1 year despite treatment; however, intravenous methylprednisolone can hasten recovery. Additional evaluation for demyelinating disease and disease modifying treatment may be important (see Chapter 19, "Treatment of Multiple Sclerosis").

Masses such as a sphenoorbital meningioma, optic nerve glioma, or a craniopharyngioma may compress the optic nerve and result in visual loss with optic disc swelling. Head imaging is important when unilateral optic disc edema is noted. Foster Kennedy syndrome is characterized by optic atrophy in the ipsilateral eye and optic disc edema in the contralateral eye in addition to loss of the sense of smell. This is most commonly due to a mass (often an olfactory groove meningioma) compressing the ipsilateral optic nerve and olfactory nerve and is associated with increased intracranial pressure (hence, the contralateral disc edema).

Tobacco-Alcohol Amblyopia

Patients with tobacco-alcohol amblyopia generally present with reduced visual acuity, symmetric visual scotomas, and altered color vision. Patients may have difficulty discriminating between red and green lights. This condition is thought to be related to the cyanide from tobacco and to poor nutrition (folate deficiency) in patients who abuse tobacco and alcohol. Magnetic resonance imaging of the brain is typically normal. Treatment is cessation of tobacco and alcohol abuse and administration of vitamin therapy. Patients improve, but full recovery is not common.

Leber Hereditary Optic Neuropathy

Leber hereditary optic neuropathy is a disorder of mitochondrial DNA and is most common in males (80%–90% of cases). Patients often present with painless, acute to subacute monocular visual loss followed days to weeks later by contralateral eye involvement. Examination commonly shows reduced visual acuity, loss of color vision, scotoma, and an afferent pupillary defect (early in the course). Funduscopic examination may initially show a normal optic disc. Nerve fiber layer swelling around the optic disc may be visualized, and eventually optic atrophy develops. Evaluation includes obtaining a family history, performing an ophthalmologic examination, and ruling out other conditions that present in a similar manner. For carriers of the mutation, receiving close ophthalmologic follow-up and avoiding potential optic nerve toxins are important. If visual loss occurs, α-tocotrienol quinone, a vitamin E metabolite, may be tried. Several other treatments are being tested.

Table 46.6 • Cerebrovascular Disorders Associated With Ocular Findings

Disorder	Clinical Feature	Eye Examination	Comments
Nonarteritic anterior ischemic optic neuropathy	Often age >50 y Vascular risk factors Painless, monocular visual loss	Reduced visual acuity or altitudinal field defect Optic disc swelling acutely on funduscopic examination	Vascular evaluation and risk factor assessment are warranted Rule out arteritic ischemic optic neuropathy
Hollenhorst plaque	May be asymptomatic finding or associated with amaurosis fugax	Cholesterol embolus lodged in a retinal vessel (Figure 46.1)	May be associated with atherosclerotic carotid disease
Retinal artery occlusion	Often painless Central retinal artery occlusion causes an infarction of the whole central retinal artery with loss of central vision in the affected eye Branch retinal artery occlusion is an infarction of 1 branch of the optic nerve	Pallor of inner retinal layers from ischemia with relative preservation of the fovea (supplied by the choroidal artery), producing a cherry-red spot (Figure 46.4)	Carotid disease is suspected but not present in every patient
Terson syndrome	Occurs in patients with subarachnoid hemorrhage Patients complain of blurred vision	Evidence of vitreous hemorrhages (often bilateral) (Figure 46.6)	Present after subarachnoid hemorrhage
Susac syndrome	Cerebral ischemia Low-frequency hearing loss Visual complaints	Branch retinal artery occlusions Gass plaques in retinal arterioles	MRI findings often show white matter changes diffusely, often involving the corpus callosum
Eales disease	Often young males Bilateral visual changes Vasculitis	Perivascular phlebitis Peripheral nonperfusion Retinal neovascularization Recurrent vitreal hemorrhage	Idiopathic inflammatory venous condition
Wyburn-Mason syndrome	May have visual loss May have other neurologic symptoms related to brain AVM	Retinal AVM	Retinal AVM and brain AVM AVMs may occur in other parts of the body as well
Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)	Young, healthy adults Visual acuity may be affected significantly if the macula is involved Moderate to severe headache Metamorphopsia or micropsia Neurologic symptoms: transient aphasia, numbness, and weakness of extremities	Multiple yellow-white placoid subretinal lesions at the posterior pole	Acquired inflammatory disorder affecting the retina, retinal pigment epithelium, and choroid

Abbreviations: AVM, arteriovenous malformation; MRI, magnetic resonance imaging.

- Patients with papilledema may present with headache, transient visual obscurations (temporary unilateral or bilateral graying of the vision that lasts for seconds and is often associated with postural changes or straining), enlarged blind spots, and visual field loss (usually beginning nasally) if chronic.
- Patients with nonarteritic anterior ischemic optic neuropathy are often older than 50 years and have common vascular risk factors.
- Patients with ischemic optic neuropathy typically complain of painless acute visual loss unilaterally, although bilateral cases have been reported.
- In patients with CRAO, funduscopic examination may show a cherry-red spot and occasional retinal emboli. The cherry-red spot is distinct because the surrounding retina is ischemic and white, and the macula appears red because the cilioretinal arteries to this area are preserved.
- Optic neuritis (papillitis) is inflammation of the optic nerve. One-third of cases are intraocular; two-thirds are retrobulbar.
- Typically, patients with optic neuritis present with acute to subacute (2–3 days) visual loss that is usually unilateral but may be bilateral.
- Foster Kennedy syndrome is characterized by optic atrophy in the ipsilateral eye and optic disc edema in the contralateral eye in addition to loss of the sense of smell.

- Patients with tobacco-alcohol amblyopia generally present with reduced visual acuity, symmetric visual scotomas, and altered color vision.
- Leber hereditary optic neuropathy is a disorder of mitochondrial DNA and is most common in males (80%–90% of cases). Patients often present with painless, acute to subacute monocular visual loss followed days to weeks later by contralateral eye involvement.

Vascular Disorders Associated With Eye Findings

Several cerebrovascular conditions involve ocular complaints and findings (Table 46.6 and Figure 46.6).

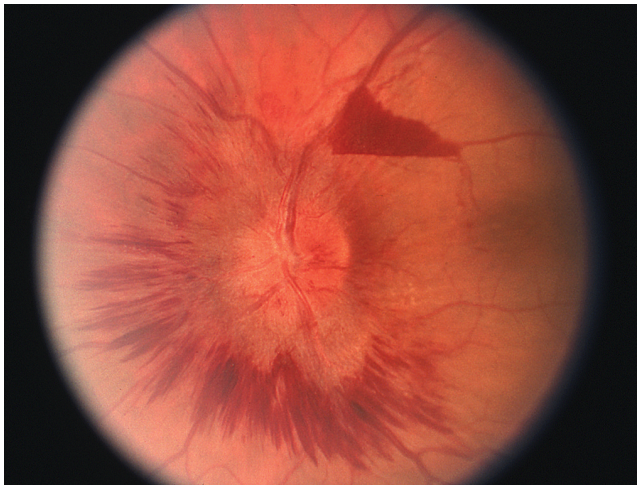

Figure 46.6 *Terson Syndrome.*
Retinal subhyaloid and peripapillary hemorrhage in the hyperacute stage in a patient with increased intracranial pressure and subarachnoid hemorrhage.
(Courtesy of Brian R. Younge, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

Pupillary Disorders

Pupillary disorders are summarized in Table 46.7.

Horner Syndrome

Horner syndrome is characterized by unilateral ptosis, miosis, and anhidrosis. The miosis is often more evident in dark or dim light. It is caused by a disruption in the sympathetic output to the Müller muscle, the pupillary dilator muscles, and the sudomotor fibers to the face. Disruption of the sympathetic output may occur anywhere along its course (Figure 46.7 and Table 46.8).

Pharmacologic testing can help confirm a diagnosis of Horner syndrome (cocaine test) and distinguish whether a third-order neuron lesion exists (hydroxyamphetamine test). Cocaine blocks the norepinephrine receptors, prolonging the action of norepinephrine on the pupillary dilator muscle. A response to cocaine requires the release of norepinephrine at the myoneural junction by a normally functioning sympathetic pathway. Cocaine ophthalmologic solution (4% or 10%) is placed in each eye. After 45 minutes, a normal pupil dilates, but a sympathetically denervated pupil does not. Hydroxyamphetamine (Paredrine) acts by releasing norepinephrine from the presynpatic membrane. A 1% topical solution is placed in each eye (≥48 hours after a cocaine test). With a third-order lesion, the pupil will not dilate (no norepinephrine to release), but with a first- or second-order neuron lesion, the pupil will dilate.

Adie Tonic Pupil

Adie tonic pupil is common in young females and is often unilateral. Patients have a dilated pupil with a poor response to light and a slow constriction to near gaze with slow redilation. They may also have an accompanying reduction of deep tendon reflexes. The cause is idiopathic in most cases but is likely localized to nerve fibers of the ciliary muscle or those innervating the iris sphincter muscle.

Afferent Pupillary Defect

An afferent pupillary defect (Marcus Gunn pupil) can be present in patients with unilateral optic neuropathy or extensive retinal damage. Cataracts, corneal scar, or vitreal abnormalities should not cause this. An afferent pupillary defect is identified with the "swinging flashlight" test. When the flashlight is swung from the normal eye to the abnormal eye, the pupil immediately dilates instead of normally constricting. When swung back to the normal eye, the pupil constricts with subsequent enlargement to an intermediate size (Figure 46.8). The reason for this response is that relatively less light is carried from the defective eye to the midbrain than is carried from the normal eye; thus, the response is to dilate. An afferent pupillary defect is unilateral only, and for detection, the patient cannot have a fixed pupillary defect.

Argyll Robertson Pupil

Argyll Robertson pupils are small and irregular with poor dilation in the dark or in response to chemical agents. The defect may be unilateral or bilateral. Pupils do not constrict to light, but they do constrict with a near response. This disorder has been associated with syphilis, diabetes mellitus, alcoholism, sarcoidosis, and multiple sclerosis.

- Horner syndrome is characterized by unilateral ptosis, miosis, and anhidrosis. The miosis is often more evident in dark or dim light.

Table 46.7 • Summary of Pupillary Disorders

Condition	Clinical Features	Examination Findings	Comments
Physiologic anisocoria	Difference in pupillary size	. . .	20% of people
Horner syndrome	Ptosis Miosis Anhidrosis	Miosis is best visualized in darkness (pupil on the normal side dilates as expected) Ptosis is often partial	Lesion anywhere along the sympathetic pathway (Figure 46.7)
Adie tonic pupil	Unilateral (rarely bilateral) More common in young females	Enlarged pupil with poor response to light Slow constriction with near response	Idiopathic Reduced deep tendon reflexes
Afferent pupillary defect (Marcus Gunn pupil)	Unilateral only	"Swinging flashlight" test: abnormal eye dilates initially and then constricts	Unilateral severe retinal disease or optic neuropathy
Argyll Robertson pupils	Unilateral or bilateral	Small, irregular pupils (unilateral or bilateral) Do not constrict with light but do constrict with accommodation	Neurosyphilis Diabetes mellitus Multiple sclerosis Alcoholism Sarcoid
Third nerve palsy	Diplopia Ptosis	Ptosis Eye is deviated down and out Pupil is large and fixed (often involved in compressive lesions)	Pupillomotor fibers on outer bundle of cranial nerve III; more likely to be involved if compressive lesion If acute and involving pupil: aneurysm or pituitary apoplexy
Pharmacologic pupillary dilatation	Health care workers Often unilateral	Dilated, unresponsive pupil	In an otherwise healthy patient, consider pharmacologic dilatation as a cause (often health care worker handling medications may have rubbed eye)
Pharmacologic pupillary constriction	Patients with glaucoma Patients with postoperative or chronic pain	Fixed miosis (unilateral or bilateral)	Opiates Pilocarpine Glaucoma agents

- Pharmacologic testing can help confirm a diagnosis of Horner syndrome (cocaine test) and distinguish whether a third-order neuron lesion exists (hydroxyamphetamine test).
- An afferent pupillary defect (Marcus Gunn pupil) can be present in patients with unilateral optic neuropathy or extensive retinal damage.
- An afferent pupillary defect is identified with the "swinging flashlight" test.

Eyelid Disorders

Eyelid opening is a function of the Müller muscle (innervated by the sympathetics) and the levator palpebrae superioris muscle (innervated by the central caudalis subnucleus of cranial nerve III). Supranuclear control of eyelid opening is from corticobulbar and extrapyramidal pathways from the frontal, occipital, and temporal lobes. Eyelid closure is a function of the orbicularis oculi muscle (innervated by cranial nerve VII).

Ptosis

Ptosis refers to dysfunction of the eyelid opening. It may be partial or complete. Ptosis may be caused by a supratentorial lesion (cortical ptosis or apraxia of the eyelid opening), a nuclear or nerve lesion (involvement of cranial nerve III or decreased sympathetic activity), a neuromuscular junction disorder (myasthenia or botulism), a myopathy, or mechanical or iatrogenic factors.

Abnormal Eyelid Closure

Abnormal eyelid closure can result in injury to the cornea and so is important to recognize. Disorders include those in which eyelid closure is insufficient (eg, a cranial nerve VII palsy), those in which the blink rate is decreased, and those in which eyelid closure is excessive.

Lid retraction is characterized by excessive elevation of the eyelid, with sclera visible above the superior corneal area. This may be congenital or acquired. Lid retraction may be seen in dorsal midbrain lesions affecting the posterior commissure, aberrant regeneration of cranial

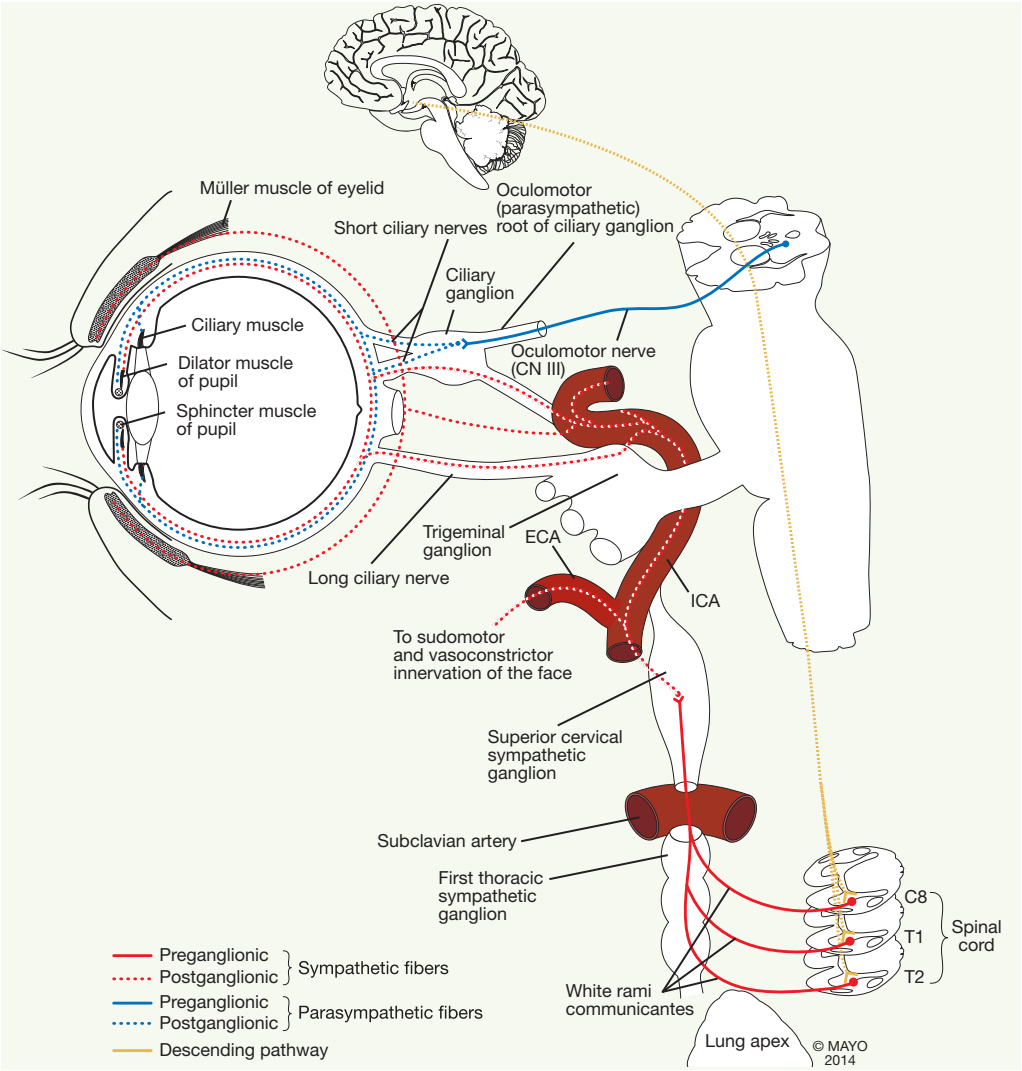

Figure 46.7 *Autonomic Innervation of the Pupil.*
CN indicates cranial nerve; ECA, external carotid artery; ICA, internal carotid artery.
(Adapted from Freeman WD, Mowzoon N. Neuro-ophthalmology. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 83–126. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 46.8 • Causes of Horner Syndrome

Location of Lesion	Disorder
First-order neuron	Thalamic lesion Lateral brainstem lesion Cervical spinal cord lesion (tumor, syrinx, demyelination, trauma)
Second-order neuron	Root (radiculopathy, dural arteriovenous fistula, tumor) Chest (pancoast tumor or apical tumor, often from lung) Anterior neck lesion (glomus tumor, adenopathy, thyroid adenoma trauma, iatrogenic)
Third-order neuron (often without anhidrosis because the sudomotor fibers to the face travel with the external carotid)	Superior cervical ganglion (trauma, tumor) Internal carotid artery (dissection, carotid surgery) Skull base (nasopharyngeal carcinoma, other tumor) Cavernous sinus (fistula, thrombosis, pituitary lesion, carotid cavernous aneurysm, Tolosa-Hunt syndrome)

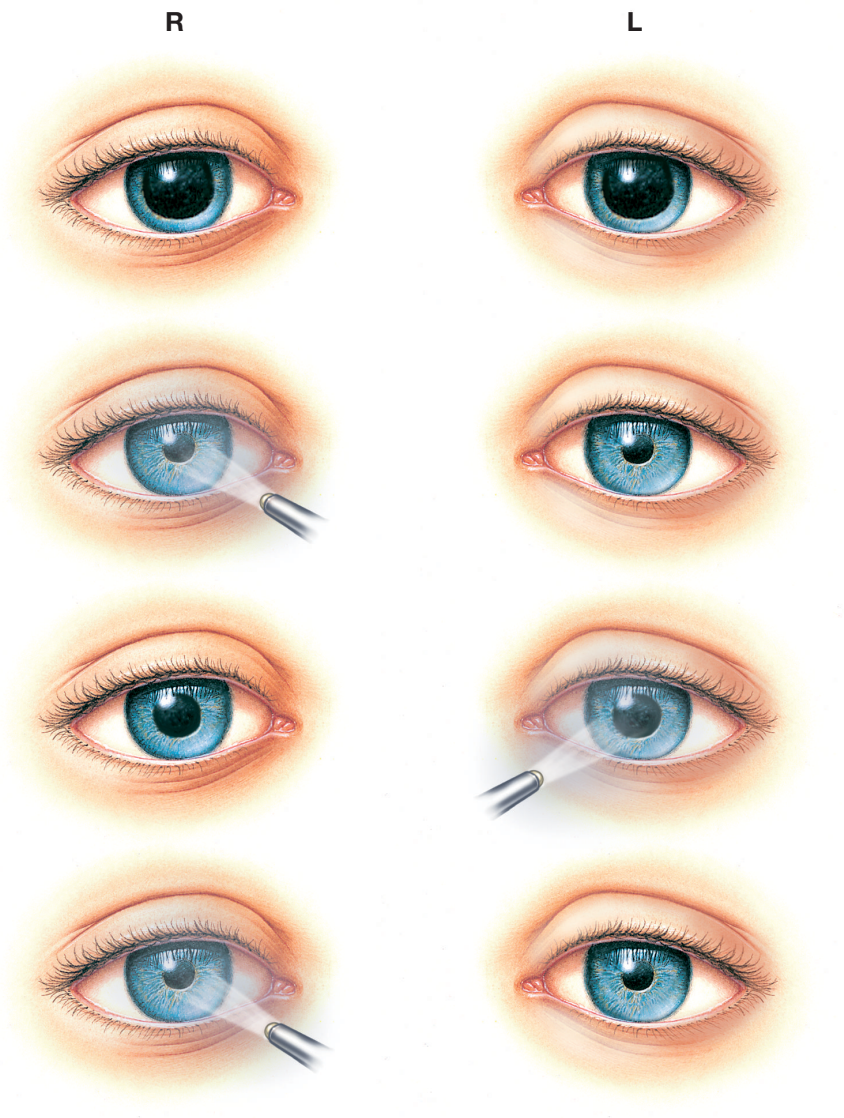

Figure 46.8 *Afferent Pupillary Defect and "Swinging Flashlight" Test.*
Light shining in the normal right (R) eye causes both pupils to constrict. Light shining in the abnormal left (L) eye causes the pupils to dilate slightly because the impaired optic nerve perceives relatively less light.
(Adapted from Kline LB. The pupil. In: Kline LB, Foroozan R, Bajandas FJ, editors. Neuro-ophthalmology review manual. 7th ed. Thorofare [NJ]: SLACK Incorporated; c2013. p. 123–37. Used with permission.)

nerve III, myasthenia gravis, thyroid disease, and other conditions.

Lid lag refers to the inability of the eyelid to follow movement of the eyeball downward, so that the upper sclera is visible. This is seen most commonly with thyroid eye disease.

- *Ptosis* refers to dysfunction of the eyelid opening. It may be partial or complete. Ptosis may be caused by a supratentorial lesion (cortical ptosis or apraxia of the eyelid opening), a nuclear or nerve lesion (involvement of cranial nerve III or decreased sympathetic activity), a neuromuscular junction disorder (myasthenia or botulism), a myopathy, or mechanical or iatrogenic factors.

47 Neuro-ophthalmology: Extraocular Muscles and Cranial Nerves III, IV, and VI[a]

PAUL W. BRAZIS, MD

Introduction

Conjugate eye movement requires voluntary and reflexive input to the final common pathway (cranial nerves III, IV, and VI and their respective muscles). More detailed anatomy of relevant structures is provided in Volume 1. This chapter briefly reviews the anatomy of the extraocular muscles and cranial nerves III, IV, and VI and focuses on related clinical syndromes or diseases. Supranuclear input to these structures and dysfunction is discussed in other chapters.

The Ocular Muscles

Anatomy

Each eye globe is moved by 6 muscles: 4 recti (superior, inferior, medial, and lateral) and 2 oblique (superior and inferior) muscles (Table 47.1). Two muscles, both in the upper eyelid, act together to widen the palpebral fissure. The Müller muscle receives sympathetic innervation. The levator of the eyelid, innervated by cranial nerve III, has the greater role in eyelid opening. Eye closure (orbicularis oculi) is effected through cranial nerve VII.

Dysfunction

Patients with ocular muscle dysfunction may present variably with double vision or ptosis (or both). The characteristics of the dysfunction (acute or chronic; static, progressive, or episodic) may help determine the cause (Table 47.2).

Thyroid Ophthalmopathy

Thyroid ophthalmopathy (Graves ophthalmopathy) is generally preceded by exophthalmos and orbital edema. The myopathy of dysthyroid orbitopathy is attributed to inflammation and fibrosis of the muscles, sparing tendinous insertions. The diplopia is usually due to a muscle that is "tight" rather than "weak." The inferior recti muscles are usually most severely affected (causing hypotropia), followed by the medial recti, superior recti, and oblique muscles (the mnemonic *I'm so glad I do not have thyroid eye disease* is useful for remembering the frequency of muscle involvement—in the words *I'm so, I* represents inferior recti; *m*, medial recti; *s*, superior recti; and *o*, oblique muscles). In thyroid ophthalmopathy, the lateral rectus muscle is rarely affected; therefore, the presence of an exotropia in a patient with thyroid ophthalmopathy should raise the possibility of concomitant myasthenia gravis. Vertical diplopia caused by asymmetric involvement of the inferior or superior recti muscles is the most common presentation. Other components of dysthyroid orbitopathy include orbital congestion, upper eyelid retraction, eyelid lag on looking down, proptosis, conjunctival injection, and optic neuropathy due to compression of the optic nerve by enlarged extraocular muscles in the orbital apex.

[a] Portions previously published in Brazis PW. Isolated palsies of cranial nerves III, IV, and VI. Semin Neurol. 2009 Feb;29(1):14–28. Epub 2009 Feb 12; Brazis PW, Lee AG, Stewart M, Capobianco D. Clinical review: the differential diagnosis of pain in the quiet eye. Neurologist. 2002 Mar;8(2):82–100; Brazis PW. Trochlear nerve (cranial nerve IV). In: Aminoff MJ, Daroff RB, editors. Encyclopedia of the neurological sciences. Amsterdam (NETHERLANDS): Academic Press; c2003. p. 570–2; and Lee AG, Brazis PW, Mughal M, Policeni F. Emergencies in neuro-ophthalmology: a case based approach. Hackensack (NJ): World Scientific; c2010. Chapter 18, Acute painful ophthalmoplegia; p. 163–8. Used with permission.

Table 47.1 • Functions of the Ocular Nerves

Cranial Nerve	Muscle	Normal Function		Dysfunction
		Primary Position[a]	Secondary Position[b]	
III	Medial rectus	Adduction	. . .	Eye is deviated down and out, with complete paralysis of cranial nerve III usually associated with ptosis and mydriasis
	Superior rectus	Elevation	Intorsion	. . .
	Inferior rectus	Depression	Extorsion	. . .
	Inferior oblique	Extorsion	Elevation	. . .
IV	Superior oblique	Intorsion	Depression	Limitation of downward gaze when eye is looking medially; extorsion of eye
VI	Lateral rectus	Abduction	. . .	Eye deviated medially

[a] *Primary position* refers to the action of the muscle when the eye is positioned in the plane of the muscle and the muscle is then contracted.

[b] *Secondary position* refers to the action of the muscle when the eye is gazing forward in the orbit.

Adapted from Benarroch EE, Daube JR, Flemming KD, Westmoreland BF. Mayo Clinic medical neurosciences: organized by neurologic systems and levels. 5th ed. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2008. Chapter 15B, The posterior fossa level: cerebellar, auditory, and vestibular systems; p. 633–67. Used with permission of Mayo Foundation for Medical Education and Research.

- In thyroid ophthalmopathy, the lateral rectus muscle is rarely affected; therefore, the presence of an exotropia in a patient with thyroid ophthalmopathy should raise the possibility of concomitant myasthenia gravis.

Cranial Nerve III (Oculomotor Nerve)

Anatomy

The general somatic efferent component of cranial nerve III innervates the inferior, superior, and medial recti muscles

Table 47.2 • Diseases Affecting Ocular Muscles

Condition	Definition	Clinical Symptoms	Associated Symptoms
Brown superior oblique ten1don sheath syndrome	Mechanical restriction of the superior oblique tendon (prevents eye from moving up while adducted)	Episodic vertical diplopia (on examination, resembles an inferior oblique palsy)	Occasionally a clicking sound is noted
Thyroid ophthalmopathy	Inflammation and fibrosis of the muscles	Exophthalmos Orbital edema Diplopia Upper eyelid retraction Eyelid lag when looking down	Tremor Sweating Weight Loss Palpitations
Myasthenia gravis	Neuromuscular junction defect	Painless Episodic ptosis or diplopia (or both) Eye findings may change and, with the changes, mimic other disorders	Generalized fatigable weakness
Botulism	Neuromuscular junction defect	Diplopia Ptosis Blurred vision (accommodation paresis)	Shortness of breath Constipation
Chronic progressive ophthalmoplegia	Kearns-Sayre syndrome	Progressive eye limitation without diplopia Ptosis Spared pupils	Retinal pigment changes Heart block Hearing loss Short stature Ataxia Upper motor neuron signs Endocrine changes

as well as the inferior oblique muscle. The general visceral component of cranial nerve III functions in accommodation and pupillary constriction.

The third nerve nuclear complex lies in the medial midbrain at the level of the superior colliculus. One unpaired and 4 paired rostrocaudal columns can be distinguished in the oculomotor nuclear complex. The unpaired column, shared by the right and left nuclei, is in the most dorsal location and contains the visceral nuclei (Edinger-Westphal nucleus) rostrally and the subnucleus for the levator palpebrae superioris caudally. The Edinger-Westphal nucleus mediates pupillary constriction. Laterally in each oculomotor complex there are 3 subnuclei: dorsal (inferior rectus), intermediate (inferior oblique), and ventral (medial rectus). The most medial subnucleus innervates the superior rectus muscle. This is the only portion of the oculomotor nucleus that sends its axons to the opposite eye. Decussating fibers actually traverse the contralateral subnucleus for the superior rectus. Hence, a nuclear third nerve lesion may result in an ipsilateral third nerve palsy in addition to bilateral ptosis and contralateral superior rectus muscle weakness.

The third nerve fascicles exit the midbrain ventrally. In the subarachnoid space, each third nerve passes between the superior cerebellar and the posterior cerebral arteries, courses forward near the medial aspect of the uncus of the temporal lobe, pierces the dura, and enters the lateral wall of the cavernous sinus. Combined oculomotor paresis and sympathetic denervation are virtually pathognomonic for a cavernous sinus lesion. The fibers then pass through the superior orbital fissure to innervate respective muscles. Lesions within the orbit that produce third nerve dysfunction usually produce other ocular motor dysfunction as well as optic neuropathy and proptosis.

A cranial nerve III palsy may result in the eye being in a down and out position because of weakness of the medial, inferior, and superior recti muscles in addition to the inferior oblique muscle. The lateral rectus muscle (innervated by cranial nerve VI) and the superior oblique muscle (innervated by cranial nerve IV) are intact and pull the eye laterally and down. The pupil may or may not be involved in a cranial nerve palsy. Cranial nerve III palsies involving the pupil are generally due to compressive lesions because the pupillomotor fibers are in the outer bundle of the nerve.

Dysfunction

Cranial nerve III may be affected anywhere along its path (Table 47.3 and Figure 47.1). A third nerve palsy suddenly involving the pupil is considered an emergency until proved otherwise. Serious causes may include an enlarging cerebral aneurysm (most commonly in the posterior communicating artery, but it may be in the basilar artery), pituitary apoplexy, a cavernous sinus mass or thrombosis, and trauma.

Table 47.3 • Disorders of Cranial Nerve III

Location of Lesion	Differential Diagnosis
Nuclear	Rare—structural lesions (tumor, abscess)
Fascicular	Stroke[a] Brain hemorrhage Demyelinating disease
Subarachnoid space	Ischemic cranial nerve III palsy (often pupil sparing) Posterior communicating artery aneurysm (often involves pupil) Meningeal inflammation (infectious, inflammatory, carcinomatous) Tumors (meningiomas, metastases, chordomas) Traumatic or neurosurgical Compression due to uncal herniation
Cavernous sinus	Compressive lesions (tumor, large aneurysm, infection) Cavernous sinus thrombosis Cavernous sinus infection (mucormycosis, aspergillosis)
Superior orbital fissure	Compression lesions (tumors, abscess) Trauma

[a] See also Chapter 10, "Ischemic Stroke: Common Causes and Diagnosis," for brainstem syndromes associated with cranial nerve III palsies.

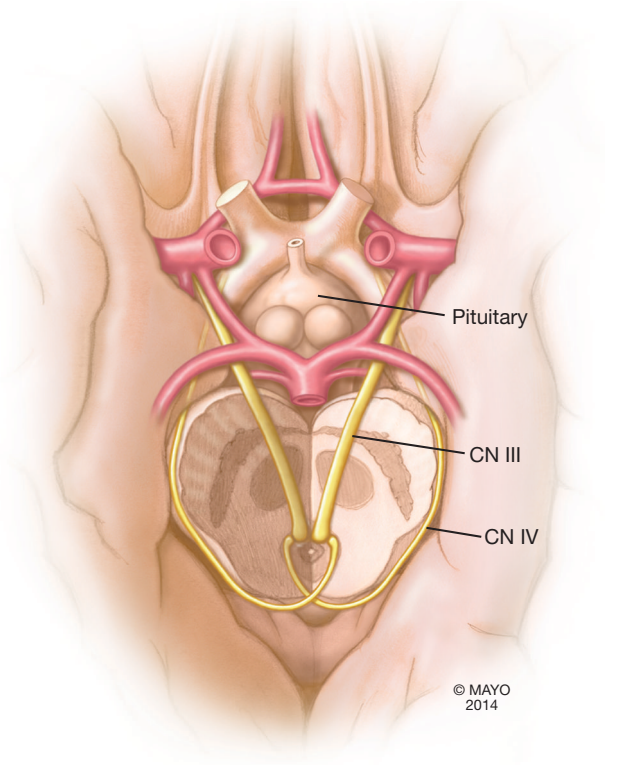

Figure 47.1 *Course of Cranial Nerve (CN) III.*
(Used with permission of Mayo Foundation for Medical Education and Research.)

Months to years after the occurrence of an oculomotor lesion, clinical findings of aberrant regeneration of the third nerve may be seen. They include elevation of the eyelid on downward gaze (pseudo–von Graefe sign) or on adduction, with eyelid depression during abduction. The eyelid-gaze synkinesis is best seen with attempted adduction on downward gaze.

Ocular Neuromyotonia

Ocular neuromyotonia is a rare disorder characterized by episodic (lasting seconds to minutes) horizontal or vertical diplopia, occurring either spontaneously or after sustained (10–20 seconds) eccentric gaze. Ocular neuromyotonia may affect the oculomotor, trochlear, or abducens nerve. Most patients have had prior radiotherapy for tumors in the sellar or parasellar region months to years before the onset of ocular neuromyotonia, although in some cases no responsible structural lesion or history of radiotherapy is noted. Ocular neuromyotonia is thought to reflect impaired muscle relaxation due to inappropriate discharges from oculomotor, trochlear, or abducens neurons or axons with unstable cellular membranes.

- A nuclear third nerve lesion may result in an ipsilateral third nerve palsy in addition to bilateral ptosis and contralateral superior rectus muscle weakness.
- Lesions within the orbit that produce third nerve dysfunction usually produce other ocular motor dysfunction as well as optic neuropathy and proptosis.
- Cranial nerve III palsies involving the pupil are generally due to compressive lesions because the pupillomotor fibers are in the outer bundle of the nerve.

Cranial Nerve IV (Trochlear Nerve)

Anatomy

Cranial nerve IV is a general somatic efferent nerve that innervates the superior oblique muscle (adduction, intorsion, and depression of the eye).

The trochlear nucleus lies caudal to the oculomotor nuclear group at the level of the inferior colliculus. The nerve fascicles course posteriorly around the aqueduct to decussate in the dorsal midbrain; they then emerge from the brainstem near the dorsal midline. After traveling through the subarachnoid space, the trochlear nerve pierces the dura into the cavernous sinus, enters the orbit through the superior orbital fissure, and innervates the superior oblique muscle.

A lesion involving the trochlear nucleus or its fascicles may result in contralateral paresis of the superior oblique muscle. A fourth cranial nerve palsy results in hypertropia of the affected eye, which increases with head tilt toward the paralyzed side (positive Bielschowsky head-tilting test). Bilateral fourth nerve palsies result in an inability to depress either eye fully in adduction.

Involvement of the trochlear nerve should always be sought in the presence of a third nerve palsy. In this instance, adduction weakness prevents the superior oblique muscle from depressing the eye. With a functional superior oblique muscle, however, intorsion of the eye occurs when the patient is asked to look down. This eye intorsion is subtle and best noted by watching the movement of a horizontally located conjunctival vessel.

Dysfunction

Lesions anywhere along the course of cranial nerve IV may result in dysfunction. In children and adults, congenital abnormalities and trauma are the most common causes of isolated unilateral or bilateral trochlear nerve palsy in which a cause can be determined. The long course of cranial nerve IV around the mesencephalon, near the edge of the tentorium, makes this nerve particularly vulnerable, and a blow to the forehead may cause a contrecoup contusion of 1 or both fourth nerves by compressing the nerve against the rigid tentorium. Severe frontal head trauma may cause bilateral fourth nerve palsies, probably due to contusion of the anterior medullary velum. Other nontraumatic causes include nuclear aplasia, mesencephalic stroke, tumor, arteriovenous malformation, and demyelination.

Myokymia of the Superior Oblique Muscle

Myokymia of the superior oblique muscle is a uniocular rotatory microtremor that may cause episodes of vertical oscillopsia, shimmering, or transient diplopia. This condition is usually benign. Neurovascular compression of the trochlear nerve at the root exit zone may be responsible for many cases of superior oblique myokymia.

- In children and adults, congenital abnormalities and trauma are the most common causes of isolated unilateral or bilateral trochlear nerve palsy in which a cause can be determined.

Cranial Nerve VI (Abducens Nerve)

Anatomy

Cranial nerve VI innervates the ipsilateral lateral rectus muscle (abduction of the eye).

Located in the dorsal pons, the abducens nucleus contains both motor neurons to the ipsilateral lateral rectus muscle and interneurons that connect through the medial longitudinal fasciculus to the contralateral third nerve nucleus. The abducens nuclear complex coordinates the action of both eyes to produce

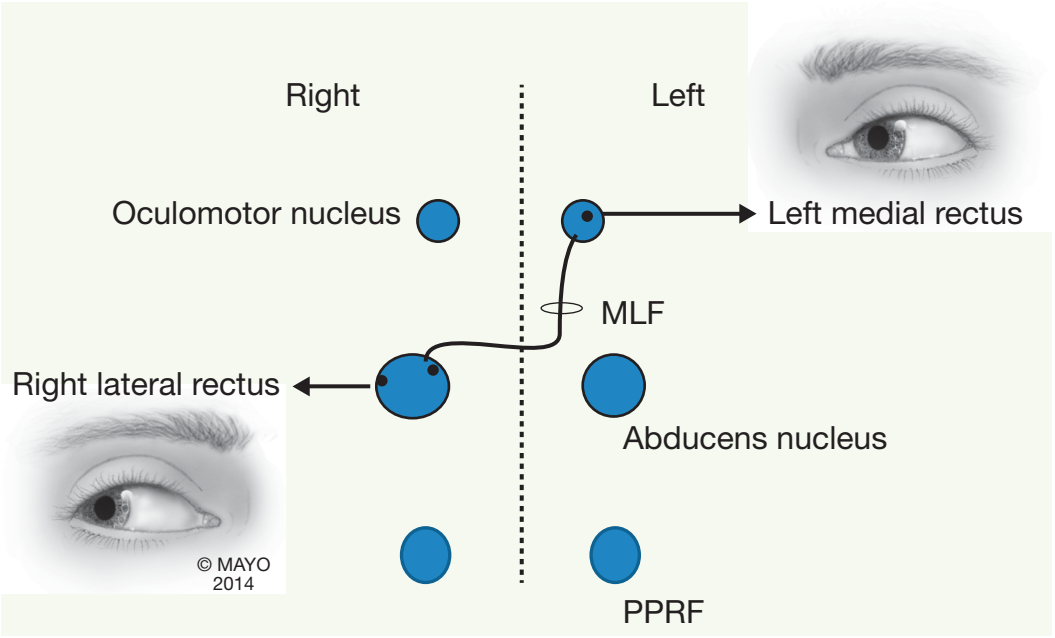

Figure 47.2 *Final Common Pathway of Horizontal Gaze. MLF indicates medial longitudinal fasciculus; PPRF, paramedian pontine reticular formation.*
(Used with permission of Mayo Foundation for Medical Education and Research.)

horizontal gaze (Figure 47.2). A nuclear cranial nerve VI palsy differs from an axonal lesion in that a nuclear lesion results in a horizontal gaze palsy, whereas an axonal lesion results in an inability to abduct the eye (Figure 47.3).

Axons of the abducens motoneurons course ventrally in the pons. The abducens nerve then ascends along the base of the pons, enters the Dorello canal, the cavernous sinus, and finally the superior orbital fissure. It may be difficult at times to determine whether the nerve has been injured within the subarachnoid space or in its petrous portion, in the Dorello canal. Concomitant involvement of the trigeminal nerve is more likely if the lesion is in the petrous portion. Other clinical findings may point to disease in the petrous bone, such as an otic discharge from chronic otitis media or mastoiditis, or deafness. Retro-orbital pain, involvement of other ocular motor nerves, and, occasionally, an ipsilateral Horner syndrome point to the cavernous sinus as the site of the lesion. The sympathetic fibers to the eye join the abducens nerve for a short distance within the cavernous sinus, and thus a unilateral abducens nerve lesion associated with an ipsilateral Horner syndrome is of localizing value.

Dysfunction

Cranial nerve VI can be affected anywhere along its course (Figure 47.4 and Table 47.4). The onset and duration may help in guiding the diagnosis.

Möbius Syndrome and Duane Retraction Syndrome

Möbius syndrome and Duane retraction syndrome are due to lesions of the abducens nucleus early in life. Patients with Möbius syndrome have facial diplegia and may have other cranial nerve abnormalities. Duane retraction syndrome is characterized by a narrowing of the palpebral fissure and occasionally globe retraction on adduction. Patients with Duane syndrome seldom complain of diplopia.

Cavernous Sinus Syndrome

Because cranial nerve VI is free floating in the cavernous sinus, it is most likely to be affected by cavernous sinus pathology (aneurysm, fistula, thrombosis, or neoplasm) (Figure 47.5). Cranial nerves III, IV, and V (ophthalmic branch and maxillary branch) are invested in the lateral edge of the cavernous sinus dura, but they may also be affected. Horner syndrome may develop because the cavernous segment of the carotid artery also travels through this structure and the sympathetic fibers travel with it.

Gradenigo Syndrome

An infectious or neoplastic process that spreads to the tip of the petrous bone may result in Gradenigo syndrome, which includes abducens nerve paresis, ipsilateral facial pain (usually retro-orbital), and deafness.

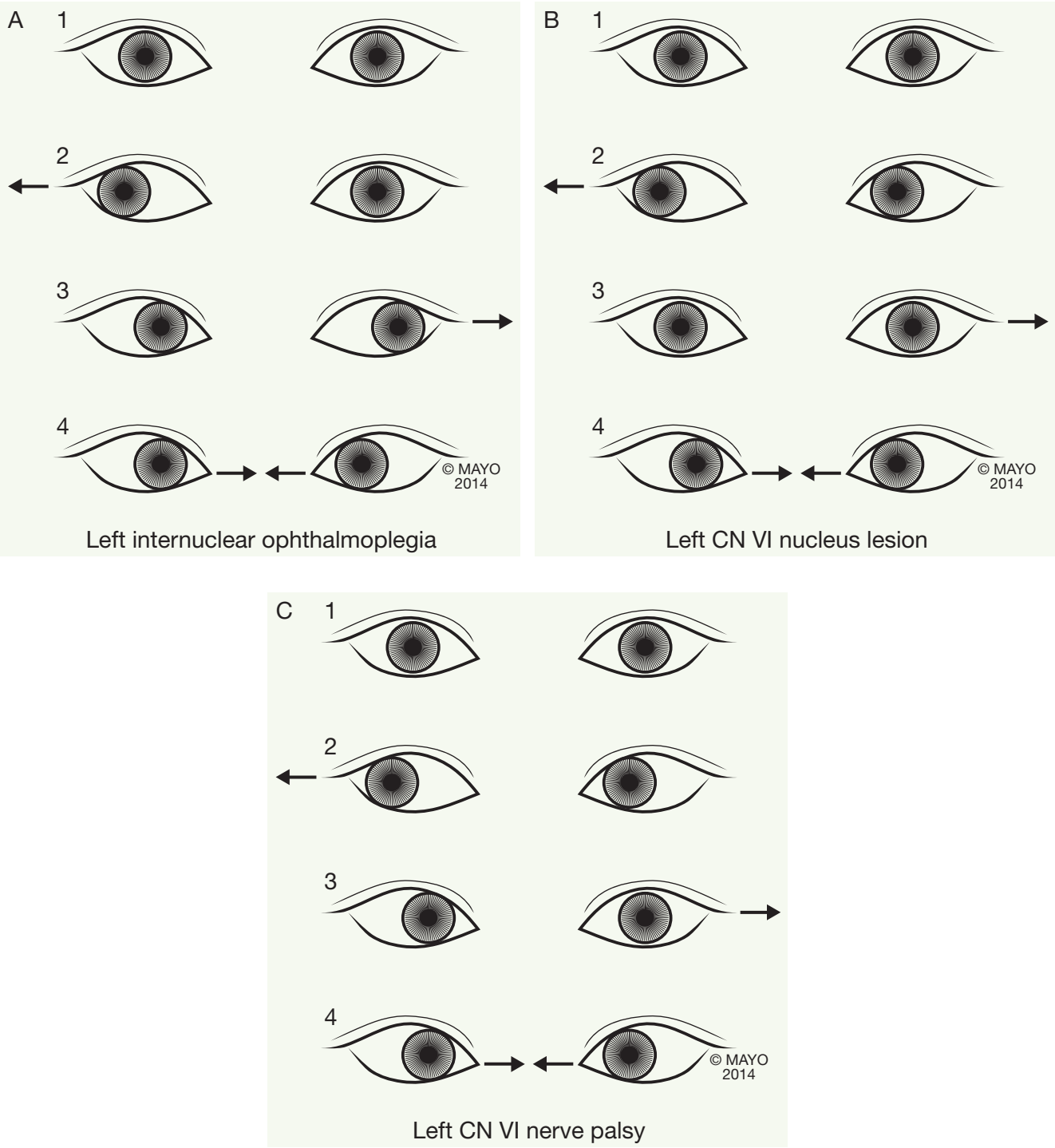

Figure 47.3 *Pathologic Eye Movements.A, Left internuclear ophthalmoplegia. When the patient looks in the direction of the arrow in 2, to the right, the left eye cannot adduct. However, the patient can abduct the left eye (3) and converge the eyes (4). B, Left cranial nerve (CN) VI nucleus lesion. A lesion of this nucleus involves axons innervating the ipsilateral lateral rectus muscle and axons crossing the midline and projecting through the medial longitudinal fasciculus to the neurons in the oculomotor nucleus that innervate the medial rectus muscle. The result is that the patient cannot abduct the left eye or adduct the right eye (3). C, Left CN VI palsy. In contrast to a nuclear lesion, a left CN VI palsy results in an inability to abduct the left eye (3); however, the right eye can adduct because the medial longitudinal fasciculus is still intact.*

(Adapted from Benarroch EE, Daube JR, Flemming KD, Westmoreland BF. Mayo Clinic medical neurosciences: organized by neurologic systems and levels. 5th ed. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2008. Chapter 15B, The posterior fossa level: cerebellar, auditory, and vestibular systems; p. 633–67. Used with permission of Mayo Foundation for Medical Education and Research.)

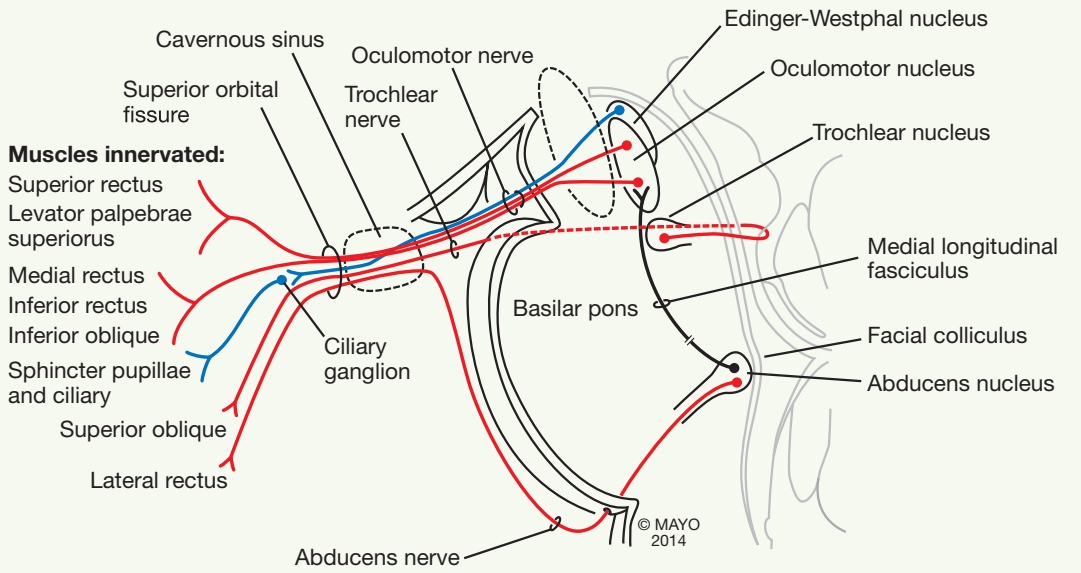

Figure 47.4 *Course of Cranial Nerve VI.*
(Used with permission of Mayo Foundation for Medical Education and Research.)

Table 47.4 • Disorders of Cranial Nerve VI

Location of Lesion	Differential Diagnosis
Nucleus	Structural lesion: stroke, hemorrhage, demyelination, tumor, abscess Möbius syndrome Duane retraction syndrome
Fascicles	Structural lesions (as above)[a] Wernicke encephalopathy
Subarachnoid space	Increased intracranial pressure Spontaneous intracranial hypotension Ischemic nerve (diabetes mellitus, collagen-vascular disease, giant cell arteritis, infectious) Vertebrobasilar dolichoectasia or aneurysms Clival tumor (chordoma, chondrosarcoma) Other tumors (meningioma, nasopharyngeal carcinoma, schwannoma)
Dorello canal (temporal bone)	Infectious or neoplastic process of the petrous bone (Gradenigo syndrome)
Cavernous sinus	Tumor (pituitary adenoma, nasopharyngeal carcinoma, craniopharyngiomas, and metastases) Large carotid cavernous aneurysms
Superior orbital fissure	Tumors Trauma

[a] See also Chapter 10, "Ischemic Stroke: Common Causes and Diagnosis," for stroke syndromes with associated cranial nerve VI palsies.

Neoplasms

Pituitary adenomas, nasopharyngeal carcinomas, craniopharyngiomas, and metastases most commonly affect the abducens nerve at the cavernous sinus and superior orbital fissure. Sphenoid sinus carcinoma often causes a sphenocavernous syndrome, but patients may also present with an isolated sixth nerve palsy. Nasopharyngeal carcinoma may compress the sixth nerve because many of these tumors arise

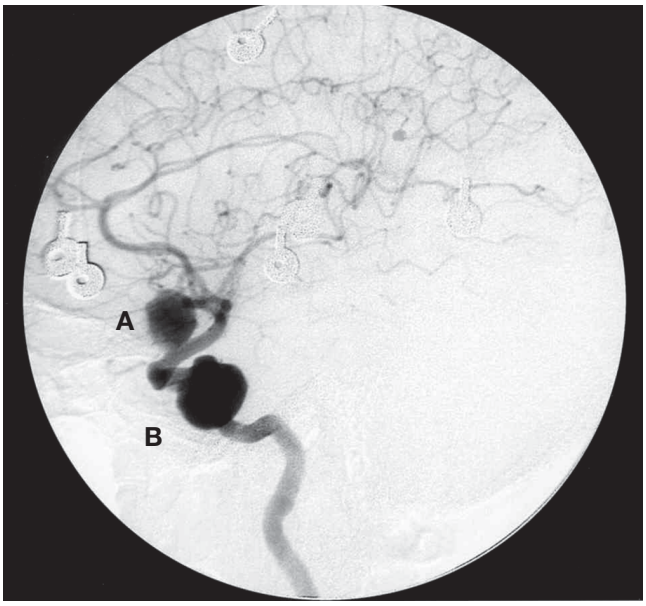

Figure 47.5 *Sixth Nerve Palsy.*
Angiography revealed 2 aneurysms (A and B). The aneurysm at the cavernous segment (B) is the aneurysm responsible for the patient's symptoms.

from the fossa of Rosenmüller immediately beneath the foramen lacerum. Extension of nasopharyngeal carcinoma through the foramen lacerum may cause a trigeminal sensory loss (eg, affecting the maxillary nerve [V2] distribution) and a sixth nerve palsy. Thus, the combination of facial pain or maxillary nerve (V2) sensory loss with a sixth nerve palsy is a common presentation of nasopharyngeal carcinoma.

- A nuclear cranial nerve VI palsy differs from an axonal lesion in that a nuclear lesion results in a horizontal gaze palsy, whereas an axonal lesion results in an inability to abduct the eye.
- Extension of nasopharyngeal carcinoma through the foramen lacerum may cause a trigeminal sensory loss (eg, affecting the maxillary nerve [V2] distribution) and a sixth nerve palsy. Thus, the combination of facial pain or maxillary nerve (V2) sensory loss with a sixth nerve palsy is a common presentation of nasopharyngeal carcinoma.

48 Clinical Neurotology[a]

SCOTT D. EGGERS, MD

Introduction

Normal balance is the consequence of continuous interaction between visual, vestibular, and proprioceptive mechanisms. The vestibular system is a system in which head movements and positions cause mechanical forces to be transduced into electrochemical signals that are relayed to the central nervous system for the purpose of maintaining clear stable vision and equilibrium. With a basic understanding of physiology, common disease processes, and examination techniques, a correct diagnosis can generally be made at the bedside.

The anatomy and physiology of cranial nerve VIII and its pathways are discussed in Volume 1. This chapter focuses on the clinical approach and diagnosis of clinical neurotologic disorders.

The History From Patients With Dizziness and Vertigo

The history is the most important part of the vestibular evaluation but is often challenging and tedious because of vague symptoms and imprecise vocabulary. Rather than the description of the symptom characteristics themselves, an accurate description of the tempo and circumstances and any related symptoms often provides the most useful diagnostic information.

What the patient means by *dizziness* or *vertigo* should be expanded upon. Does the patient describe internal vertigo (subjective sensation of self-motion) or external vertigo (visual illusion of environmental spinning or flowing)? Are symptoms referable to the semicircular canals (sense of rotation) or otolith organs (sense of translation or tilt) or to their connections? Does the patient describe oscillopsia (illusion that the environment is oscillating) with the head still or only while in motion, or is the dizziness nonvertiginous (sensation of disturbed or impaired spatial orientation such as floating, rocking, or swaying)? Does the patient describe light-headedness, with the sensation of an impending faint? Does the patient describe accompanying postural symptoms, such as unsteadiness or a sensation of directional pulsion?

The tempo can usually be divided into acute persisting symptoms (first attack lasting hours to days), recurrent episodic symptoms, and chronic symptoms. Episodic and chronic symptoms may need to be separated. Important determinations include how the symptoms began and how chronic symptoms fluctuate, how quickly spells reach their maximum intensity, the duration of spells and how they end, and how often the spells occur.

Circumstances provide important diagnostic clues. Are the symptoms truly spontaneous and unprovoked? Can they occur in any position (lying, sitting, standing, and walking), or do they tend to occur while lying down, rolling over, looking up, turning the head, or standing up? Can they be triggered by the Valsalva maneuver or loud noise? Are they better with the eyes open or closed? Are symptoms aggravated by visual motion or complex visual environments? Are they accompanied by any other neurologic or auditory symptoms (hearing loss, aural fullness, or tinnitus)?

[a] Portions previously published in Eggers SD, Zee DS. Evaluating the dizzy patient: bedside examination and laboratory assessment of the vestibular system. Semin Neurol. 2003 Mar;23(1):47–58 and Maldonado Fernandez M, Birdi JS, Irving GJ, Murdin L. Pharmacological treatment for the prevention of vestibular migraine (protocol). Hoboken (NJ): The Cochrane Library/John Wiley & Sons; c2013. p. 1–24. Used with permission.

Abbreviations: APV, acute peripheral vestibulopathy; AVS, acute vestibular syndrome; BPPV, benign paroxysmal positional vertigo; CT, computed tomography; HIT, head impulse test; MRI, magnetic resonance imaging; VOR, vestibuloocular reflex

Examination of Vestibular and Auditory Function

The bedside neurotologic examination includes evaluation of static vestibular balance as well as dynamic vestibular function. Positional testing, assessment of hearing, and other provocative maneuvers can aid in diagnosis. A thorough ocular motor examination should be performed for all patients. Vestibulospinal reflexes can be assessed with gait and station.

Static Vestibular Imbalance

Spontaneous nystagmus with the head stationary is the hallmark of a static uncompensated imbalance in vestibular tone from the vestibuloocular reflex at the level of the semicircular canals or their afferent connections. When peripheral in origin, vestibular nystagmus is typically suppressed by visual fixation. Elicitation of vestibular nystagmus may require eliminating visual fixation by having the patient stare at a blank background, by observing movements of the optic disc during funduscopy while covering the other eye, or by using Frenzel goggles.

Peripheral vestibular nystagmus is a jerk nystagmus (with a slow phase and a fast phase), and the axis of rotation (trajectory) aligns with the action of 1 or more affected semicircular canals. Acute loss of function causes vestibular slow phases toward the side of the lesion because of unopposed tonic activity from the unaffected side, with nystagmus quick phases beating away from the lesion (Figure 48.1). Conversely, abnormal stimulation of a semicircular canal causes nystagmus beating toward the affected side. Although peripheral vestibular nystagmus should not reverse directions in different gaze positions, the law of Alexander describes how vestibular nystagmus is typically most intense when the patient is looking in the direction of the quick phases.

The affected canal or canals can be deduced from the nystagmus trajectory. A horizontal canal process causes horizontal nystagmus, but a vertical canal disorder causes mixed vertical-torsional nystagmus when the eyes are looking straight ahead because of the orientation of the canal and the extraocular muscles that it acts on. A disease affecting the entire labyrinth causes a mixed horizontal-torsional nystagmus due to the combined canal effects.

Pure vertical or pure torsional nystagmus cannot be explained by involvement of a single canal or single labyrinth and implies a central cause. The brisk nystagmus seen in acute peripheral vestibular lesions gradually decreases in intensity until disappearing as the central vestibular system compensates for the imbalance. Therefore, brisk nystagmus persisting for days to weeks suggests involvement of central mechanisms.

Dynamic Vestibular Function

The dynamic function of the vestibulo-ocular reflex (VOR) can be assessed by determining the effect of head rotation on visual acuity and by observing the eye movements in response to low- and high-frequency head rotations. Dynamic visual acuity can be determined by passively rotating the patient's head horizontally or vertically at a frequency of about 2 Hz while the patient views a distance eye chart; the patient is observed for significant loss of visual acuity compared with when the head is still. Such impairment is commonly associated with head motion–induced oscillopsia in a patient with bilateral vestibular loss.

The VOR should be examined as the head is slowly and passively rotated horizontally and vertically through the entire oculomotor range. This slow oculocephalic "doll's eye" maneuver assesses brainstem integrity in comatose patients. It is usually normal (the eyes maintain steady fixation on the target) in ambulatory patients even if they have unilateral or bilateral vestibular hypofunction, as long as the smooth pursuit system is working properly to substitute for a deficient VOR at low frequencies of head rotation.

The head impulse test (HIT) can be performed with alert patients to assess the high-frequency VOR. With the patient's eyes fixated on the examiner's nose, a brief, high-acceleration head impulse is carefully performed to rotate the head no more than about 15° to 1 direction. With an intact VOR, the gaze will hold steady. If the VOR is deficient because of that ear, the eyes will move in the direction of head rotation. The key examination finding is a *catch-up saccade* that immediately follows the head movement required to refixate the eyes back to the target. The catch-up saccade implies that the VOR slow phase was inadequate. An abnormal HIT generally indicates peripheral vestibular dysfunction.

Provocative Maneuvers

Positional testing should be performed primarily to identify benign paroxysmal positional vertigo (BPPV), although some central conditions can also cause positional nystagmus. The Dix-Hallpike test is performed by rotating the head of the seated patient 45° to the side and rapidly moving the patient straight back to the supine head-hanging position to maximally stimulate the posterior semicircular canal, which is affected in most patients (>80%) with BPPV. If the test is negative bilaterally, the supine roll test can be used to assess for horizontal canal BPPV.

Caloric testing is generally reserved for the laboratory evaluation of ambulatory patients, but bedside ice water caloric testing is useful to assess brainstem integrity in comatose patients. If the brainstem pathways are intact, ice water irrigation into the ear of a supine comatose patient causes tonic conjugate eye deviation toward the side of

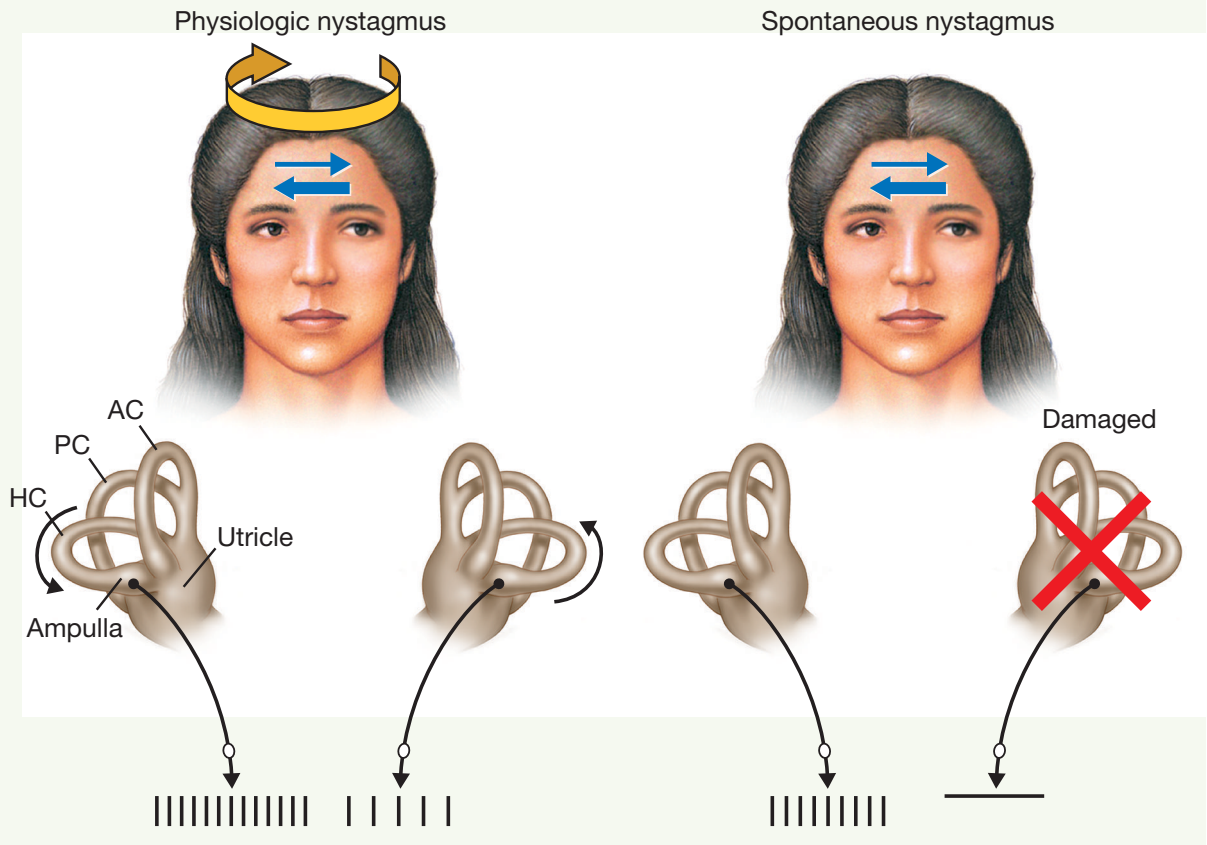

Figure 48.1 *The Vestibuloocular Reflex (VOR) in Physiologic and Pathologic States.*
At rest the primary vestibular afferent firing rate is equal on each side and the eyes remain stationary. Physiologic nystagmus can be generated by rotation of the head to either side. With rotation to the right side, the primary afferent firing rate increases on the right side and decreases on the left side. When the firing rate is greater on the right side, the VOR moves the eyes toward the left (slow component of nystagmus) as long as the patient is not consciously fixating a target. The fast component of nystagmus is generated centrally and moves the eyes quickly in the opposite direction. Thus, the eyes appear to beat toward the right side (right-beat nystagmus). With spontaneous nystagmus from an acute lesion of the left peripheral vestibular system, the eyes similarly appear to be beating toward the right side because the left side has a slower firing rate than the right. With a left peripheral vestibular lesion, the afferent firing rate is greater on the right side than on the left side. Thus, the VOR moves the eyes toward the left (slow phase). This movement is corrected centrally with fast eye movements that direct the eyes toward the right side (right-beat nystagmus). Thin straight arrows indicate the direction of the slow components of nystagmus; thick straight arrows indicate the direction of the fast components of nystagmus; the curved arrow at the top of the patient's head shows the direction of head movement; the curved arrows near the horizontal canals show the direction of endolymph flow in the horizontal semicircular canals. AC indicates anterior canal; HC, horizontal canal; PC, posterior canal.
(Adapted from Baloh RW. Dizziness, hearing loss, and tinnitus. Philadelphia [PA]: F. A. Davis; c1998. p. 36. Used with permission.)

irrigation because of the inhibitory stimulus. (Oppositely directed nystagmus quick phases occur only in awake patients, as described by the phrase "cold opposite, warm same" and the mnemonic *COWS*.)

Clinical Assessment of Hearing

After performing otoscopy, a rough assessment of hearing can be made with a ticking watch, rubbing fingers, or whispering words into each ear. If hearing loss is identified, determine whether it is conductive (external or middle ear) or sensorineural (cochlear or eighth nerve) with a 512-Hz tuning fork.

During the Rinne test, the base of the vibrating tuning fork is placed on the mastoid process (to test bone-conducted hearing), and then the prongs of the fork are placed in front of the ear (to test air-conducted hearing); the patient is asked which is louder. Air conduction is louder in a normal, positive Rinne test (a pattern that is retained in sensorineural hearing loss), but bone conduction is louder in a negative Rinne test with patients who have conductive

hearing loss, such as with otosclerosis, otitis media, or other destructive middle ear processes.

During the Weber test, the base of the tuning fork is placed on the midline of the forehead or on the vertex. Sound will be louder in the ear that has a conductive hearing loss or opposite the ear that has a sensorineural hearing loss.

Laboratory Evaluation

Audiograms should be widely used as part of the evaluation of patients with vestibular symptoms. The frequency and pattern of any hearing loss, comparison of air- and bone-conducted hearing, word recognition, and immittance testing (tympanometry and acoustic reflexes) all provide valuable information in certain vestibular disorders. Basic vestibular function testing consists of video- or electro-oculography for measuring nystagmus in various gaze and head positions, other ocular motor tasks (eg, saccades and pursuit), and bithermal caloric testing. Such testing is ideal for distinguishing peripheral signs from central signs and for measuring the degree of unilateral horizontal semicircular canal paresis. Rotary chair testing (ideal for assessing bilateral vestibular weakness), computerized platform posturography, and vestibular evoked myogenic potentials (for assessing the otolith organs) are performed in more specialized centers.

Imaging Studies

Imaging studies are used to rule out structural causes of vestibular symptoms, although restraint should be exercised since the most common causes of vertigo (BPPV, vestibular neuritis, vestibular migraine, and Meniere disease) produce no imaging abnormalities. Magnetic resonance imaging (MRI) is warranted if symptoms or signs suggest cranial nerve or central nervous system disease (eg, pure vertical or torsional nystagmus, gaze-evoked nystagmus, or atypical positional nystagmus). A vestibular schwannoma (acoustic neuroma) or other cerebellopontine angle mass may be suggested by progressive unilateral hearing loss associated with vestibular and balance signs and is best evaluated by MRI with gadolinium-enhanced axial and coronal internal auditory canal cuts. Computed tomography (CT) of the temporal bone is usually reserved for evaluation of superior semicircular canal dehiscence.

- Peripheral vestibular nystagmus should not reverse directions in different gaze positions.
- Pure vertical or pure torsional nystagmus cannot be explained by involvement of a single canal or single labyrinth and implies a central cause.
- The HIT can be performed with alert patients to assess the high-frequency VOR.
- An abnormal HIT generally indicates peripheral vestibular dysfunction.
- Positional testing should be performed primarily to identify BPPV, although some central conditions can also cause positional nystagmus.
- If the brainstem pathways are intact, ice water irrigation into the ear of a supine comatose patient causes tonic conjugate eye deviation toward the side of irrigation because of the inhibitory stimulus. (Oppositely directed nystagmus quick phases occur only in awake patients, as described by the phrase "cold opposite, warm same" and the mnemonic *COWS*.)

Vestibular Syndromes and Disorders

Introduction

This section reviews commonly encountered vestibular disorders. It is useful to categorize them into groups based on clinical presenting features (Box 48.1).

Acute Vestibular Syndrome

Acute vestibular syndrome (AVS) is the rapid onset (in seconds to hours) of vertigo, nausea and vomiting, imbalance, head motion intolerance, and nystagmus that lasts days to weeks. Of course, the ultimate duration is uncertain when a patient presents with a first-ever attack of vertigo, which may be only the first attack of an episodic vestibular disorder.

Vestibular Neuritis

When the AVS is due to a peripheral vestibular cause, it is called acute peripheral vestibulopathy (APV). Most

Box 48.1 • Differential Diagnosis of Common Vestibular Disorders

Acute
- Vestibular disorder
  - Neuritis
  - Labyrinthitis
- Brainstem disorder
  - Infarction

Episodic
- BPPV
- Meniere disease
- Vestibular migraine
- Superior semicircular canal dehiscence

Chronic
- Bilateral vestibulopathy
- Cerebellopontine angle tumor

Abbreviation: BPPV, benign paroxysmal positional vertigo.

commonly considered a viral or postviral inflammatory condition of the eighth cranial nerve, APV is diagnosed as labyrinthitis if the patient has ipsilateral hearing loss and as vestibular neuritis if the patient does not have any hearing loss. Vestibular neuritis is the second most common peripheral vestibular disorder after BPPV. Vestibular neuritis begins in minutes to hours as severe spinning vertigo, nausea and vomiting, and imbalance without hearing loss or other focal neurologic symptoms or signs. Patients avoid head movement. Symptoms begin improving in 1 to 3 days, and most patients achieve complete symptomatic recovery through a combination of return of vestibular function and "central compensation."

Diagnosis involves identifying an acute vestibular tone imbalance due to unilateral peripheral vestibular loss as described above. A key examination sign is spontaneous horizontal-torsional nystagmus with slow phases toward the affected ear and quick phases away from it. The nystagmus intensifies when the patient looks toward the quick-phase direction and diminishes (but does not reverse) when the patient looks toward the slow-phase direction (the law of Alexander). A second key examination feature is an abnormal HIT when the patient's head is rotated toward the affected ear. Patients are usually unsteady but can take steps with assistance, falling toward the side of the lesion with Romberg testing. Timely vestibular function testing is useful to confirm the presence and severity of peripheral vestibular weakness. An audiogram can be used to rule out hearing loss that may suggest an alternative diagnosis.

The natural history of vestibular neuritis without treatment is generally excellent, with most patients achieving full symptomatic recovery within weeks to months. Symptomatic treatment of vertigo and nausea includes antihistamines, benzodiazepines, phenothiazines, and anticholinergics, although use of such vestibular suppressants should be discontinued after a few days if the acute symptoms subside. Oral corticosteroids (but not antivirals) may improve medium- and long-term outcomes. Vestibular rehabilitation therapy should be started early.

Labyrinthitis and Other Peripheral Disorders

APV associated with acute hearing loss is referred to as *acute labyrinthitis* or *neurolabyrinthitis*. The vestibular manifestations and signs are the same as in vestibular neuritis. *Bacterial labyrinthitis* is typically associated with acute and chronic otitis media or mastoiditis. *Suppurative labyrinthitis* generally causes profound and permanent loss of auditory and vestibular function. *Syphilitic labyrinthitis* may cause recurrent episodes of vertigo and hearing loss that usually progress to severe bilateral dysfunction over months. Features of *herpes zoster oticus* (Ramsay Hunt syndrome) include 1 or more of the following: ear pain, vesicular eruption in the ear canal, hearing loss, vertigo, and facial weakness. *Labyrinthine infarction* can occur from occlusion of the internal auditory artery due to all the same factors that cause other forms of vertebrobasilar ischemia.

Brainstem and Cerebellar Infarction

Distinguishing patients who have an APV such as vestibular neuritis from those who have an acute brainstem or cerebellar infarction can be challenging and is a common source of misdiagnosis in the emergency department. Clear, localizing neurologic signs on examination, such as dysarthria, limb dysmetria, and a complete Wallenberg syndrome are often absent, especially in medial cerebellar infarctions. Hearing loss does not always imply a peripheral labyrinthine cause since an anterior inferior cerebellar artery territory infarction can cause labyrinthine infarction with vertigo and hearing loss as well as lateral pontine and cerebellar ischemia. CT is insensitive to acute infarction in the posterior fossa. Furthermore, AVS may also be the first manifestation of an episodic disorder such as vestibular migraine or Meniere disease.

In emergency department patients with AVS, a brainstem or cerebellar stroke or another central lesion (eg, multiple sclerosis plaque) is highly suggested by the presence of any of the following: a normal HIT, direction-changing nystagmus in eccentric gaze, or skew deviation on cover testing. Severe truncal ataxia (an inability to sit unassisted) also predicts a central lesion. Conversely, the combination of an abnormal HIT, a direction-fixed nystagmus beating toward the unaffected ear, *and* the absence of skew deviation on cover testing is consistent with an acute peripheral vestibulopathy (Table 48.1).

- APV is diagnosed as labyrinthitis if the patient has ipsilateral hearing loss and as vestibular neuritis if the patient does not have any hearing loss.

Episodic Vertigo

Causes of episodic vertigo are compared in Table 48.2. Triggers, duration of the attacks, and any accompanying features must be identified to distinguish these entities.

Benign Paroxysmal Positional Vertigo

BPPV is the most common vestibular disorder. The mean age at onset is about 50 years. Uncommon before age 35, BPPV may develop after head trauma or weeks after vestibular neuritis. BPPV is caused by dislodged otoconia from the utricle that float into a semicircular canal and render it abnormally excited by changes in head position with respect to gravity. Few conditions other than BPPV cause brief, purely positional episodes of isolated vertigo. Symptoms of BPPV consist of brief (<30 seconds) episodes of spinning vertigo triggered by changes in head position that occur with looking up, lying down, or rolling over or upon sitting up first thing in the morning. Aside from nausea and imbalance, other neurologic and otologic

Table 48.1 • Clues to Distinguish Vestibular Neuritis From an Acute Central Cause

Feature	Vestibular Neuritis	Acute Central Cause (eg, Stroke)
History	Vertigo No dysarthria or other focal symptoms	May have accompanying focal neurologic symptoms: dysarthria, diplopia, sensorimotor changes
Precipitating factor	Recent illness	In young patients, an inferior cerebellar or lateral medullary stroke may be due to dissection
Neurologic examination	No focal symptoms Typically able to walk	Focal neurologic symptoms should be sought, including Horner syndrome, dysarthria, dysmetria, and gait disturbance Patients may have severe gait ataxia or truncal ataxia (or both)
Nystagmus	Unidirectional (does not change direction with the gaze) Usually horizontal	Spontaneous vertical or bidirectional gaze-evoked nystagmus (ie, the direction of nystagmus changes with the gaze)
Head impulse test	Abnormal	Normal

Adapted from Kerber KA. Acute constant dizziness. Continuum (Minneap Minn). 2012 Oct;18(5 Neuro-otology):1041–59. Used with permission.

symptoms are absent. Attacks generally recur over a limited period that may be days, weeks, or (exceptionally) months.

BPPV affects the posterior semicircular canal in 80% to 90% of patients. Diagnosis consists of identifying mixed upbeat-torsional nystagmus with the Dix-Hallpike test, which usually begins after a few seconds of latency, lasts 10 to 20 seconds, is fatigable with repeated testing, and may reverse directions upon sitting up again. Simple office treatments include the Epley canalith repositioning procedure (Figure 48.2) and the Semont liberatory maneuver; both are highly effective at moving the offending canaliths back into the utricle. BPPV affects the horizontal canal about 10% of the time and should be considered when the Dix-Hallpike test is negative. Diagnosis with the supine roll test involves turning the head of the supine patient 90° to the right and then to the left and observing for horizontal nystagmus that most commonly beats toward the ground. Several repositioning maneuvers exist for horizontal canal BPPV.

Meniere Disease

Meniere syndrome is an inner ear disorder characterized by recurrent spontaneous attacks of vertigo, fluctuating sensorineural hearing loss, aural fullness, and tinnitus. When not attributed to an identifiable cause (eg, syphilis), it is called Meniere disease. Meniere disease is the third most common peripheral vestibular disorder after BPPV and vestibular neuritis. It typically affects 1 ear, although contralateral involvement can develop. Distortion of the membranous labyrinth due to endolymphatic hydrops is thought to be the pathologic basis of Meniere disease. Ruptures in the membranous labyrinth are thought to allow mixing of endolymph and perilymph fluid, leading to an excitatory and then an inhibitory nystagmus during attacks.

The unpredictable episodes of rotatory vertigo generally last 30 minutes to a few hours. Sudden unexplained falls without vertigo or loss of consciousness can occur as *Tumarkin otolithic crises* or *drop attacks*. Sensorineural hearing loss is fluctuating but progressive, and it affects predominantly low frequencies early on. Often the auditory symptoms herald an impending attack of vertigo. Occasionally, auditory symptoms are initially lacking but become apparent within the first year. Diagnosis is clinical. Audiometric testing is essential to document the presence of fluctuating

Table 48.2 • Causes of Episodic Vertigo

Cause	Clinical Features	Associated Symptoms	Treatment
BPPV	Brief (<30 s) episodes of vertigo triggered by positional change	None	Canalith repositioning
Meniere disease	Spontaneous episodes of vertigo that last from 30 min to hours	Hearing loss Tinnitus	Salt restriction Diuretic Intratympanic corticosteroid or gentamicin
Vestibular migraine	Spontaneous episodes of vertigo that last from minutes to days	Migraine (usually not at times of vertigo)	Migraine prophylactic medication
Superior semicircular canal dehiscence	Spontaneous episodes of vertigo that may be triggered by the Valsalva maneuver	Autophony Mild hearing loss	Surgery

Abbreviation: BPPV, benign paroxysmal positional vertigo.

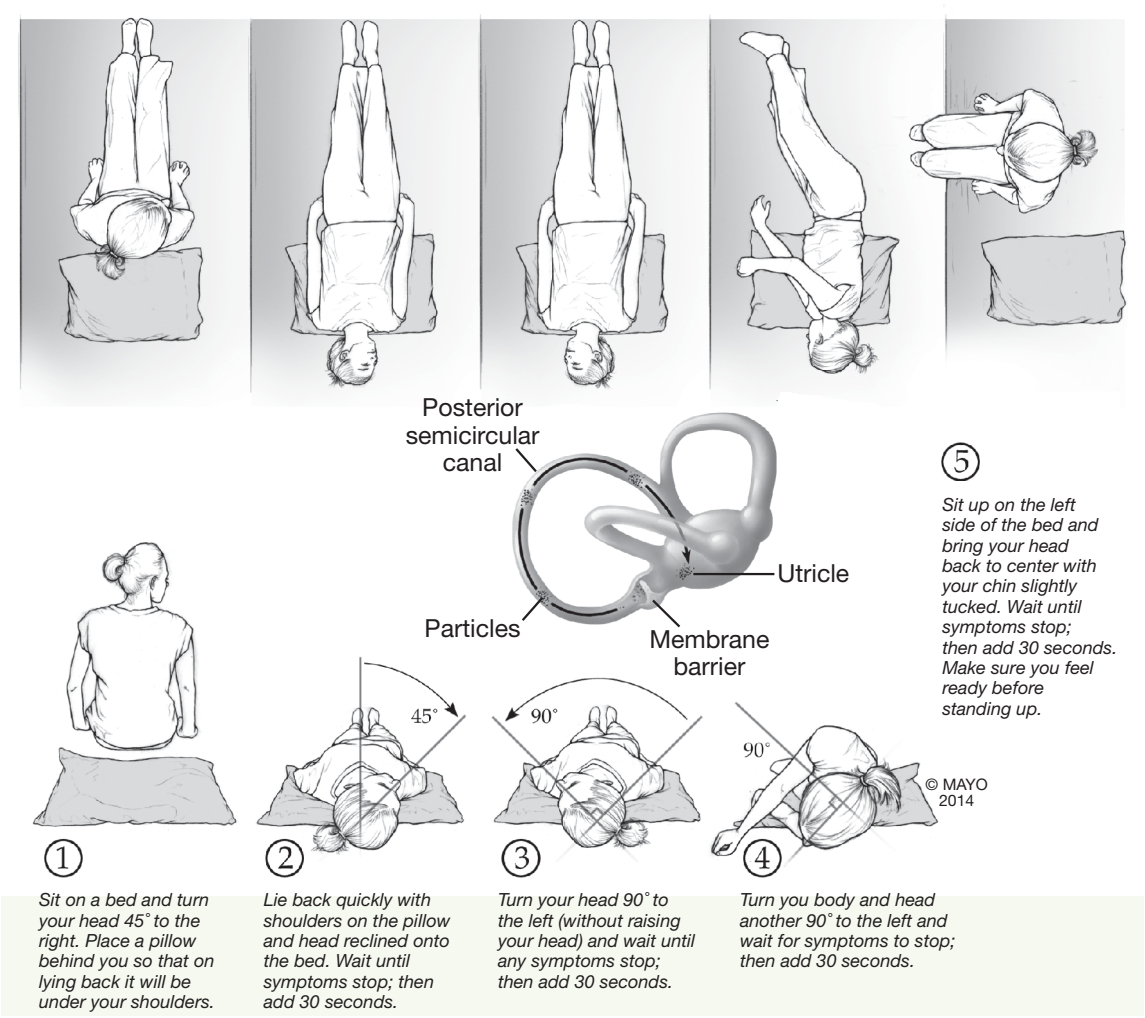

Figure 48.2 *Canalith Repositioning Procedure for Self-Treatment of Right Posterior Canal Benign Paroxysmal Positional Vertigo.*

(Used with permission of Mayo Foundation for Medical Education and Research.)

(low-frequency) sensorineural hearing loss. Treatment is aimed at controlling the frequency of vertigo. Medical therapy typically begins with salt restriction and diuretics. Intratympanic corticosteroids or gentamicin can be helpful, but more ablative surgical procedures are sometimes pursued.

Vestibular Migraine

Migraine is an increasingly recognized and studied cause of episodic vertigo that may affect up to 1% of the general population and may be the most common cause of recurrent nonpositional attacks of vertigo. Diagnostic criteria for vestibular migraine include the following:

1. At least 5 episodes of vestibular symptoms of moderate or severe intensity lasting 5 minutes to 72 hours and fulfilling #3.
2. A current or past history of migraine with or without aura according to the International Classification of Headache Disorders.
3. At least 50% of episodes are associated with at least one of the following migraine features: migrainous headache (2 of 4: unilateral, pulsating, moderate/severe, aggravation with routine activity), photophobia and phonophobia, or visual aura.
4. Not better accounted for by another disorder.

Vertigo attacks can occur during headaches but often occur during headache-free intervals. Only about 25% of patients reliably experience headaches during vertigo attacks. Vertigo attacks typically last from minutes to days. If examined during an attack, patients with vestibular migraine may show spontaneous or positional nystagmus that can have central or peripheral features, but examination findings are normal between attacks. Minor auditory symptoms are common, but objective hearing loss is not. These features can cause diagnostic ambiguity with Meniere disease or BPPV. Only 1% to 2% of patients with vestibular migraine meet criteria for migraine with brainstem aura.

Prospective treatment trials are lacking, so vestibular migraine is managed with general migraine prophylactic strategies and vestibular suppressants as needed for acute attacks.

Superior Semicircular Canal Dehiscence

Superior semicircular canal dehiscence is a condition in which the bony roof of the superior semicircular canal, which separates it from the floor of the middle cranial fossa, is open, changing the fluid dynamics and transmission of sound energy through the labyrinth. This can result in brief episodes of vertigo and nystagmus (mainly torsional) in response to ipsilateral loud noise (Tullio phenomenon), the Valsalva maneuver, nose blowing, or other changes in middle ear pressure. A low-frequency conductive hearing loss may mimick otosclerosis, but the patient may have remarkably good hearing to bone-conducted sound, producing a lateralizing Weber test and an air-bone gap on audiometric testing. Patients with superior semicircular canal dehiscence may describe autophony (hearing their own voice too loudly in the affected ear) or pulsatile tinnitus. Diagnosis is based on provoking the symptoms and nystagmus on examination with provocative maneuvers, demonstrating the dehiscence with high-resolution temporal bone CT, and finding certain abnormalities with vestibular-evoked myogenic potential testing. Treatment is surgically plugging the canal.

- Symptoms of BPPV consist of brief (<30 seconds) episodes of spinning vertigo triggered by changes in head position that occur with looking up, lying down, or rolling over or upon sitting up first thing in the morning.
- Meniere disease is the third most common peripheral vestibular disorder after BPPV and vestibular neuritis.
- Vestibular migraine may be the most common cause of recurrent nonpositional attacks of vertigo, affecting up to 1% of the general population.
- Superior semicircular canal dehiscence can result in brief episodes of vertigo and nystagmus (mainly torsional) in response to ipsilateral loud noise (Tullio phenomenon), the Valsalva maneuver, nose blowing, or other changes in middle ear pressure.
- Patients with superior semicircular canal dehiscence may describe autophony (hearing their own voice too loudly in the affected ear) or pulsatile tinnitus.

Progressive Imbalance

Typically, patients with slowly progressive imbalance without vertigo have a condition other than a peripheral vestibular disorder, such as cerebellar ataxia, progressive supranuclear palsy, or myelopathy. Patients with vestibular disorders may present occasionally with slowly progressive imbalance in the absence of vertigo.

Bilateral Vestibulopathy

Patients with progressive bilateral loss of vestibular function often report oscillopsia or visual blurring of images during head or whole body movements, such as while walking quickly or riding on a bumpy road, because of VOR failure. In the absence of other neurologic problems, sensory ataxia may be relatively mild but will be worse in the dark, on uneven surfaces, or with the tandem Romberg test in the office. Bedside diagnosis requires demonstration of bilaterally impaired dynamic vestibular function with the HIT and dynamic visual acuity as described above. Hearing loss may or may not be an accompanying feature.

The causes of bilateral vestibulopathy are broad (Table 48.3). Unless a specific treatable cause is identified, vestibular rehabilitation therapy is the mainstay of management.

Cerebellopontine Angle Tumors

Vestibular schwannomas (also called acoustic neuromas), the most common temporal bone tumors, are benign nerve sheath tumors that usually arise in the medial portion of the internal auditory canal. Most patients (95%) present with progressive (or occasionally sudden), unilateral, high-frequency sensorineural hearing loss and tinnitus. Balance symptoms can occur. Most often, they are a slowly progressive unsteadiness due to gradual unilateral vestibular hypofunction with concomitant central compensation. If the patient hyperventilates, ipsilesional nystagmus may be induced. Rarely, these tumors enlarge within the cerebellopontine angle and compress adjacent cranial nerves or the cerebellum. Patients who have progressive unilateral (or significantly asymmetric) sensorineural hearing loss, especially with imbalance or vestibular dysfunction, warrant MRI of the brain.

Meningiomas account for 10% of cerebellopontine angle tumors and can usually be differentiated from vestibular schwannomas with MRI. Only 60% of

Table 48.3 • Causes of Bilateral Vestibulopathy

Category	Disorder
Infectious	Bilateral vestibular neuritis Meningoencephalitis
Inflammatory	Cogan syndrome Autoimmune conditions
Neoplastic	Bilateral vestibular schwannoma (neurofibromatosis type 2)
Toxic or metabolic	Aminoglycoside antibiotics (especially gentamicin)
Degenerative	Spinocerebellar ataxia Multiple systems atrophy
Other	Bilateral Meniere disease

meningiomas are associated with unilateral hearing loss, but they are more likely than vestibular schwannomas to invade other cranial nerves and the middle ear.

- Vestibular schwannomas (also called acoustic neuromas), the most common temporal bone tumors, are benign nerve sheath tumors that usually arise in the medial portion of the internal auditory canal. Most patients (95%) present with progressive (or occasionally sudden), unilateral, high-frequency sensorineural hearing loss and tinnitus.

Auditory Disorders

Hearing Loss

The auditory symptoms described in the preceding section are accompanied by other vestibular or neurologic symptoms or signs that would prompt neurologic referral and guide diagnosis. Isolated hearing loss is rarely caused by central nervous system injury because of the redundant crossed and uncrossed auditory pathways. Evaluation of hearing loss begins with distinguishing between conductive loss (from external auditory canal occlusion, tympanic membrane disease, ossicular chain dysfunction, or middle ear fluid or mass) and sensorineural loss (from cochlear or, less commonly, auditory nerve dysfunction due to aging, noise, infection, ototoxins, autoimmune, or congenital causes). Congenital hearing loss can be part of Waardenburg syndrome, Alport syndrome, or Usher syndrome or be nonsyndromic. Noise exposure (typically high-frequency noise with a 4,000-Hz "notch") is the most common preventable cause of sensorineural hearing loss.

Sudden or rapidly progressive unilateral or bilateral sensorineural hearing loss (abrupt or within <48 hours) occurs in various vasculitides and systemic autoimmune diseases. Nonsyphilitic interstitial keratitis suggests Cogan syndrome; branch retinal artery occlusions, vestibulopathy, and encephalopathy preferentially affecting the corpus callosum occur in Susac syndrome. Isolated, sudden hearing loss is often considered to result from a viral infectious, autoimmune, or vascular cause and, without good data, is treated empirically with high-dose systemic or intratympanic corticosteroids.

Box 48.2 • Differential Diagnosis of Pulsatile Tinnitus

- Internal carotid artery pathology (atherosclerosis, dissection)
- Arteriovenous malformation
- Dural arteriovenous fistula
- Highly vascular tumors (glomus jugulare tumor)
- Increased intracranial pressure (usually bilateral pulsatile tinnitus)
- Superior semicircular canal dehiscence
- High-riding jugular bulb or jugular bulb dehiscence
- Increased outflow (aortic stenosis, hyperthyroidism)

Pulsatile Tinnitus

Fluctuating nonpulsatile tinnitus is a typical feature of Meniere disease, and steady tinnitus frequently occurs with other causes of sensorineural hearing loss. Pulsatile (pulse-synchronous) tinnitus often suggests an arterial or venous cause; however, the differential diagnosis is broad (Box 48.2). Essential palatal myoclonus causes rapid ear clicking that can be confused for tinnitus. Palatal tremor due to brainstem disease in the Guillain-Mollaret triangle does not generally cause auditory symptoms.

- Isolated hearing loss is rarely caused by central nervous system injury because of the redundant crossed and uncrossed auditory pathways.
- Nonsyphilitic interstitial keratitis suggests Cogan syndrome; branch retinal artery occlusions, vestibulopathy, and encephalopathy preferentially affecting the corpus callosum occur in Susac syndrome.

49 Disorders of the Cranial Nerves and Brainstem

KELLY D. FLEMMING, MD

Introduction

The comprehensive anatomy of the cranial nerves is covered in Volume 1. This chapter summarizes the anatomy of the cranial nerves and discusses clinical disorders affecting the cranial nerves and brainstem. More specifically, this chapter covers cranial nerves I, V, VII, and IX through XII and the brainstem. Cranial nerves III, IV, and VI are covered in Chapter 47 ("Neuro-ophthalmology: Extraocular Muscles and Cranial Nerves III, IV, and VI"), and cranial nerve XIII is covered in Chapter 48 ("Clinical Neurotology"). The cranial nerves, their components, and their functions are summarized in Table 49.1.

Cranial Nerve I (Olfactory Nerve)

Anatomy

The olfactory nerve is a special visceral afferent nerve that functions in the sense of smell. The axons of the olfactory receptor cells within the nasal cavity extend through the cribriform plate to the olfactory bulb. These olfactory receptor cell axons synapse with mitral cells in the olfactory bulb. Mitral cell axons project to the primary olfactory cortex and amygdala. The olfactory cortex interconnects with various autonomic and visceral centers.

Dysfunction

Specific terminology is used to describe disorders of smell. *Anosmia* refers to a lack of sense of smell; *hyposmia*, to a decreased sense of smell; and *hyperosmia*, to an increased sense of smell. *Cacosmia* refers to the perception of a bad smell. *Dysosmia* describes a distorted smell perception, which can occur with seizure disorders of the temporal lobe.

Disorders of cranial nerve I can occur anywhere along its pathway. The differential diagnosis of olfactory nerve disorders is listed in Table 49.2. Head trauma and neurodegenerative disease are among the most common causes of a reduced sensation of smell.

Cranial Nerve II (Optic Nerve)

Cranial nerve II is covered in Chapter 45 ("Neuro-ophthalmology: Visual Fields") and Chapter 46 ("Neuro-ophthalmology: Disorders of Visual Perception, Pupils, and Eyelids").

Cranial Nerve III (Oculomotor Nerve)

Cranial nerve III is covered in Chapter 47, "Neuro-ophthalmology: Extraocular Muscles and Cranial Nerves III, IV, and VI."

Cranial Nerve IV (Trochlear Nerve)

Cranial nerve IV is covered in Chapter 47, "Neuro-ophthalmology: Extraocular Muscles and Cranial Nerves III, IV, and VI."

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging

Table 49.1 • Summary of Cranial Nerves

Cranial Nerve	Type	Ganglion or Nucleus	Function
I Olfactory	SVA	Olfactory receptor cells Olfactory bulb or tract	Sense of smell
II Optic	SSA	Retinal ganglion cells	Vision
III Oculomotor	GSE	Oculomotor nucleus	Innervates inferior, medial, and superior recti and inferior oblique muscles
	GVE	Edinger-Westphal nucleus Ciliary ganglion	Preganglionic parasympathetic to pupil and ciliary muscle
IV Trochlear	GSE	Trochlear nucleus	Innervates superior oblique muscle
V Trigeminal	SVE	Motor nucleus of V	Innervates muscles of mastication
	GSA	Trigeminal ganglion Spinal tract and nucleus of V	Ipsilateral pain and temperature sensation of face and supratentorial dura mater
	GSA	Trigeminal ganglion Principal sensory nucleus of V	Vibration, proprioception, tactile discrimination of ipsilateral face
	GSA	Mesencephalic nucleus of V	Unconscious proprioception of jaw; reflexive chewing
VI Abducens	GSE	Abducens nucleus	Innervates lateral rectus muscle
VII Facial	SVE	Facial nucleus (motor nucleus of VII)	Innervates muscles of facial expression and stapedius muscle
	GVE	Superior salivatory nucleus Submandibular ganglion	Innervates submandibular and sublingual glands (salivation)
		Superior salivatory nucleus (lacrimal nucleus) Pterygopalatine ganglion	Lacrimation (tearing) and nasal mucosa
	SVA	Geniculate ganglion Nucleus solitarius (rostral)	Taste buds of anterior two-thirds of tongue
	GSA	Trigeminal ganglion Spinal nucleus of V	Somatic sensation of external ear
VIII Vestibulocochlear	SSA	Vestibular ganglion Vestibular nuclei	Controls posture and movement of body and eyes relative to angular and linear acceleration
	SSA	Spiral ganglion	Hearing
IX Glossopharyngeal	SVE	Nucleus ambiguus	Innervates stylopharyngeus muscle
	GVE	Inferior salivatory nucleus Otic ganglion	Innervates parotid gland (salivation)
	GVA	Inferior ganglion	Input from carotid sinus baroreceptors and carotid body chemoreceptors
		Nucleus solitarius (caudal)	Tactile input from posterior third of tongue, pharynx, middle ear, and auditory canal
	SVA	Inferior ganglion Nucleus solitarius (rostral)	Taste buds of posterior third of tongue
	GSA	Superior ganglion Spinal nucleus of V	Somatic sensation of external ear
X Vagus	SVE	Nucleus ambiguus	Innervates muscles of pharynx and larynx
	GVE	Dorsal motor nucleus of X	Preganglionic parasympathetic to viscera, including heart, lungs, and gastrointestinal tract
	GVA	Inferior ganglion Nucleus solitarius (caudal)	Visceral sensation
	SVA	Inferior ganglion Nucleus solitarius (rostral)	Taste buds on epiglottis and pharyngeal wall
	GSA	Superior ganglion Spinal nucleus of V	Somatic sensation of external ear
XI Accessory	SVE	Cranial: nucleus ambiguus Spinal: ventral horn cells (cervical)	Innervates muscles of larynx (with X) Innervates sternocleidomastoid and trapezius muscles
XII Hypoglossal	GSE	Hypoglossal nucleus	Tongue movement

Abbreviations: GSA, general somatic afferent; GSE, general somatic efferent; GVA, general visceral afferent; GVE, general visceral efferent; SSA, special somatic afferent; SVA, special visceral afferent; SVE, special visceral efferent.

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

Table 49.2 • Causes of Anosmia and Hyposmia

Location of Disorder	Cause
First-order neuron	Nasal and paranasal sinus inflammatory disease Nasal neoplasms: esthesioneuroblastoma, melanoma, squamous cell carcinoma Head trauma Upper respiratory tract infection Drugs: cocaine Iatrogenic interventions (surgery, radiotherapy)
Olfactory bulb	Intracranial neoplasms: olfactory groove or cribriform plate meningioma, frontal lobe glioma, other frontal or temporal lobe tumors—Foster Kennedy syndrome (ipsilateral reduction in smell, ipsilateral optic atrophy, and contralateral papilledema generally due to tumor affecting olfactory bulb and optic nerve) Developmental: Kallmann syndrome (hypogonadism, anosmia) Infectious: meningitides, syphilis
Other	Aging Degenerative disorders: Alzheimer disease, Parkinson disease, Huntington disease Endocrine: diabetes mellitus, hypothyroidism, adrenal insufficiency, pseudohypoparathyroidism Metabolic: vitamin A, B_6, or B_{12} deficiency; zinc or copper deficiency; kidney or liver disease; malnutrition Toxins or drugs: cigarette smoking, benzene, carbon disulfide, chlorine, formaldehyde, solvents, sulfuric acid, lead, cadmium, nickel, silicon dioxide Medications (numerous): common offenders include chemotherapeutic agents, antipsychotics, certain antibiotics Radiotherapy of head and neck Epilepsy or migraine (olfactory aura) Psychiatric

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

Cranial Nerve V (Trigeminal Nerve)

Anatomy

The trigeminal nerve has both motor and sensory components. The motor portion of V innervates muscles of mastication in addition to the anterior belly of the digastric, mylohyoid, and tensor tympani muscles. These muscles aid in opening and closing the jaw. The motor portion of V exits the skull at the foramen ovale. An ipsilateral motor V palsy results in the jaw deviating to the weak side. Because there is bilateral corticobulbar input, a unilateral upper motor neuron lesion does not cause weakness of the jaw.

The sensory division of V carries pain and temperature of the face (via the spinal nucleus of V), light touch (via the chief sensory nucleus of V), and unconscious jaw proprioception (via the mesencephalic nucleus of V).

The sensory portion of V has 3 divisions: ophthalmic (V1), maxillary (V2), and mandibular (V3). Receptors from each division carry general somatic afferent information to the brainstem. The entry points into the skull are clinically important: V1 enters at the superior orbital fissure and travels through the cavernous sinus before reaching the trigeminal ganglion; V2 enters at the foramen rotundum and, in most people, also passes through the cavernous sinus to the trigeminal ganglion; and V3 enters at the foramen ovale. A lesion of the sensory component of V may reduce the sensation of pain, temperature, and touch of the face on the ipsilateral side relevant to the division affected (Figure 49.1).

Dysfunction

Lesions may affect cranial nerve V anywhere along its course (Figure 49.2). The differential diagnosis of cranial nerve V lesions is listed by location in Table 49.3.

Trigeminal neuralgia is a common disorder affecting cranial nerve V (see Chapter 53, "Secondary Headache Disorders").

Trigeminal sensory neuropathy is less common than trigeminal neuralgia. Patients typically present with a gradual onset of loss of sensation in a trigeminal distribution. Pain is distinctly absent. Trigeminal sensory neuropathy may be idiopathic (inflammation of the trigeminal ganglion); however, it is commonly associated with connective tissue disorders. Treatment of this condition, if idiopathic, is limited, although corticosteroid therapy has been tried. If the V1 distribution is affected, the cornea must be protected.

- Trigeminal sensory neuropathy may be idiopathic (inflammation of the trigeminal ganglion); however, it is commonly associated with connective tissue disorders.

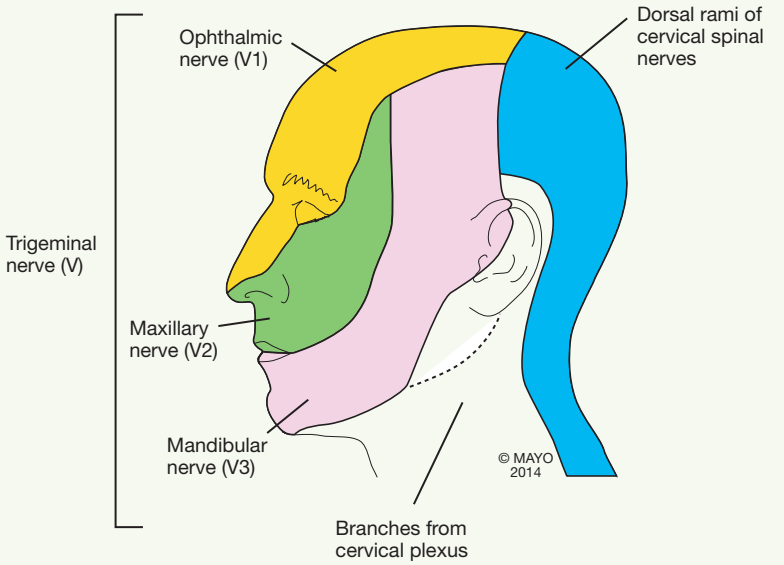

Figure 49.1 *Sensory Innervation of the Face and Scalp.*
The 3 divisions of cranial nerve V are ophthalmic (V1), maxillary (V2), and mandibular (V3).
(Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.)

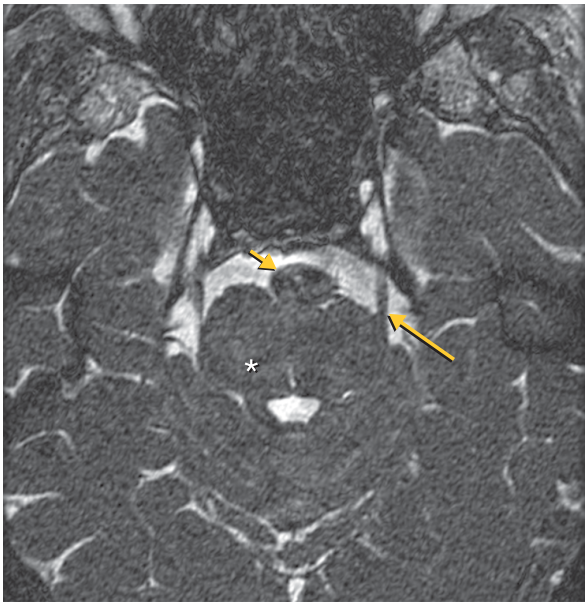

Figure 49.2 *Trigeminal Nerve.*
This T2-weighted magnetic resonance image at the level of the pons (asterisk) shows the large trigeminal nerve (long arrow) as it exits the pons ventrally toward the Meckel cave. Note also the midline, enlarged basilar artery (short arrow).

Cranial Nerve VI (Abducens Nerve)

Cranial nerve VI is covered in Chapter 47, "Neuro-ophthalmology: Extraocular Muscles and Cranial Nerves III, IV, and VI."

Cranial Nerve VII (Facial Nerve)

Anatomy

Cranial nerve VII has both sensory and motor components. The general somatic efferent component of VII innervates the muscles of facial expression as well as the stapedius muscle. A lower motor neuron lesion of the motor component of VII results in weakness of the upper and lower part of the face (Figure 49.3). However, an upper motor neuron lesion results in weakness of only the contralateral lower part of the face because of the mixed corticobulbar input. A lesion at or below the stylomastoid foramen affects only the ipsilateral side of the face. However, if the lesion is at the internal acoustic canal or near the geniculate ganglion, the motor fiber to the stapedius muscle would also be affected and result in less dampened sound or louder sound in the ipsilateral ear, as in Bell palsy.

Cranial nerve VII has 2 general visceral efferent portions: One portion innervates the lacrimal gland (tear production) and nasal mucosa (mucus production), and the other innervates the submandibular and sublingual glands (saliva production). Dysfunction of this component may result in dry mouth and dry eye on the ipsilateral side.

Taste from the anterior two-thirds of the tongue is carried by the special visceral afferent component of VII. Dysfunction of this component may result in a decrease of the taste sensation (cranial nerves IX and X also have a component involved with taste).

Cranial nerve VII also has a clinically irrelevant general somatic afferent component from the external ear.

Table 49.3 • Disorders of the Trigeminal Nerve (Cranial Nerve V)

Location of Lesion	Component Affected	Cause
Upper motor neuron	SVE	No appreciable deficit because of bilateral corticobulbar input to motor nucleus of V
Nuclear or intramedullary	SVE GSA	Lateral medullary or lower pontine stroke, or demyelinating or mass lesion may cause dysfunction of spinal tract and nucleus of V Paramedian or lateral midpontine stroke, hemorrhage, demyelinating lesion, mass lesion (tumor, abscess), or syringobulbia may impair the chief sensory nucleus of V or the motor nucleus of V
Trigeminothalamic tract	GSA	Mass lesion, stroke, hemorrhage, or demyelinating lesions may result in decreased sensation of contralateral side of face
Meningeal (nerve)	All	Vascular: dolichoectasia of vertebrobasilar system, aneurysm Inflammatory: sarcoidosis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculopathy, systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disorder (trigeminal sensory neuropathy), Gradenigo syndrome Infectious: basilar meningitides, herpes zoster, tuberculosis Neoplastic: schwannoma, meningioma, metastasis, lymphoma Toxic-metabolic: diabetes mellitus, vitamin B_{12} or B_6 deficiency, trichloroethylene Other: idiopathic trigeminal neuralgia, trigeminal autonomic cephalgia, cluster headache
Cavernous sinus	Sensory V1, V2	Vascular: carotid-cavernous fistula, cavernous sinus thrombosis, cavernous sinus aneurysm Mass lesion Tolosa-Hunt syndrome Trauma
Foramen ovale	Sensory V3, motor V	Mass lesion can cause sensory loss in distribution of V3 and ipsilateral jaw deviation Trauma
Foramen rotundum	Sensory V2	Mass lesion can cause sensory loss in distribution of V2 Trauma
Superior orbital fissure	Sensory V1	Mass lesion can cause sensory loss in distribution of V1 and extraocular movement abnormalities Tolosa-Hunt syndrome Trauma
Extracranial distal nerve	V1, V2, or V3	Jaw trauma Jaw surgery

Abbreviations: GSA, general somatic afferent; SVE, special visceral efferent; V1, ophthalmic division of cranial nerve V; V2, maxillary division of cranial nerve V.

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

Cranial nerve VII exits the pons and travels through the internal acoustic meatus. The motor fibers exit the skull at the stylomastoid foramen.

Dysfunction

Lesions may affect cranial nerve VII anywhere along its course. The differential diagnosis of disorders of cranial nerve VII is listed in Table 49.4. The differential diagnosis of disorders of taste is reviewed in Box 49.1.

Idiopathic Bell Palsy

Idiopathic Bell palsy is a common disorder of cranial nerve VII that typically affects people in their fourth decade. Acute lower motor neuron facial weakness in addition to abnormal taste and increased sound perception are typical presenting symptoms. It has been thought that Bell palsy may relate to latent herpes simplex virus reactivation; however, few pathologic data are available. In 1 autopsy case, inflammatory changes in the geniculate ganglion were noted to extend from the internal auditory canal to the stylomastoid process, with demyelinating changes.

The diagnosis of Bell palsy is generally based on clinical course and examination. One must consider other causes of cranial neuropathies and determine whether other cranial nerves are involved. The ear canal should be examined for active herpes lesions, which may suggest the diagnosis of Ramsay Hunt syndrome (see below). In addition, other systemic symptoms should be evaluated

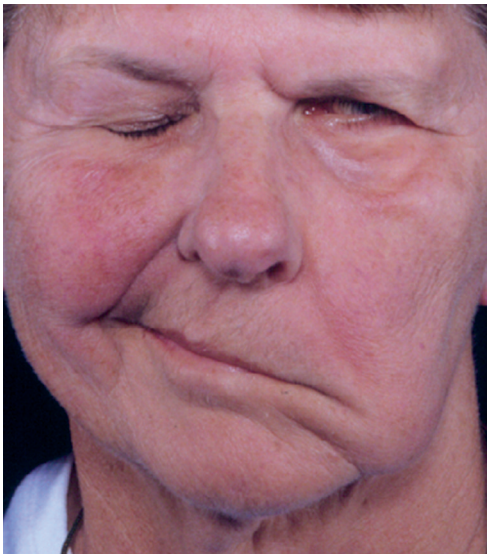

Figure 49.3 *Facial Palsy From Lower Motor Neuron Lesion of Cranial Nerve VII.*
In this left lower motor neuron facial weakness, the incomplete closure of the left eye indicates that the upper portion of cranial nerve VII is also weak.

because patients with Lyme disease, human immunodeficiency virus infection, sarcoid, or neoplastic disease may present initially with facial paralysis. Imaging is recommended if other cranial nerves are involved or if symptoms progress or fail to improve. Magnetic resonance imaging (MRI) with gadolinium may show enhancement of the internal acoustic meatal segment of cranial nerve VII on the ipsilateral side. Nerve conduction studies and electromyography may be useful for prognostic purposes.

One week of high-dose corticosteroids is generally prescribed for patients with Bell palsy, preferably within 3 days after symptom onset. Antiviral therapy may be considered in severe cases. If eye closure is poor, the cornea requires special attention.

Ramsay Hunt Syndrome

Ramsay Hunt syndrome is characterized by herpes zoster oticus and ipsilateral facial nerve palsy. In addition to the ipsilateral facial paralysis in a lower motor neuron pattern, patients often complain of ipsilateral ear pain, and there is evidence clinically of herpetic vesicles in the auditory canal. The involvement of cranial nerve VIII can result clinically in tinnitus, hearing loss, vertigo, and nystagmus

Table 49.4 • Disorders of the Facial Nerve (Cranial Nerve VII)

Location of Lesion	Component Affected	Cause
Upper motor neuron	SVE	Vascular: stroke Demyelinating disease Infection: abscess Neoplasm
Nuclear (facial nucleus)	SVE	Vascular Demyelinating disease Infection: abscess Neoplasm Syringobulbia Developmental: Möbius syndrome
Meningeal	All	Vascular: subarachnoid hemorrhage, dolichoectasia of vertebrobasilar system Infectious: basilar meningitides, Lyme disease, HIV Inflammatory: Guillain-Barré syndrome, sarcoidosis Neoplasms: schwannoma, meningioma Toxic or metabolic: diabetes mellitus, hypothyroidism, porphyria, arsenic Other: hemifacial spasm, amyloidosis
Internal acoustic meatus, ganglion	All	Inflammatory: Gradenigo syndrome Idiopathic Bell palsy
Stylomastoid foramen	SVE only	Mass lesion: squamous cell carcinoma, parotid neoplasm
Chorda tympani nerve	SVA; GVE	Mass lesion
Extracranial nerve	SVE	Facial trauma Parotid surgery Parotid neoplasm Botulinum toxin Melkersson-Rosenthal syndrome

Abbreviations: GVE, general visceral efferent; HIV, human immunodeficiency virus; SVA, special visceral afferent; SVE, special visceral efferent.
Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

Box 49.1 • Causes of Disorders of Taste

Infectious: oral infections

Inflammatory: Sjögren syndrome, multiple sclerosis, Bell palsy

Neoplastic: tumors of the oral cavity or skull base along the path of cranial nerves VII, IX, or X

Metabolic: vitamin B_{12} deficiency, zinc or copper deficiency, kidney or liver failure, adrenal insufficiency, diabetes mellitus, hypothyroidism, Cushing syndrome

Toxins: solvents, benzene, chlorine, formaldehyde, sulfuric acid, chromium, lead, copper

Medications: numerous

Trauma

Irradiation

Oral appliances or procedures

Other: aging, migraine or seizure aura, psychiatric

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

as well. Rarely, other lower cranial nerves may be affected (cranial nerves V, IX, and X). Ramsay Hunt syndrome is thought to be related to a reactivation of varicella-zoster virus within the geniculate ganglion. The viral inflammation leads to edema and nerve compression. Treatment is generally antiviral therapy.

Möbius Syndrome

Möbius syndrome is a disorder characterized by bilateral facial weakness. It may or may not be associated with other cranial nerve abnormalities, most commonly abnormalities affecting cranial nerve VI bilaterally, but also those affecting cranial nerves III, IX, and XIII. The condition is congenital and related to nuclear hypoplasia. Additional congenital defects may include cardiac anomalies, musculoskeletal systemic anomalies (Klippel-Feil syndrome and rib defects), cranial malformations (bifid uvula, ear deformities, and micrognathia), and limb malformations (syndactyly, polydactyly, and brachydactyly).

Melkersson-Rosenthal Syndrome

Melkersson-Rosenthal syndrome is a disorder of cranial nerve VII characterized by recurrent facial palsy, often alternating sides, in addition to ipsilateral facial edema and tongue changes (lingua plicata). This condition typically presents in childhood or adolescence. Some patients are treated with corticosteroids or facial nerve decompression (or both), although there is no proven therapy.

- Typical presenting symptoms of patients with idiopathic Bell palsy include acute lower motor neuron facial weakness in addition to abnormal taste and increased sound perception. It has been thought that Bell palsy may relate to latent herpes simplex virus reactivation; however, few pathologic data are available.
- One week of high-dose corticosteroids is generally prescribed for patients with Bell palsy, preferably within 3 days after symptom onset.
- Ramsay Hunt syndrome is characterized by herpes zoster oticus and ipsilateral facial nerve palsy.
- Möbius syndrome is a disorder characterized by bilateral facial weakness.

Cranial Nerve VIII (Vestibulocochlear Nerve)

Cranial nerve VIII is covered in Chapter 48, "Clinical Neurotology."

Cranial Nerve IX (Glossopharyngeal Nerve)

Anatomy

Cranial nerve IX has mixed motor and sensory components. It innervates the stylopharyngeus muscle and provides parasympathetic output to the parotid gland (salivation). Cranial nerve IX receives visceral input from chemoreceptors and baroreceptors as well as tactile sensation from the posterior tongue and pharynx. Thus, it is important clinically in the baroreceptor reflex and gag reflex. Cranial nerve IX also receives input about taste from the posterior third of the tongue. Cranial nerve IX is at the level of the medulla. It exits the skull at the jugular foramen.

Dysfunction

Cranial nerve IX can be affected anywhere along its course. The differential diagnosis of disorders of cranial nerve IX is listed in Table 49.5.

Glossopharyngeal neuralgia results from an irritation of cranial nerve IX and potentially X. Patients generally present with lancinating throat pain. Patients may also be susceptible to syncope due to irritation of the carotid sinus reflex. (See also Chapter 53, "Secondary Headache Disorders.")

Cranial Nerve X (Vagus Nerve)

Anatomy

Cranial nerve X is a mixed nerve with sensory and motor components. It receives taste information from the epiglottis and posterior pharynx. In addition, it receives visceral

Table 49.5 • Disorders of the Glossopharyngeal Nerve (Cranial Nerve IX)

Location of Lesion	Cause
Medulla (nuclear)	Stroke Demyelinating disease Mass lesions: tumor, abscess Syringobulbia
Meninges	Infectious: meningitides, diphtheria, syphilis Inflammatory: Guillain-Barré syndrome Neoplasic: cerebellopontine angle tumors[a] Metabolic: diabetes mellitus
Jugular foramen	Neoplasm: glomus jugulare (paraganglioma), schwannoma, metastases, chordoma Trauma Osteomyelitis
Retropharyngeal	Tumor Abscess Glossopharyngeal neuralgia

[a] See Chapter 48, "Clinical Neurotology."
Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

sensation from aortic baroreceptors and visceral receptors, and it receives tactile sensation from the larynx, upper esophagus, and pharynx. The special visceral motor component of cranial nerve X innervates muscles of the pharynx and larynx. The vagus nerve also provides parasympathetic input to the visceral organs.

The vagus nerve exits the medulla and travels through the jugular foramen along with cranial nerves IX and XI. The vagus nerve descends through the neck and is retropharyngeal within the carotid sheath. It enters the thorax, passing anterior to the subclavian artery on the right and anterior to the aortic arch on the left. The major trunk of the vagus then continues behind the roots of the lungs and down the esophagus to the visceral organs. The recurrent laryngeal nerves branch off the vagus at the level of the aortic arch. The left recurrent laryngeal nerve loops under the arch of the aorta, and the right loops around the right subclavian artery. The nerves rise posteriorly to innervate the larynx. A lesion of the recurrent laryngeal component of cranial nerve X or the nucleus ambiguus results in a hoarse voice.

Dysfunction

Cranial nerve X can be affected anywhere along its course. The differential diagnosis of disorders of cranial nerve X is listed in Table 49.6. An example of traumatic irritation to the vagus nerve, which resulted in syncope, is shown in Figure 49.4.

Table 49.6 • Disorders of the Vagus Nerve (Cranial Nerve X)

Location of Lesion	Cause
Brainstem	Lateral medullary stroke (PICA) Demyelinating disease Mass lesions: tumor, abscess, syringobulbia Degenerative: multiple system atrophy, motor neuron disease
Meninges	Infectious: meningitides, sarcoidosis, Lyme disease, diphtheria Inflammatory: Guillain-Barré syndrome Neoplastic: schwannoma, carcinomatous meningitis
Jugular foramen	Neoplastic: glomus jugulare, schwannoma, metastases, chordoma Trauma Osteomyelitis
Retropharyngeal, vagus nerve	Vascular: carotid artery dissection Infectious: retropharyngeal abscess, diphtheria Neoplastic Toxic-metabolic: alcoholic neuropathy, vincristine neuropathy, neuritic beriberi
Recurrent laryngeal nerve	Neoplastic Intrathoracic lesion: mediastinal lymph node enlargement, carcinoma of bronchus or esophagus Neck lesion: head and neck cancers Surgery: carotid artery surgery, neck dissection, thyroid surgery Trauma: endotracheal tube placement Metabolic: diabetes mellitus Idiopathic

Abbreviation: PICA, posterior inferior cerebellar artery.
Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

Cranial Nerve XI (Accessory Nerve)

Anatomy

The accessory nerve is a pure motor nerve. The spinal component arises from the ventral horn cells of the upper cervical segments. It rises through the foramen magnum and joins the intracranial portion from the nucleus ambiguus. The joined segment exits the skull at the jugular foramen and innervates the trapezius and sternocleidomastoid muscles.

A lower motor neuron cranial nerve XI palsy causes weakness of the ipsilateral shoulder (trapezius muscle) and a slight tilt of the head ipsilaterally due to weakness of the ipsilateral sternocleidomastoid muscle and an intact contralateral sternocleidomastoid muscle.

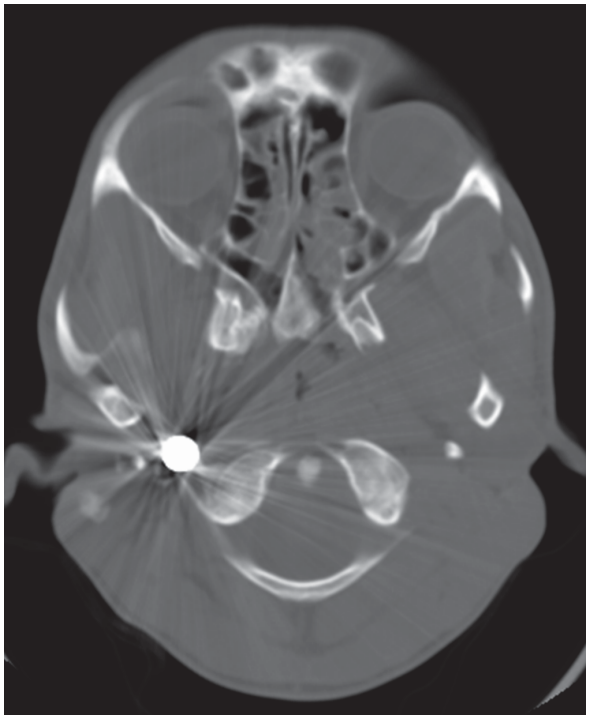

Figure 49.4 *Syncope and Neck Pain.*
This patient presented with recurrent episodes of syncope and pain in the neck. Computed tomography of the head shows a bullet in the region of the foramen magnum. The bullet likely resulted in irritation of the vagus or glossopharyngeal nerve, upsetting the baroreceptor reflex pathway and resulting in syncope.

Dysfunction

The differential diagnosis of disorders of cranial nerve XI is listed in Table 49.7.

Cranial Nerve XII (Hypoglossal Nerve)

Anatomy

The hypoglossal nerve is a pure motor nerve. It innervates the muscles of the tongue. A lower motor neuron lesion of the hypoglossal nerve results in weakness of the tongue, and the tongue deviates to the side of the lesion. Corticobulbar input is crossed. Thus, a right hemisphere lesion near the area of the tongue along the homunculus may result in the tongue deviated to the left.

The hypoglossal nerve exits the preolivary sulcus from the medulla and exits the skull through the hypoglossal canal. The hypoglossal nerve passes near the carotid artery and is sometimes injured with carotid surgery or carotid dissection.

Dysfunction

The differential diagnosis of disorders of cranial nerve XII is listed in Table 49.8.

Table 49.7 • Disorders of the Accessory Nerve (Cranial Nerve XI)

Location of Lesion	Cause
Nuclear	Vascular Mass lesion: neoplasm, abscess Infectious or inflammatory: demyelinating disease, poliomyelitis Degenerative: motor neuron disease Syringobulbia
Jugular foramen	Neoplasm: glomus jugulare, schwannoma, metastases, skull base meningioma Trauma Osteomyelitis
Retropharyngeal, peripheral	Infection: abscess Head and neck tumors Neck radiotherapy Surgical procedure Trauma

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

- A lower motor neuron lesion of the hypoglossal nerve results in weakness of the tongue, and the tongue deviates to the side of the lesion.
- The hypoglossal nerve passes near the carotid artery and is sometimes injured with carotid surgery or carotid dissection.

Cranial Neuropathies and Brainstem Disorders

Multiple Cranial Neuropathies

Some disorders affect predominantly a single cranial nerve. Others involve multiple cranial nerves. Localization may involve cranial nerves converging in a particular region (eg, at a foramen of the skull or the cerebellopontine angle), or the nerves may be involved because of a diffuse process of the meninges or a toxic or metabolic disorder. The contents of the jugular foramen and the carotid sheath sinus are listed in Box 49.2. Clinical syndromes involving multiple lower cranial neuropathies have been described (Table 49.9). The differential diagnosis of multiple cranial neuropathies is listed in Table 49.10.

Tolosa-Hunt syndrome is a granulomatous inflammatory process involving the cavernous sinus regions. It is characterized by episodic attacks of boring, retro-orbital pain, ophthalmoplegia (cranial nerves III, IV, and VI), reduced sensation in V1, and Horner syndrome (involvement of sympathetics as they travel

Table 49.8 • Disorders of the Hypoglossal Nerve (Cranial Nerve XII)

Location of Lesion	Cause
Nuclear	Vascular: medial medullary ischemia, cavernous malformation Infectious or inflammatory: poliomyelitis, Guillain-Barré syndrome Mass lesion: tumor, abscess, syringobulbia Motor neuron disease
Meningeal	Vascular: vertebral artery aneurysm, vasculitis Infectious: chronic meningitides, mononucleosis Inflammatory: sarcoidosis Neoplastic: metastases, carcinomatous meningitis Metabolic: diabetes mellitus Developmental: Arnold-Chiari malformation
Hypoglossal canal	Neoplastic: glomus tumor, skull base meningioma, schwannoma, chordoma, cholesteatoma Infectious: osteitis
Carotid sheath, retropharyngeal region	Internal carotid artery dissection or internal carotid artery aneurysm Endarterectomy Retropharyngeal abscess Head and neck neoplasms Trauma Surgical procedures
Other	Idiopathic

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

Box 49.2 • Contents of the Jugular Foramen and the Carotid Sheath

Contents of the jugular foramen
- Cranial nerves IX-XI
- Inferior petrosal sinus as it drains into the jugular vein
- Sigmoid sinus as it drains into the jugular vein
- Meningeal branch of the ascending pharyngeal artery and meningeal branch of the occipital artery

Contents of the carotid sheath[a]
- Carotid artery
- Jugular vein
- Cranial nerves IX, X, and XII

[a] The superior sympathetic ganglion is *outside* the carotid sheath.

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

along the carotid cavernous segment). Episodes occur at recurrent intervals and each attack typically lasts days to weeks. Other cavernous sinus pathology, such as trauma, aneurysm, neoplasm, or another infectious process must be ruled out. The differential diagnosis of painful ophthalmoplegia is listed in Table 49.11. With Tolosa-Hunt syndrome, MRI may show a nonspecific, intermediate signal on T1-weighted imaging in the area of the cavernous sinus and enhancement with gadolinium. Cerebrospinal fluid (CSF) analysis, magnetic resonance angiography, and serologic studies are often

Table 49.9 • Clinical Syndromes of the Lower Cranial Nerves

Syndrome	Site of Lesion	Cranial Nerve	Symptoms
Vernet syndrome	Jugular foramen	IX	Ipsilateral decrease in taste sensation of posterior third of tongue
		X	Ipsilateral soft palate weakness
		X	Hoarseness
		XI	Ipsilateral SCM and trapezius muscle weakness
Collet-Sicard syndrome	Retropharyngeal space	IX and X	Gag reflex decreased ipsilaterally
		X	Ipsilateral soft palate weakness
		X	Hoarseness, dysphagia
		XI	Ipsilateral SCM and trapezius muscle weakness
		XII	Ipsilateral tongue weakness
Villaret syndrome	Retropharyngeal space	IX-XII and sympathetic nerves	All the above and ipsilateral Horner syndrome

Abbreviation: SCM, sternocleidomastoid muscle.

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

Table 49.10 • Differential Diagnosis of Multiple Cranial Neuropathies

Category	Disorder
Vascular	Vasculitis
Infectious	Viral infection: Epstein-Barr virus, cytomegalovirus, varicella zoster virus, human immunodeficiency virus, hepatitis B virus Bacterial infection: Lyme disease, syphilis, diphtheria, *Listeria* infection Fungal meningitis *Mycobacterium* infection: tuberculosis
Inflammatory	Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculopathy Sarcoidosis Vasculitides: Wegener granulomatosis, Sjögren syndrome, systemic lupus erythematosus, Churg-Strauss syndrome Tolosa-Hunt syndrome
Neoplastic, paraneoplastic	Lymphoma Paraneoplastic disorder Carcinomatous meningitis Paraproteinemias
Toxic or metabolic	Diabetes mellitus Porphyria Hypothyroidism

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

required to rule out other causes. A biopsy may be necessary to confirm the diagnosis and rule out other causes. Treatment is with corticosteroids.

Brainstem Disorders

Details of brainstem anatomy are covered in Volume 1, Chapter 8, "Brainstem and Cranial Nerves: Overview and Medulla"; Chapter 9, "Brainstem and Cranial Nerves: The Pons"; and Chapter 10, "Brainstem and Cranial Nerves: The Midbrain." Vascular clinical brainstem syndromes are covered in Chapter 10, "Ischemic Stroke: Common Causes and Diagnosis." Many diseases of the central nervous system may involve the brainstem in addition to other places, although some diseases are isolated to this region. The differential diagnosis of brainstem disorders is broad (Table 49.12). A few of these diseases deserve further attention. (See Chapter 20, "Mimickers of Multiple Sclerosis.")

Table 49.11 • Differential Diagnosis of Painful Ophthalmoplegia

Location of Lesion	Cause
Cavernous sinus, parasellar region	Vascular: carotid cavernous fistula, carotid cavernous aneurysm, cavernous sinus thrombosis Infectious: bacterial sinusitis, periostitis, mucormycosis, syphilis, *Mycobacterium tuberculosis* infection Inflammatory: sarcoidosis, Wegener granulomatosis, Tolosa-Hunt syndrome Neoplastic: pituitary adenoma, sarcoma, neurofibroma, epidermoid, craniopharyngioma, meningioma, chordoma, chondroma, giant cell tumor, metastases, lymphoma, carcinomatous meningitis
Orbit	Infectious: extension of sinusitis, mucormycosis Inflammatory: giant cell arteritis, idiopathic orbital inflammation (orbital pseudotumor) Neoplastic: metastases, lymphoma, leukemia Metabolic: multiple cranial neuropathies associated with diabetes mellitus
Other	Ophthalmoplegic migraine Trauma

Adapted from Flemming KD. Disorders of the cranial nerves. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 127–62. Used with permission of Mayo Foundation for Medical Education and Research.

Table 49.12 • Disorders Involving the Brainstem or Posterior Fossa

Category	Disorder
Vascular	Posterior circulation stroke Vertebrobasilar dolichoectasia Vertebrobasilar aneurysm Superficial siderosis Vascular malformation Susac syndrome
Infectious	Cerebellitis Brainstem abscess Whipple disease
Inflammatory	Multiple sclerosis Acute disseminated encephalomyelitis Behçet syndrome Sarcoid Miller Fisher syndrome, Guillain-Barré syndrome Bickerstaff brainstem encephalitis
Neoplastic	Tumors of the cerebellopontine angle Acoustic neuroma (schwannoma) (most common) Meningioma Epidermoid Metastases Tumors of the brainstem Glioma Pilocytic astrocytoma Metastases Lymphoma Paraneoplastic disorder
Toxic or metabolic	Central pontine myelinolysis Vitamin B_{12} deficiency
Degenerative or congenital	Pontocerebellar atrophy Dandy-Walker malformation Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)
Traumatic	Duret hemorrhages Trauma

Central Pontine Myelinolysis

Central pontine myelinolysis is caused by osmotic demyelination in the pons, usually occurring with rapid correction of hyponatremia. Patients usually have comorbid conditions of alcoholism or severe medical illness. In addition to focal brainstem signs, alteration in consciousness and quadriparesis occur frequently. Demyelination in the central pons is noted on MRI. CSF examination results are most often normal.

Bickerstaff Brainstem Encephalitis

Bickerstaff brainstem encephalitis is an inflammatory brainstem syndrome in young adults typically accompanied by a headache and overall malaise. Deafness can occur with Bickerstaff brainstem encephalitis. MRI may show white matter abnormalities. CSF examination shows pleocytosis but does not show immunoglobulin G abnormalities or oligoclonal bands. Antibodies to GQ1 are present in the serum and CSF of most patients.

Whipple Disease

Whipple disease is an infectious disease caused by *Tropheryma whipplei*. Common manifestations include arthralgias, diarrhea, and abdominal pain as well as weight loss. When the central nervous system is involved, patients may have brainstem manifestations (oculomasticatory myorhythmia or cerebellar ataxia) but also cortical symptoms (encephalopathy, myoclonus, or seizures). Patients may have multifocal enhancing areas on MRI. Diagnosis is often confirmed by small bowel biopsy.

- Tolosa-Hunt syndrome is a granulomatous inflammatory process involving the cavernous sinus regions. It is characterized by episodic attacks of boring, retro-orbital pain, ophthalmoplegia (cranial nerves III, IV, and VI), reduced sensation in V1, and Horner syndrome (involvement of sympathetics as they travel along the carotid cavernous segment).
- Antibodies to GQ1 are present in the serum and CSF of most patients who have Bickerstaff brainstem encephalitis.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

VIII.1. You are asked to evaluate a 32-year-old man who has vertigo. Which of the following would most strongly suggest a central mechanism for his symptoms?
a. Recent viral upper respiratory infection
b. Ability to walk independently
c. Horizontal diplopia associated with the symptoms
d. Abnormal head impulse test
e. Unidirectional horizontal nystagmus

VIII.2. Which of the following statements regarding episodic vertigo is most correct?
a. Vertigo regardless of position or movement is most suggestive of benign paroxysmal positional vertigo (BPPV)
b. Migrainous vertigo may be prolonged, lasting hours to days
c. The presence of significant hearing loss argues against the diagnosis of Meniere disease
d. Most patients with BPPV complain of associated tinnitus
e. Surgery is not an effective treatment option for patients with superior semicircular canal dehiscence syndrome

VIII.3. A 19-year-old woman who is otherwise healthy is sent to you for evaluation of "whooshing" in her ears. On further clarification, you realize that she is describing pulsatile tinnitus. Neurologic examination findings are normal, and you do not hear cranial bruits. Which of the following is the *least likely* cause of her symptoms?
a. Meniere disease
b. Dural arteriovenous fistula
c. Glomus jugulare tumor
d. Superior semicircular canal dehiscence syndrome
e. Idiopathic intracranial hypertension

VIII.4. Which of the following cranial nerve descriptions is most accurate?
a. The trigeminal nerve serves as a general somatic efferent
b. The olfactory nerve serves as a special somatic afferent
c. The vestibulocochlear nerve serves as a special visceral afferent
d. The vagus nerve serves as a special somatic afferent
e. The abducens nerve serves as a general somatic efferent

VIII.5. On examination of a 57-year-old man, you note that his left pupil does not dilate as briskly or completely as his right pupil in a dark room, and he has mild left-sided ptosis. You diagnose Horner syndrome. Which of the following lesions would be most likely to impair the second-order cranial sympathetic neuron?
a. Brainstem glioma
b. Apical lung tumor
c. Carotid artery dissection
d. Metastasis to the skull base
e. Carotid-cavernous sinus fistula

VIII.6. A 55-year-old woman presents to your clinic for evaluation of recent monocular visual loss. After examination, you diagnose anterior ischemic optic neuropathy. Which of the following is most important to evaluate next?
a. Serum creatinine level
b. Cerebrospinal fluid cytology
c. Serum glucose level
d. Erythrocyte sedimentation rate
e. Urine protein level

VIII.7. On examination of a 28-year-old woman who has transient left hemiparesthesias, you note that her right pupil dilates on the swinging flashlight test. Which of the following localizations would best account for this finding?
a. Right optic nerve lesion
b. Left optic tract lesion
c. Right lateral geniculate body lesion
d. Left parietal optic radiation lesion
e. Left occipital cortex lesion

VIII.8. A 78-year-old man with atrial fibrillation comes to the emergency department after abrupt visual changes. You note on examination that he has left homonymous hemianopia. Which of the following localizations would best account for this finding?
a. Left retinopathy
b. Right optic neuropathy
c. Midline chiasmal lesion
d. Left temporal optic radiation lesion
e. Right occipital cortical lesion

VIII.9. A 32-year-old man complains of patchy binocular visual loss. On tangent screen testing at 1 m, he has a 15° central loss of vision in both eyes. The size of the field deficit remains unchanged when testing is repeated at 2 m. Which of the following is the most likely explanation for the visual symptoms?
a. Bilateral paraneoplastic optic neuropathies
b. Chiasmal lesion affecting both Wilbrand knees
c. Nonorganic (psychiatric) visual symptoms
d. Bithalamic lesion due to venous sinus thrombosis
e. Bioccipital lesion resulting from prior head trauma

VIII.10. An endocrinologist asks you to evaluate a 42-year-old woman for recent vertical diplopia. She has newly diagnosed severe hyperthyroidism. You ultimately diagnose dysthyroid ophthalmopathy. Which of the following statements regarding this diagnosis is most correct?
a. The lateral rectus is the muscle most likely involved
b. Orbital muscle weakness is the usual mechanism for the diplopia
c. The associated diplopia characteristically fluctuates throughout the day
d. Optic neuropathy occasionally develops because of swollen orbital muscles
e. The presence of exophthalmos argues against the diagnosis

VIII.11. A colleague asks you to review a cerebral angiogram from a patient with proptosis. It shows a ruptured internal carotid artery aneurysm in the cavernous sinus. In this patient, an associated cranial neuropathy is most likely to involve which of the following nerves?

a. Cranial nerve IV
b. Ophthalmic division of cranial nerve V
c. Maxillary division of cranial nerve V
d. Mandibular division of cranial nerve V
e. Cranial nerve VI

VIII.12. A 24-year-old man is referred to you for further evaluation of abnormal eye movements. On examination, you note moderate nonfatigable paresis of eye movement bilaterally in essentially all directions of gaze along with symmetric ptosis. He does not report diplopia. You also note bilateral retinal pigment abnormalities, hearing loss, and an ataxic gait. Which of the following is the most likely cause for this patient's syndrome?

a. Möbius syndrome
b. Chronic progressive ophthalmoplegia
c. Botulism
d. Myasthenia gravis
e. Thyroid ophthalmopathy

Answers

VIII.1. **Answer c.**
Eggers SD, Zee DS. Evaluating the dizzy patient: bedside examination and laboratory assessment of the vestibular system. Semin Neurol. 2003 Mar;23(1):47–58.

VIII.2. **Answer b.**
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VIII.3. **Answer a.**
Eggers SD, Zee DS. Evaluating the dizzy patient: bedside examination and laboratory assessment of the vestibular system. Semin Neurol. 2003 Mar;23(1):47–58.

VIII.4. **Answer e.**
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VIII.5. **Answer b.**
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VIII.6. **Answer d.**
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VIII.7. **Answer a.**
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VIII.8. **Answer e.**
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VIII.9. **Answer c.**
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VIII.10. **Answer d.**
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VIII.11. **Answer e.**
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Section
IX

Headache and Pain

Christopher J. Boes, MD, *editor*

50 Introduction and Approach to Headache

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Introduction

Headache is an experience that 93% of men and 99% of women have at some time in their lives. It is the most common complaint treated by neurologists and the seventh most common complaint treated by primary care providers. Although most headaches in the general population meet the criteria for tension-type headache, migraine is the most common headache treated in clinical practice (Table 50.1) and affects 18% of women and 6% of men, typically in their peak years of productivity. The high prevalence of mild, nondisabling headache in the population likely contributes to the stigma of migraine as being "just a headache." A large proportion of persons with headache do not have first-hand experience with the disabling features that occur with migraine and some other primary headache disorders.

Table 50.1 • Prevalence of Headache in the General Population and in Primary Care Patients

Headache Type	General Population, %	Primary Care Patients, %
Tension-type	78	3
Migraine	16	76
"Migrainous"	0	18
Other	6	3

Approach to the Patient With Headache

Initial Evaluation

Evaluation of headache should include a thorough history and general, musculoskeletal, and neurologic examinations. Paramount in the headache evaluation is the proper identification of red flags that may indicate an underlying secondary cause of headache.

A useful mnemonic to assist in identifying secondary causes of headache is *SNOOP4* (ie, SNOOP4 red flags) (Box 50.1): systemic symptoms and signs, neurologic symptoms or signs, onset sudden, onset at age older than 50 years, progression of headache, precipitation of headache with Valsalva maneuver, postural headache, and papilledema. Systemic symptoms and signs include fevers, chills, night sweats, and weight loss. Neurologic symptoms and signs can be global or focal (eg, altered mental status or unilateral weakness). Onset that is sudden may indicate a thunderclap headache, which has a differential diagnosis of mostly secondary headache disorders. It is highly unusual for a primary headache disorder to begin after age 50; thus, this is of concern for a secondary cause. *P4* refers to a progressive headache that continues to worsen with loss of pain-free periods; precipitation by the Valsalva maneuver (eg, with coughing, sneezing, bending over, or heavy lifting); postural aggravation (ie, worsening of headache with moving from a supine to an upright position or vice versa); and papilledema on funduscopic examination.

Every headache history and physical examination must include an inquiry for these red flag symptoms and signs to ensure that a secondary headache is not missed. Depending on which red flags are identified, further evaluation should be performed to develop a diagnosis and a management plan. Although computed tomography of the head and subsequent lumbar puncture are usually indicated for a suspected secondary headache disorder, magnetic resonance imaging of the brain and neurovascular imaging are often required for accurate diagnosis and management.

Abbreviation: *ICHD, International Classification of Headache Disorders*

Box 50.1 • Mnemonic: *SNOOP4* Red Flags in the Headache History

S—Systemic signs and symptoms that may predispose the patient to a secondary headache related to a known malignancy, immunocompromised state, or the presence of fever

N—Neurologic findings on examination

O—Older patients: new-onset headaches in patients older than 50 years

O—Onset of headache that is sudden or abrupt, such as a thunderclap headache, which is defined as an abrupt-onset headache that reaches maximal intensity in <1 minute and which patients frequently refer to as the "worst headache of my life"

P—Postural headache: positional features that either worsen or improve with movement from a supine to an upright position

P—Precipitation of headache with Valsalva maneuver or exertion, such as when coughing, sneezing, bending, straining, or engaging in sexual activity

P—Progression of headache from a particular pattern or frequency to a more frequently occurring and refractory pattern

P—Presence of papilledema

A complete neurologic examination is essential, but general and musculoskeletal examinations are also important. Specific attention should be given to palpation of the skull base and examination of the head and neck, including occipital nerves, supraorbital nerves, temporomandibular joints, temporal arteries, upper cervical facets, pericranial muscles, cervical paraspinal muscles, and sinuses. Abnormalities may suggest the presence of underlying disorders contributing to headache and may also yield clues regarding potential treatment options, such as regional nerve blockade, trigger point injections, or workup for a temporomandibular joint disorder.

In the absence of red flags and examination abnormalities, the diagnostic yield from neuroimaging of patients with migraine or tension-type headache is negligible. Results of a large meta-analysis suggested that 99.8% of such neuroimaging examinations have normal or unrelated findings. Although insufficient data exist to support recommendations for selecting between computed tomography and magnetic resonance imaging in nonacute headache, magnetic resonance imaging has higher resolution and is clearly superior for identifying more subtle findings, such as white matter lesions.

Specific Red Flags

Thunderclap Headache

A thunderclap headache should raise a red flag to practitioners. Thunderclap headache is commonly described by patients as the sudden onset of the "worst headache of my life" and should always be considered a neurologic emergency. By definition, a thunderclap headache is abrupt in onset and reaches maximal intensity in less than 1 minute. This can be the heralding symptom for serious conditions, such as subarachnoid hemorrhage, reversible cerebrovasoconstrictive syndrome, and other vascular disorders. The broad differential diagnosis is covered in Chapter 53, "Secondary Headache Disorders."

Postural Headache

Patients with headaches that worsen in the upright position may have traumatic or spontaneous leak of cerebrospinal fluid. Patients with headaches that are worse in the supine position may have increased intracranial pressure due to various reasons.

Exertional Headache

Although headaches with exertion may be benign, it is important to rule out increased intracranial pressure due to various causes and Chiari type I malformations.

- A useful mnemonic to assist in identifying secondary causes of headache is *SNOOP4*.
- In the absence of red flags and examination abnormalities, the diagnostic yield from neuroimaging of patients with migraine or tension-type headache is negligible.
- Thunderclap headache is commonly described by patients as the sudden onset of the "worst headache of my life" and should always be considered a neurologic emergency.

Classification of Headache Disorders

After red flags have been addressed and the presence of underlying pathology has been ruled out, a primary headache diagnosis can be determined. Currently, no biomarkers reliably identify primary headache disorders, so diagnoses are based on the characteristics and associated features reported by the patient. Since headache diagnoses are based entirely on phenotype, accurate and consistent diagnoses depend on the use of a universally accepted classification system.

In 1962, the National Institutes of Health designed the first headache classification system, but as the field of headache medicine evolved, the existing framework for diagnosis was determined to be inadequate. The International Headache Society published the first edition of the *International Classification of Headache Disorders (ICHD)* in 1988, and this achievement is considered by some to be the most important advancement in headache medicine. The second edition (*ICHD-II*) was published in 2004, and the third edition (*ICHD-III*) was published in 2013.

When applying *ICHD* diagnostic criteria, important headache features to note include the headache duration, including the time frame in which the headache has occurred, and the duration of each episode. Location is another important feature, with specific attention given to location of the pain and whether the attacks are unilateral or bilateral. Other important diagnostic clues may relate to the identification of associated features occurring with the headache, including photophobia, phonophobia, nausea and vomiting, and cranial autonomic features such as lacrimation, conjunctival injection, rhinorrhea, ptosis, and periorbital edema.

Other chapters in this section review the *ICHD* criteria for specific headache types.

51 Primary Headache Disorders: Migraine, Tension-Type, and Chronic Daily Headaches

HOSSEIN ANSARI, MD; F. MICHAEL CUTRER, MD

Introduction

Primary headache disorders are those in which the headache is the primary feature of the disorder and is not otherwise explained by a significant structural, genetic, or metabolic cause. This chapter reviews the clinical features, diagnosis, and treatment of common primary headache disorders, including migraine, tension-type, and chronic daily headaches.

Migraine

Epidemiology

Migraine usually starts during adolescence, and 90% of migraine patients have their first attack by age 40. In childhood, there is a slight male predominance. After puberty, a 3:1 female predominance is established. The highest reported prevalence of migraine is in patients aged 30 to 39 years.

Pathophysiology

As with most common diseases, migraine is probably a complex genetic disorder with multiple variants that are capable of conferring susceptibility. At a basic level, migraine is a disorder of neuronal dysfunction, with vascular changes occurring secondarily. The common final pathway in a migraine attack is activation of the trigeminovascular system.

The trigeminovascular system consists of primary afferent neurons, which arise in the trigeminal ganglion and upper cervical spinal ganglia and project to the meninges and cerebral vessels. From the trigeminal ganglion, there are central projections of the second-order neurons in the superficial lamina of the trigeminal nucleus caudalis in the lower medulla. From the trigeminal nucleus caudalis, there are projections to other brainstem nuclei and to the thalamus—specifically, the ventral posteromedial nucleus, which in turn projects mainly to trigeminal areas of the primary and secondary somatosensory cortices and insular cortices, where pain is probably localized. Other trigeminal neurons projecting to the thalamic posterior, lateral posterior, and lateral dorsal nuclei in turn project to trigeminal and extratrigeminal areas of the primary and secondary somatosensory cortices and to the parietal association, auditory, ectorhinal, retrosplenial, visual, and motor cortices, where they likely have different roles in the transmission of nociceptive information from the meninges to the cortex.

Glutamate is the primary neurotransmitter in trigeminal C fibers, although other peptides, such as calcitonin gene-related peptide, are also released during migraine attacks. Serotonin (5-HT) is another neurotransmitter that is a primary target for several therapeutic agents used for the short-term treatment of migraine.

Activation of the contralateral thalamus (ventral posteromedial nucleus) has been shown to occur in human functional imaging studies during migraine attacks, suggesting a role for the thalamus in the pathophysiology of

Abbreviations: FDA, US Food and Drug Administration; 5-HT, serotonin; *ICHD-III, International Classification of Headache Disorders*, 3rd Edition; NSAID, nonsteroidal anti-inflammatory drug; TTH, tension-type headache

migraine. However, the same activation pattern has also been shown in other headache disorders (eg, cluster headache), indicating that the activation may be linked to headache and may not be unique for migraine.

Increasing evidence indicates that migraine auras arise from a phenomenon called *cortical spreading depression*. This is an electrophysiologically measurable wave of hyperexcitation and increased blood flow followed by a period of reduced neuronal firing and reduced blood flow that spreads across areas of contiguous cortex in experimental animals after electrical or chemical stimulation at a rate of 2 to 5 mm/min. Glutamate is the neurotransmitter and potassium is the ion involved in cortical spreading depression. Propagation of cortical spreading depression requires activation of *N*-methyl-D-aspartate receptors in cortical neurons. The bimodal pattern in cortical spreading depression (activation followed by suppression) may explain the migraine aura characterized by positive symptoms (eg, scintillations of visual aura or tingling of sensory aura) followed by negative symptoms (eg, scotoma of visual aura or numbness of sensory aura). Decreased cortical blood flow in humans during the migraine aura are insufficient to cause injury in a normal brain; however, in a brain that has already been damaged (eg, stroke), cortical spreading depression could potentially increase the infarct size.

Genetics

The genetic basis of migraine will likely prove complex and heterogeneous. About 90% of migraineurs have a family history positive for migraine. Three distinct, single defects in genes coding for transmembrane channels have been linked to the rare hemiplegic form of migraine (Table 51.1). However, multiple other genetic loci have been reported in the more common forms of migraine; unfortunately, most have not been replicated. The potassium channel subfamily K member 18 gene (*KCNK18*) has recently been linked to migraine.

Another gene known to be associated with migraine is the *NOTCH3* gene on chromosome 19, which is associated with a rare neurologic syndrome, CADASIL syndrome (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (see Chapter 11, "Ischemic Stroke: Uncommon and Special Situations").

Clinical Features

A typical migraine attack has 4 clinical phases: 1) prodrome, 2) aura, 3) headache, and 4) postdrome.

Prodrome

The prodrome can occur hours to days before the onset of headache and may include physiologic symptoms (eg, irritability, mood changes, drowsiness, and euphoria), general nonspecific symptoms (eg, food and liquid craving or anorexia, change in bowel habits, and neck tightness), and neurologic symptoms (eg, concentration difficulty, photophobia, phonophobia, and osmophobia). The prodromal symptoms are often specific to the migraineur. Conversely, the same person may experience different prodromal symptoms during different attacks.

Aura

Aura is a focal neurologic symptom that develops slowly. According to criteria in the *International Classification of Headache Disorders*, 3rd Edition (*ICHD-III*), typical auras last at least 5 minutes but not more than 60 minutes; however, cases with more prolonged auras are not uncommon. Aura occurs in about 25% to 30% of migraineurs (ie, classic migraine), and it precedes or accompanies the periodic headaches. Auras do not necessarily accompany each migraine attack in classic migraine. In fact, people with classic migraines usually also have attacks without aura (ie, common migraine). Auras can also occur without headache, which is considered a migraine equivalent (ie, acephalgic migraine). Migraine aura without headache occurs more commonly in older people who have a previous history of migraine with aura but can occur in people who have never had migrainous headaches.

Visual aura is the most common type of aura and has different manifestations. Multiple terms are used to categorize these visual symptoms, which are generally referred to as *teichopsia* (Table 51.2). Positive scintillations are

Table 51.1 • Genes and Chromosomes Related to Each Type of Familial Hemiplegic Migraine (FHM) and Their Related Neurologic Disorders

Type of FHM	Gene	Chromosome	Channel	Related Disease With Same Mutation
FHM1	*CACNA1A*	19	Calcium (P/Q type)	Spinocerebellar ataxia type 6 Episodic ataxia type 2
FHM2	*ATP1A2*	1	Sodium-potassium–adenosine triphosphatase	Sporadic hemiplegic migraine
FHM3	*SCN1A*	2	Sodium (*SCN1A*)	Severe myoclonic epilepsy of infancy (SMEI) Generalized epilepsy with febrile seizure plus (GEFS+)

Table 51.2 • Common Types of Visual Auras in Migraine

Type	Description
Scintillating scotoma	Shimmering arc of white or colored lights followed by a blind spot or field cut
Fortification spectrum	Zigzag appearance of lines in the visual field
Metamorphopsia	Changes in the perception of the shape of viewed objects

often followed by a spreading zone of vision loss (negative scotoma) as briefly explained above in the Pathophysiology section. Some patients initially describe positive scintillations with phrases that describe vague visual symptoms, such as *blurry vision, uneven vision*, or *foggy vision*. These descriptions must be clarified in a detailed history.

The second most common type of aura is *sensory aura*, which usually starts unilaterally, with a gradually spreading paresthesia (positive symptoms) followed by numbness (negative symptoms), and is most common in the face (involving the tongue) and hand (cheiro-oral). The slowly spreading quality of the sensory symptoms in migraine aura is a key feature distinguishing it from transient ischemic attack, in which symptoms are more abrupt without spread.

Language aura is the third most common type of aura, which can vary from mild to severe aphasia. The distinction must be made between pain-related difficulty with word finding, which is common during the headache phase of migraine, and language aura which often occurs while the headache intensity is still relatively mild.

Motor aura (also called *hemiplegic migraine*) is the least common type of aura and usually occurs unilaterally in the limbs or facial muscles. However, the motor weakness in hemiplegic migraine is usually hemiparesis rather than hemiplegia. Almost all patients who have motor auras have another type of aura also—pure motor aura is extremely uncommon. Motor aura has been well described among people who have the familial type of hemiplegic migraine. Sometimes distinguishing a motor aura from a cerebrovascular event is challenging, especially if patients have prolonged aura.

Headache

A typical migraine headache starts unilaterally, attains moderate to severe intensity, has a throbbing (pulsating) quality, lasts 4 to 72 hours, and worsens with routine physical activity. Either 1) nausea or vomiting or 2) photophobia and phonophobia must be present during the headache phase to fulfill the *ICHD-III* criteria for migraine (Box 51.1). Neck and shoulder pain and stiffness, sinus pressure, and osmophobia may also be noted during the headache phase.

Box 51.1 • *ICHD-III* Diagnostic Criteria for Migraine

A. Patient has ≥5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has ≥2 of the following 4 characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache, ≥1 of the following:
   1. Nausea or vomiting (or both)
   2. Photophobia and phonophobia
E. Not better accounted for by another *ICHD-III* diagnosis

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

Adapted from Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013 Jul;33(9):629–808. Used with permission.

Postdrome

Postdrome is the period after the spontaneous throbbing headache has ended and is associated with concentration difficulty and fatigue. Brief pain or throbbing can be induced by sudden head movements or Valsalva maneuvers. Other reported symptoms include irritability, euphoria, a general feeling of weakness, and anorexia.

Migraine Variants

Retinal Migraine

The patient with retinal migraine must have had at least 2 attacks of monocular visual disturbance associated with migraine headache. The visual disturbance could be the same as visual aura (some patients have hemianopia), but the key point is that patients complain of visual disturbance in only 1 eye. Also, retinal migraine does not typically occur in the absence of headache, and its onset is more abrupt than the onset of visual aura. This variant is very uncommon, and prechiasmal lesions should be excluded.

Ophthalmoplegic Migraine

A very rare form of migraine, opthalmoplegic migraine could be confused with retinal migraine. In this variant, recurrent attacks of migraine headache are associated with paresis involving 1 or more oculomotor nerves, of which cranial nerve III is the most common. The differential diagnosis includes other causes of painful ophthalmoplegia, specifically Tolosa-Hunt syndrome.

Migrainous Vertigo

Patients with migrainous vertigo, or vertiginous migraine, present with episodic vertigo and a history of migraine or other clinical features of migraine (photophobia, phonophobia, visual aura, etc). Vestibular symptoms do not always result from vertigo and could simply indicate light-headedness or unsteadiness. Migrainous vertigo seems to be a heterogeneous condition and the diagnosis involves excluding other causes. A therapeutic trial with migraine preventive medications may be useful.

Pediatric Variants

Cyclical vomiting, abdominal migraine, benign paroxysmal vertigo of childhood, and benign paroxysmal torticollis are considered migraine variants (equivalents) in children, primarily because they have been observed to be precursors of migraine.

Hormones and Migraine

Changes in migraine frequency and severity may occur at different hormonal stages in females. Menstrual-related migraine may consist of attacks that occur about 1 day before and up to 4 days after the onset of menses and most likely results from estrogen withdrawal.

During pregnancy, about 25% of women with migraine do not experience any change in their migraines. Menstrual migraine usually improves during pregnancy, probably because of sustained high estrogen levels. When migraines worsen during pregnancy, they are worst in the first trimester.

Oral contraceptives have variable effects on migraine. For women with aura, the combination of oral contraceptives and smoking is a known risk factor for ischemic stroke. Progesterone-only contraceptives may not increase ischemic stroke risk.

Migraine decreases with physiologic menopause in about 70% of women. Surgical menopause may worsen migraine.

Diagnosis

The diagnosis of migraine is typically made on a clinical basis according to *ICHD-III* criteria (Box 51.1). For patients with clinical migraine, an imaging study is not indicated unless the pattern of headache or aura changes, focal neurologic findings appear, or the question of other neurologic illness arises (eg, seizure or multiple sclerosis). If imaging is indicated, magnetic resonance imaging with gadolinium is preferred.

Status migrainosus is a migraine attack lasting for more than 72 hours without a headache-free interval of more than 4 hours.

Treatment

The 2 types of pharmacologic treatment of migraine are abortive and preventative. Before starting treatment, though, patients should be educated about common migraine triggers, so that they may avoid them as much as possible. Triggers differ among patients, but common triggers for migraine are alcohol, food containing monosodium glutamate, some cheeses, certain odors, weather (specifically, barometric pressure change), sleep hygiene (too much or too little sleep), stress, and anxiety.

The next step is to decide whether the patient needs a preventive agent. The frequency threshold for starting preventive medication is usually when the patient has more than 1 headache day per week, but the decision of whether to start daily prophylaxis is influenced by other factors, such as the intensity of each attack, a lack of response to abortive agents or limitations with their use, the occurrence of prolonged or severe neurologic symptoms during the attacks, and the effect of migraine on the patient's lifestyle.

Abortive Agents

Agents used for abortive treatment of migraine are listed in Box 51.2.

Analgesics

The usual first-line abortive agents are simple analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), and most patients use them before seeing a physician. The common mistake when patients use over-the-counter analgesic agents relates to dosage. For example, for migraine, the adult dosage of acetaminophen is 1,000 mg daily and the adult dosage of ibuprofen is 600 to 800 mg daily. The other key in using abortive agents is timing. All abortive agents are more effective if taken at the onset of the headache. Simple analgesics have the lowest risk of inducing medication-overuse headaches (also called rebound headaches).

Caffeine-containing analgesics are another medication that many patients take before seeing a physician. The combination analgesics usually contain acetaminophen and aspirin with caffeine. Caffeine-containing analgesics carry a higher risk of medication-overuse headaches. If these agents are taken more than 2 days weekly, patients

Box 51.2 • Agents Used for Abortive Treatment of Migraine

- Simple analgesics (with or without caffeine)
- Triptans
- Ergotamine
- Isometheptene-containing agents
- Barbiturate-containing agents
- Agents administered intravenously in status migrainosus: antidopaminergic agents, sodium valproate, corticosteroids, magnesium

may have a withdrawal and rebound pattern that results in awakening with a morning headache.

Triptans

The 5-HT receptors are a main target for migraine-specific abortive agents. The triptan agents, of which sumatriptan is the prototype, share agonist activity at the 5-HT_{1B} and 5-HT_{1D} receptors, although some also have activity at 5-HT_{1F} receptors. The 5-HT_{1B} receptors are localized in cranial blood vessels and in trigeminal nerve terminals, but 5-HT_{1D} receptors are absent from cranial vascular smooth muscle.

Currently, 7 triptan agents are available in the United States (Table 51.3). The main differences among them are half-life, bioavailability, and protein binding. Each triptan has features that need to be considered before administration. Potential adverse effects, which are mainly secondary to smooth muscle vasoconstriction, include pressure and tightness in the chest (an asthma-like attack), head, and neck and paresthesias.

The US Food and Drug Administration (FDA) has issued an alert about serotonin syndrome as a potential risk for patients taking selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors with triptans. Considering that triptans do not have any agonist action on the 5-HT_{2A} receptor, which is the main receptor implicated in the pathogenesis of serotonin syndrome, there is not a strong scientific basis for this concern. Contraindications for using triptans are pregnancy, coronary artery disease, uncontrolled hypertension, cerebrovascular disease (transient ischemic attack or infarct), severe peripheral vascular disease, and severe liver disease. The use of triptans in hemiplegic and basilar migraine is contraindicated by the manufacturers.

The 5-HT_{1F} receptor is a potential new target for migraine-specific treatments because preliminary data indicate that agents specific for 5-HT_{1F} receptors may be effective without vasoconstriction.

Ergots

Although oral ergotamine tartrate preparations are difficult to obtain in the United States, they are used in some other countries. An ergot derivative, dihydroergotamine, is an important treatment for status migranosus in most headache centers. Besides its agonist effect on 5-HT_{1B} and 5-HT_{1D} receptors, dihydroergotamine also has agonist activity on most of the other 5-HT_1 receptor subtypes (except 5-HT_{1C}). It is also a strong agonist of dopaminergic receptors (specifically D_2). Because of this, pretreatment with antidopaminergic agents before injecting dihydroergotamine is important so as to minimize severe nausea, vomiting, and abdominal discomfort. Other potential side effects include acroparesthesia, chest tightness, and leg cramps. Dihydroergotamine is contraindicated in coronary, cerebral, or peripheral vascular disease or uncontrolled hypertension. It is also contraindicated in pregnancy and advanced hepatic or renal failure.

Isometheptene-Containing Agents

Isometheptene, a sympathomimetic agent that is combined with acetaminophen and dichloralphenazone (Midrin) or with acetaminophen and caffeine (Prodrin), is effective in migraine attacks in some patients and may be better

Table 51.3 • Triptans Available in the United States

Triptan	Half-life, h	Key Features
Sumatriptan	2	First triptan The only triptan available in 3 different forms (oral tablet, nasal spray, subcutaneous injection)
Rizatriptan	2–3	Metabolism is decreased by propranolol (not other β-blockers); if the patient is taking propranolol, the dose of rizatriptan should be decreased by half (ie, to 5 mg)
Zolmitriptan	3	Has the lowest protein binding among the short-acting triptans; therefore, has the least likelihood of interacting with other drugs Nasal spray available
Almotriptan	3–4	Has the highest bioavailability and multiple pathways of metabolism; therefore, has fewer drug-drug interactions and fewer side effects FDA approved for adolescents (older than 12 y)
Eletriptan	4	Has the highest protein binding; therefore, has the highest probability of interacting with other drugs metabolized by CYP3A4 hepatic enzyme and is contraindicated in patients taking CYP3A4 inhibitors (eg, ketoconazole, macrolide antibiotics)
Naratriptan	6	Sometimes called the gentle triptan because it has fewer adverse effects Long acting: Used as short-term prophylaxis in menstrual-related migraine
Frovatriptan	26	Highest bioavailability and longest half-life Long acting, used as a short-term prophylaxis in menstrual-related migraine

Abbreviations: CYP3A4, cytochrome P450 3A4 isozyme; FDA, US Food and Drug Administration.

tolerated than triptans. Contraindications include uncontrolled hypertension, coronary artery disease, and ischemic stroke.

Intravenous Antidopaminergic Agents

Intravenous antidopaminergic agents have been effective for acute attacks of migraine in emergency department patients. These agents are usually administered in combination with NSAIDs. Study results have shown that prochlorperazine has the highest rates of effectiveness; however, other agents, such as metoclopramide, promethazine, and chlorpromazine, can also be used.

Opioid Analgesics

Owing to the high risk of dependency, the use of opiates and opioid agents in the treatment of acute migraine should be limited to patients who are pregnant or who have clear contraindications or a lack of response to triptans or dihydroergotamine.

Barbiturate-Containing Agents

Barbiturates may be an effective backup treatment when other abortive agents provide inadequate results or are contraindicated; however, because of the high risk of overuse (the highest risk of rebound headaches among all abortive agents) and the risk of withdrawal, their use should be limited and carefully monitored.

Other Agents

Other drugs (eg, valproate sodium, lidocaine, corticosteroids, and magnesium via intravenous administration) have been used in migraine attacks with reports of mixed success in different studies and may be effective in certain patients.

Preventive Therapy

In general, the goal of preventive therapy is to decrease the severity and frequency of migraine attacks by at least 50% by preventing the progression from episodic migraine to chronic migraine or, in the event that chronic migraine has already developed, by converting chronic migraine to episodic migraine. Prophylactic treatments are not curative. According to epidemiologic studies, about 38% of migraineurs need preventive therapy, but only about 13% of them use it.

No single preventive agent is preferred. The general principles for prophylactic treatment of migraine are the following:

- Pick a medication that is compatible with or beneficial for the comorbid conditions present in the patient.
- If the patient does not have any comorbid conditions, pick the medication with the lowest side effect profile.
- Start treatment with a low dose and titrate gradually.
- Make sure that the medication has an adequate therapeutic trial; attain a therapeutic dose and maintain it for 4 to 6 weeks.
- If the patient is using any other medication, check for drug-drug interactions.
- Make sure that the patient is not overusing analgesics, which may increase the chance that the preventive agent will not benefit the patient.
- For women of childbearing age, inquire about contraceptive status for the following reasons: 1) Most preventive agents are class C (*except sodium valproate*, which is class D), and they should not be used if there is any chance of pregnancy. 2) If the patient is taking an oral contraceptive, investigate its interaction with the preventive agent.

Headache specialists have different opinions about the efficacy and selection of preventive agents for migraine. The American Academy of Neurology published evidence-based guidelines for preventive treatments in 2012. The most commonly used preventive agents are shown in Box 51.3.

In some patients, a combination of preventive agents is needed, which requires specific attention to drug-drug interactions. Specific contraindications, precautions, and adverse effects need to be considered. For example, if a patient has a history of kidney stones (calcium phosphate), topiramate would typically be avoided or used with caution and fluid. If a patient has a cardiac rhythm abnormality, wariness should accompany consideration of the following medications: tricyclic antidepressants (can cause prolongation of the QT interval), calcium channel blockers (can cause heart block), and β-blockers (can cause bradycardia). An increased risk of suicidal ideation which should be considered for specific patients is a rare but important adverse effect of most of the antiepileptics (specifically, topiramate) and some antidepressants.

- Migraine usually starts during adolescence, and 90% of migraine patients have their first attack by age 40.
- About 90% of migraineurs have a family history positive for migraine.
- *Visual aura* is the most common type of aura and has different manifestations.
- A typical migraine headache starts unilaterally, attains moderate to severe intensity, has a throbbing (pulsating) quality, lasts 4–72 hours, and worsens with routine physical activity.
- Cyclical vomiting, abdominal migraine, benign paroxysmal vertigo of childhood, and benign paroxysmal torticollis are considered migraine variants (equivalents) in children.
- Status migrainosus is a migraine attack lasting for >72 hours without a headache-free interval >4 hours.

Box 51.3 • Medications Used as Migraine Preventives

Antihypertensives
- β-Blockers
  - Propranolol[a]
  - Metoprolol
  - Timolol[a]
  - Atenolol
  - Nadolol
  - Nebivolol
  - Pindolol
  - Bisoprolol
- Calcium channel blockers
  - Verapamil
  - Nimodipine
- ACE inhibitors and ARBs
  - Lisinopril
  - Candesartan

Antidepressants
- TCAs
  - Amitriptyline
  - Nortriptyline
  - Protriptyline
- SSRIs and SSNRIs
  - Fluoxetine
  - Venlafaxine[b]

Antiepileptics
- Divalproex sodium[a]
- Topiramte[a]
- Gabapentin

Herbals, vitamins, and minerals
- *Petasites hybridus* (butterbur) extract
- Riboflavin (vitamin B_2)
- MIG-99 (*Tanacetum parthenium* [feverfew])
- Magnesium
- Coenzyme q10

Other agents
- Onabotulinum toxin A[c]
- Cyproheptadine
- Melatonin
- Methysergide[d]

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; SSNRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] US Food and Drug Administration–labeled indication.

[b] At our institution, we have encountered an increased frequency of migraine with this drug.

[c] US Food and Drug Administration approval for only chronic migraine.

[d] Not available in the United States.

- Common triggers for migraine are alcohol, food containing monosodium glutamate, some cheeses, certain odors, weather (specifically, barometric pressure change), sleep hygiene (too much or too little sleep), stress, and anxiety.
- Caffeine-containing analgesics carry a higher risk of medication-overuse headaches. If these agents are taken more than 2 days weekly, patients may have a withdrawal and rebound pattern that results in awakening with a morning headache.
- The 5-HT receptors are a main target for migraine-specific abortive agents.

Tension-Type Headache

Introduction

Tension-type headache (TTH) is the most common type of headache in the general population; however, it is fairly uncommon among patients seeking medical treatment for headaches. The diagnostic criteria for TTH are not as distinct as for migraine or most other headache types (Box 51.4), and sometimes it is challenging to distinguish TTH from symptomatic headaches caused by an underlying disorder.

Epidemiology

The average age at onset is from 20 to 30 years, and the male to female ratio is 4:5. The prevalence of TTH varies from 27% to 58%; however, the prevalence of chronic TTH, which is 2% to 3%, is quite uniform across studies. The 1-year prevalence rate for episodic TTH in the general population is about 80%.

Box 51.4 • Key Features for Diagnosis of Tension-Type Headache According to *ICHD-III*

Patient must have ≥2 of the following 4 features:
- Location: bilateral
- Quality: nonthrobbing, steady (pressure-like)
- Intensity: mild to moderate
- Not worse with physical exertion

Patient must have both of these 2 features:
- Absence of nausea and vomiting (but presence of anorexia does not rule out the diagnosis)
- Absence of photophobia and phonophobia together (presence of only 1 does not rule out the diagnosis)

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

Pathophysiology

The origin of pain in TTH seems unclear and is probably heterogenous. Myofascial nociception may be more important in episodic TTH, and central sensitization generated by prolonged nociceptive input from the periphery is likely crucial in the pathophysiology of chronic TTH. Genetic predisposition is suggested, and environmental and psychologic factors can initiate the pain cycle. Genetic factors may have a more pronounced role in chronic TTH.

Clinical Features

For diagnosis of TTH, the patient must experience at least 10 headaches, each lasting 30 minutes to 7 days, with the features shown in Box 51.4. The most challenging aspect of diagnosis is the evaluation of pain intensity, which varies among patients. For example, moderate pain in 1 patient could be considered mild or severe pain in other patients.

Chronic TTH

Chronic TTH is defined as 15 or more days with headache per month and is a subtype of chronic daily headache. As outlined in the chronic migraine and chronic daily headache sections below, patients with chronic migraine can have some headaches that have a TTH phenotype. The diagnosis of chronic TTH can be made only when all the days with headache have the criteria for TTH. For example, the headaches of a patient who has chronic daily headache with 8 days of migraine headache and 8 days of TTH per month would be classified as chronic migraine, not chronic TTH.

Treatment

Abortive Therapy

Simple analgesic medications are the mainstay of abortive treatment of TTH. NSAIDs may be slightly superior to acetaminophen. The key features are early administration and correct dosage. Combination analgesics, which contain caffeine, are usually second-line agents; however, the risk of rebound headache is higher when combination medication is used.

Other combinations of analgesics that contain isometheptene (Midrin and Prodrin) are used for migraine and may be effective in TTH, specifically if the patient has an inadequate response to other treatment options. Combination analgesics containing barbiturates or codeine are not recommended because of the risk of dependence or the development of medication-overuse headache.

Preventive Therapy

If the frequency (>1–2 days weekly) and intensity of headache cause significant disability or if abortive therapy provides an inadequate response or is contraindicated, preventive therapy may be warranted. Not many large controlled trials have studied TTH. Tricyclic antidepressants are considered the mainstay of preventive treatment of TTH. Amitriptyline is usually the preferred agent. Anticonvulsants (gabapentin) and muscle relaxants (tizanidine) may be used in TTH. Behavioral treatments, such as biofeedback, have been shown to be effective in TTH.

- For diagnosis of TTH, the patient must experience at least 10 headaches, each lasting 30 minutes to 7 days.
- Tricyclic antidepressants are considered the mainstay of preventive treatment of TTH. Amitriptyline is usually the preferred agent.

Chronic Daily Headache

Introduction

Chronic daily headache is a general categorical term defined as the presence of headache 15 or more days per month for 3 or more months. It is not a specific type of headache. The 1-year population prevalence is estimated to be 2% to 4% of the general population. It is important to differentiate between primary and secondary chronic daily headache (Box 51.5); however, these 2 groups often over-

Box 51.5 • Subtypes of Chronic Daily Headache (CDH)

Primary CDH
- Chronic tension-type headache (CTTH)
- Chronic migraine (CM)
- Chronic cluster headache
- New daily persistent headache (NDPH)
- Hemicrania continua
- Primary stabbing headache

Secondary CDH
- Medication-overuse headache (MOH)
- Trauma (posttraumatic headache)
- Sleep disorder (eg, sleep apnea)
- CSF pressure abnormality (low or high)
- Structural abnormalities
  - Cervical spine (cervicogenic headache)
  - Temporomandibular joint disorder
  - Sinusitis and other rhinonasal abnormalities

Abbreviation: CSF, cerebrospinal fluid.

lap. For example, chronic migraine and medication-overuse headache, which probably are the most common types of chronic daily headache in headache clinics, frequently occur together.

Chronic Migraine

To be considered chronic migraine, not all the 15 or more days of headache need to be migraine. If at least 8 days of the total number of headaches per month fulfill *ICHD-III* diagnostic criteria for migraine, the diagnosis of chronic migraine is confirmed.

The other key feature is the absence of ongoing medication overuse. Besides medication-overuse headache, which may be the most important risk factor for the transformation from episodic migraine to chronic migraine, all other factors listed for secondary chronic daily headache in Box 51.5 could be risk factors for chronic migraine. Other risk factors include a high frequency of baseline migraine attacks, social stressors, obesity, depression, anxiety, lower socioeconomic status, increased caffeine consumption, and being female or white.

Treatment

The abortive and preventive medications discussed above for migraine treatment are used to treat chronic migraine. Preventives are the main focus of chronic migraine pharmacologic treatment (Box 51.3). Onabotulinum toxin A is approved by the FDA for the preventive treatment of chronic migraine. Besides medical therapy, other management options include lifestyle modification, behavioral therapy, patient education, support for managing expectations, and close follow-up care. In some intractable cases, specifically if medication-overuse headache is involved, inpatient management may be indicated. Most preventive agents are ineffective for chronic migraine if the patient has medication-overuse headache. In that situation, only topiramate and onabotulinum toxin A have been partially effective.

- *Chronic daily headache* is a general categorical term defined as the presence of headache ≥15 days per month for ≥3 months.
- Besides medication-overuse headache, which may be the most important risk factor for the transformation from episodic migraine to chronic migraine, all other factors listed for secondary chronic daily headache in Box 51.5 could be risk factors for chronic migraine.
- Onabotulinum toxin A is approved by the FDA for the preventive treatment of chronic migraine.

52 Primary Headache Disorders: Trigeminal Autonomic Cephalgias, Headaches With Specific Triggers, and Other Primary Headache Disorders

RASHMI B. HALKER SINGH, MD; BERT B. VARGAS, MD

Introduction

Primary headache disorders are those in which headache is the predominant clinical feature and there is no obvious underlying structural, genetic, or metabolic cause. Chapter 51 ("Primary Headache Disorders: Migraine, Tension-Type, and Chronic Daily Headaches") reviews the common primary headache disorders of migraine, tension-type headache, and chronic daily headache. The present chapter reviews less common primary headache disorders, such as the trigeminal autonomic cephalgias (TACs) and headaches with certain triggers. A careful history, physical examination, and additional testing are often necessary to rule out a secondary cause. Red flag symptoms for secondary causes are reviewed in Chapter 50 ("Introduction and Approach to Headache").

TACs and Other Side-Locked Headaches

Introduction

The TACs are characterized by severe, unilateral, and side-locked head pain, typically involving the first division of the trigeminal nerve, and accompanying autonomic features ipsilateral to the side of pain, such as lacrimation, rhinorrhea, and conjunctival injection. Cluster headache (CH) is the most common TAC. Other TACs are paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome. Features of selected primary headache disorders are compared in Table 52.1.

Hemicrania continua (HC) and primary stabbing headache (PSH), described below, share some similarities with the TACs but also have important distinctions.

Cluster Headache

Epidemiology

CH occurs in about 0.1% of the population and is more common in men than women. Peak incidence occurs between the ages of 20 and 40 years.

The 2 main aspects of CH are 1) the *cluster attack*—the individual episode of pain, which can last minutes to hours—and 2) the *cluster bout*—the period, usually weeks to months, when a person is susceptible to cluster attacks.

Clinical Features and Criteria

Box 52.1 lists the criteria for CH from the *International Classification of Headache Disorders*, 3rd Edition (*ICHD-III*). The pain associated with CH makes CH arguably the most painful primary headache condition, with patients describing the pain as more intense than

Abbreviations: CH, cluster headache; HC, hemicrania continua; *ICHD-III, International Classification of Headache Disorders*, 3rd Edition; MRI, magnetic resonance imaging; PH, paroxysmal hemicrania; PSH, primary stabbing headache; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; TAC, trigeminal autonomic cephalgia

Table 52.1 • A Comparison of Primary Headaches

Headache Type	Predominance	Attacks	Associated Symptoms	Frequency	Comments
SUNCT	Male	5–240 s	Conjunctival injection and lacrimation	Up to 200 daily Very frequent	Therapy: lamotrigine Indomethacin not beneficial
Cluster	Male	15–180 min Severe	Ipsilateral autonomic	1–8 daily	Indomethacin not beneficial Alcohol may precipitate attacks
Paroxysmal hemicrania	Female	2–30 min	Ipsilateral autonomic	Frequent 2–40 daily	Therapy: indomethacin
Hemicrania continua	Female	Continuous Exacerbations last hours	Superimposed jabs	Continuous Severity varies	Therapy: indomethacin
Hypnic	Age >50 y	During sleep 10–180 min	No autonomic	>15 times monthly	Indomethacin may or may not be beneficial
Trigeminal neuralgia	Female	<1 s	No autonomic	Variable	Therapy: carbamazepine; surgical
Primary stabbing	Female	<1 s Sharp jabs, ice pick	No autonomic	Variable	Therapy: indomethacin, celecoxib, melatonin Check for GCA in older patients

Abbreviations: GCA, giant cell arteritis; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Box 52.1 • *ICHD-III* Criteria for Cluster Headache

A. At least 5 attacks fulfilling criteria B through E

B. Severe or very severe unilateral orbital, supraorbital, or temporal pain lasting 15–180 min if left untreated

C. Either or both of the following:

1. At least 1 of the following symptoms or signs, ipsilateral to the headache:
   a. Conjunctival injection or lacrimation (or both)
   b. Nasal congestion or rhinorrhea (or both)
   c. Eyelid edema
   d. Forehead and facial sweating
   e. Forehead and facial flushing
   f. Sensation of fullness in the ear
   g. Miosis or ptosis (or both)
2. A sense of restlessness or agitation

D. Attacks have a frequency between 1 every other day and 8 daily for more than half the time when the disorder is active

E. Not better accounted for by another *ICHD-III* diagnosis

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

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childbirth and renal colic. There are published reports of persons directing violent self-harm to the site of the pain or attempting suicide to resolve the intense discomfort. Patients describe the pain as a constant burning, boring, piercing, or tearing or like a hot poker in the eye. The pain reaches peak intensity within minutes of onset, and, on average, attacks last about an hour. Autonomic symptoms, occurring ipsilateral to the side of the pain and most commonly consisting of lacrimation and rhinorrhea, can be profuse during an attack. Autonomic features are generally limited to each cluster attack, but a persistent Horner syndrome may occur in patients who have experienced recurrent cluster attacks for years. Unlike patients with migraine, most patients during a cluster attack are restless and cannot sit or lie still, preferring instead to pace about a room or rock back and forth. During a cluster bout, attacks may be spontaneous and unprovoked. They can also be triggered by alcohol, nitroglycerine, histamine, high altitude, and volatile substances, such as solvents and oil-based paints.

Circadian periodicity is a key feature of CH. During a cluster bout, most patients have 1 to 2 attacks daily that occur at predictable times. For many patients, cluster attacks peak between 1 and 2 AM, and between 1 and 3 PM, and around 9 PM. Many patients with CH also have attacks nocturnally, about 90 minutes after going to sleep, suggesting that a relationship may exist between CH and sleep phase, particularly rapid eye movement sleep. Patients with CH have a higher incidence of obstructive sleep apnea and should be screened for obstructive sleep apnea.

Clinical Course

About 80% of patients with CH have *episodic CH*, typically characterized by recurrent bouts that last at least 1 week each and are separated by at least 1 month. One quarter of patients have only a single bout of CH with no recurrence; however, CH generally occurs in bouts lasting 1 to 3 months, with each bout occurring every 6 to 24 months. Twenty percent of patients have *chronic CH*, defined by either remission periods lasting less than a month or no remission occurring within 1 year.

CH often has a circannual periodicity, with cluster bouts occurring more frequently in the spring and autumn. The occurrence of cluster bouts correlates with the increasing and decreasing of daylight hours with 2 main peaks of cluster: 7 to 10 days after the longest day of the year and 7 to 10 days after the shortest day. In other patients, cluster bouts may occur at regular, predictable intervals that are unique for each person.

Differential Diagnosis

The differential diagnosis for CH includes migraine, other TACs (PH and SUNCT syndrome), and hypnic headache. Secondary headache disorders that mimic CH must be excluded before making the diagnosis. Any atypical components in the history or abnormalities on the neurologic examination warrant a thorough workup for potential secondary causes in patients who may have vascular, neoplastic, and infectious conditions and symptoms similar to those of patients with primary CH. At the bare minimum, when a patient presents with symptoms suggestive of CH, magnetic resonance imaging (MRI) of the brain with dedicated views of the pituitary gland should be done, even in the absence of atypical features because pituitary lesions can mimic TACs, including CH.

Treatment

Treatment of CH can be divided into acute, transitional, and prophylactic therapy (Table 52.2). During a cluster bout, patients should be advised to avoid known triggers, including alcohol, certain medications, volatile substances, and even afternoon naps because sleep can be a trigger in some.

One potentially effective acute treatment of CH is 100% oxygen, administered with a nonrebreather face mask for 15 to 20 minutes at a rate of 7 to 15 L/min. CH is the only primary headache disorder with a body of evidence suggesting that it may respond to oxygen and that oxygen may even completely abort an attack. Oxygen is a relatively safe treatment that is safe to use multiple times daily and may be administered in combination with other abortive and preventive treatments. Given that a high proportion of patients with CH are smokers, they must be cautioned that oxygen is a highly combustible gas and that smoking in its presence is extremely dangerous.

Triptans and ergot derivatives, such as dihydroergotamine, can also provide effective abortive therapy for CH. Given the rapid time to peak pain and short duration of individual attacks, medications should be administered by a parenteral or pulmonary route instead of orally for faster absorption. Options include sumatriptan 6 mg subcutaneous injection, sumatriptan 20 mg nasal spray, zolmitriptan 5 mg nasal spray, and dihydroergotamine 1 mg subcutaneous injection. For patients who have a contraindication to triptan and ergot use, intranasal lidocaine and octreotide are reasonable acute therapy options.

Corticosteroids can effectively prevent short-term cluster attacks until long-term prophylactic medication becomes effective. They may be administered orally (prednisone 60 mg tapered by 10 mg every 2–3 days to allow for 12–18 days of treatment) or as an occipital nerve block (2.5 mL 0.5% bupivacaine with 20 mg methylprednisolone) ipsilateral to the side of the attacks.

Verapamil is the first-line preventive medication for CH; the starting dosage of 40 to 80 mg 3 times daily may be titrated as high as 240 mg 3 times daily depending on patient tolerability and headache response. Some anecdotal reports suggest that the immediate-release formulation may be more effective than the long-acting formulation.

Table 52.2 • Treatment of Cluster Headache

	Therapy		
Feature	**Acute**	**Transitional**	**Prophylactic**
Timing	Administered during attacks	Administered to rapidly prevent attacks	Administered to maintain headache freedom for the duration of the typical bout in episodic cluster Long-term use in chronic cluster headache
Agents	Oxygen 7–15 L/min Triptans Dihydroergotamine Intranasal lidocaine	Corticosteroids Occipital nerve block	Verapamil Lithium Melatonin Topiramate Gabapentin Methysergide

An electrocardiogram should be obtained before treatment with verapamil and repeated periodically during treatment, particularly with dose increases, because of the potential risk of heart block. Other prophylactic options include valproic acid, lithium carbonate, ergotamine tartrate, methysergide, topiramate, and gabapentin. In episodic CH, the effective preventive dose is continued for the typical duration of the bout and then for a 2-week pain-free period before it is slowly tapered.

Although CH is not considered to be an indomethacin-responsive headache disorder, there are reports of some CH patients having a positive response. These patients likely have PH with a CH phenotype. Consequently, treatment-resistant CH patients should be offered an indomethacin trial, starting with the immediate-release formulation at 25 mg 3 times daily, and titrating up to 50 to 75 mg 3 times daily if a response does not occur within a week. Long-term treatment with indomethacin should also include coadministration of a gastrointestinal tract prophylactic agent such as a proton pump inhibitor.

Paroxysmal Hemicrania

Clinical Features and Criteria

PH is a TAC that is similar to CH in terms of its attack characteristics and associated autonomic symptoms; however, attacks tend to be shorter and can occur more frequently during a day. There is a slight female predominance. Peak incidence is in the mid 30s. Most patients have chronic PH, with daily or near daily attacks occurring for at least a year, rather than the episodic form (defined by the presence of pain-free periods lasting at least a month).

Diagnosis

The *ICHD-III* diagnostic criteria for PH are listed in Box 52.2. As when CH is suspected, when a diagnosis of PH is suspected, MRI of the brain with coronal gadolinium-enhanced sequences should be done because pituitary lesions can mimic PH.

Treatment

By definition, as an indomethacin-responsive headache disorder, PH responds to indomethacin, typically within hours to days after therapy is started. Patients should begin taking the immediate-release formulation at a dosage of 25 mg 3 times daily and increasing the dosage every 3 to 5 days until a response occurs or to a maximum of 75 mg 3 times daily. After symptoms improve, the dose can be cautiously decreased to the lowest therapeutic dose of indomethacin needed to provide adequate prophylaxis. Given the potential for gastrointestinal adverse effects with long-term use of nonsteroidal anti-inflammatory drugs, mucosal protection should be provided and patients should be advised to take indomethacin with food.

Box 52.2 • *ICHD-III* Diagnostic Criteria for Paroxysmal Hemicrania

A. At least 20 attacks fulfilling criteria B through E
B. Severe unilateral orbital, supraorbital, or temporal pain lasting 2–30 min
C. At least 1 of the following symptoms or signs, ipsilateral to the pain:
   1. Conjunctival injection or lacrimation (or both)
   2. Nasal congestion or rhinorrhea (or both)
   3. Eyelid edema
   4. Forehead and facial sweating
   5. Forehead and facial flushing
   6. Sensation of fullness in the ear
   7. Miosis or ptosis (or both)
D. Attacks occur more frequently than 5 daily for more than half the time
E. Attacks are prevented absolutely by therapeutic doses of indomethacin
F. Not better accounted for by another *ICHD-III* diagnosis

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

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Spontaneous remission of PH can occur, so periodically the dose should be decreased or tapered to zero. If patients cannot take indomethacin, they may receive some benefit from other options, such as gabapentin, melatonin, topiramate, verapamil, cyclooxygenase-2 inhibitors, acetylsalicylic acid, and occipital nerve blocks.

SUNCT Syndrome

Clinical Features

SUNCT syndrome is another TAC similar to CH and PH, characterized by severe unilateral pain and associated autonomic features. SUNCT syndrome differs from CH and PH in that the attacks are much shorter, lasting from seconds to minutes, and can recur up to hundreds of times daily.

Diagnosis

The differential diagnosis for SUNCT syndrome includes other TACs and trigeminal neuralgia. Unlike trigeminal neuralgia, this condition is accompanied by prominent autonomic symptoms and is more likely to affect the first division of the trigeminal nerve (V1), whereas V2 and V3 are more likely to be involved with trigeminal neuralgia.

When this diagnosis is suspected, patients should undergo MRI of the brain with gadolinium-enhanced coronal cuts of the pituitary gland.

Treatment

SUNCT syndrome is less responsive to treatment than any other primary headache disorder. Although typical treatments known to be effective for CH and PH are generally ineffective for this condition, patients should be offered these treatment options, and an indomethacin trial should be considered because of the overlap with PH. SUNCT syndrome is more likely to respond to lamotrigine, gabapentin, and topiramate. Intravenous lidocaine, administered with concomitant cardiac monitoring, can also be beneficial.

Hemicrania Continua

Clinical Features

HC is a side-locked primary headache disorder that shares features with migraine as well as the TACs. The pain associated with HC is strictly unilateral and continuously present but fluctuating in intensity. Exacerbations of pain can be accompanied by migrainous features, such as nausea, vomiting, photophobia, and phonophobia, as well as autonomic symptoms. Patients with HC may also feel jabs and jolts of head pain, lasting seconds and ipsilateral to the headache, and ocular discomfort, such as a sensation that there is a foreign body in the eye. This condition is slightly more prevalent in women, and it responds exquisitely to indomethacin.

Diagnosis

The *ICHD-III* diagnostic criteria are listed in Box 52.3. Patients with suspected HC should undergo MRI of the brain with and without gadolinium to rule out a secondary cause. Additional neuroimaging should be considered according to the patient's history and examination findings because there are several reports in the literature of HC due to pituitary lesions, sphenoid sinusitis, intracranial tumors, stroke, and internal carotid artery dissection.

Treatment

By definition, as an indomethacin-responsive headache disorder, HC responds to indomethacin. A reasonable indomethacin trial would consist of 25 mg 3 times daily for 3 days, then 50 mg 3 times daily for 3 days, and then 75 mg 3 times daily. HC tends to resolve within days after indomethacin therapy is started. After the headache resolves, the indomethacin dosage should be slowly tapered to the lowest effective dosage. As noted above for other trials of indomethacin, gastric protection may be useful. Every 3 to 6 months, the indomethacin dosage should be slowly tapered or discontinued to evaluate for the possibility that HC has gone into spontaneous remission.

Box 52.3 • *ICHD-III* Diagnostic Criteria for Hemicrania Continua

A. Unilateral headache fulfilling criteria B through D

B. Present for >3 mo, with exacerbations of moderate or greater intensity

C. Either or both of the following:

1. At least 1 of the following symptoms or signs, ipsilateral to the headache:
   a. Conjunctival injection or lacrimation (or both)
   b. Nasal congestion or rhinorrhea (or both)
   c. Eyelid edema
   d. Forehead and facial sweating
   e. Forehead and facial flushing
   f. Sensation of fullness in the ear
   g. Miosis or ptosis (or both)
2. A sense of restlessness or agitation, or aggravation of the pain by movement

D. Responds absolutely to therapeutic doses of indomethacin

E. Not better accounted for by another *ICHD-III* diagnosis

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

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For patients who cannot take indomethacin, other treatment options include gabapentin, occipital nerve blockade ipsilateral to the side of the headache, corticosteroids, cyclooxygenase-2 inhibitors, other nonsteroidal anti-inflammatory drugs, methysergide, melatonin, and occipital nerve stimulation.

Primary Stabbing Headache

Epidemiology and Clinical Features

PSH is more common in women (lifetime prevalence, <2%) and is comorbid with other headache disorders, including migraine, the TACs, and HC. PSH is also known as ice pick headache, jabs and jolts syndrome, and idiopathic stabbing headache. PSH is a sudden, severe headache, lasting on the order of seconds, generally in the ophthalmic division of the trigeminal nerve.

Diagnosis

The differential diagnosis for PSH includes SUNCT syndrome and trigeminal neuralgia. SUNCT syndrome must include autonomic symptoms, whereas PSH has no associated features. Trigeminal neuralgia is more common in V2 and V3 than in V1 and can be triggered; PSH occurs

spontaneously and lacks cutaneous triggers. Other PSH mimics include intracranial lesions (meningiomas, pituitary tumors, etc), increased intraocular pressure, and giant cell arteritis. Neuroimaging should be pursued if a patient has frequent attacks, if the attacks are strictly isolated to a single location, or if the patient does not respond to indomethacin.

Treatment

PSH is an indomethacin-responsive headache disorder; patients typically respond prophylactically to 25 to 75 mg 3 times daily. Given the short duration of attacks, short-term therapy is not feasible. Other prophylactic medication options include gabapentin and melatonin.

- The TACs are characterized by severe, unilateral, and side-locked head pain, typically involving the first division of the trigeminal nerve, and accompanying autonomic features ipsilateral to the side of pain, such as lacrimation, rhinorrhea, and conjunctival injection.
- CH occurs in about 0.1% of the population and is more common in men than women.
- Unlike patients with migraine, most patients during a cluster attack are restless and cannot sit or lie still, preferring instead to pace about a room or rock back and forth.
- During a cluster bout, attacks may be spontaneous and unprovoked. They can also be triggered by alcohol, nitroglycerine, histamine, high altitude, and volatile substances, such as solvents and oil-based paints.
- For many patients, cluster attacks peak between 1 and 2 AM, and between 1 and 3 PM, and around 9 PM.
- At the bare minimum, when a patient presents with symptoms suggestive of CH, MRI of the brain with dedicated views of the pituitary gland should be done, even in the absence of atypical features because pituitary lesions can mimic TACs, including CH.
- Treatment of CH can be divided into acute, transitional, and prophylactic therapy.
- One potentially effective acute treatment of CH is 100% oxygen, administered with a nonrebreather face mask for 15–20 minutes at a rate of 7–15 L/min.
- Verapamil is the first-line preventive medication for CH.
- PH is a TAC that is similar to CH in terms of its attack characteristics and associated autonomic symptoms; however, attacks tend to be shorter and can occur more frequently during a day.
- PH responds to indomethacin, typically within hours to days after therapy is started.
- SUNCT syndrome differs from CH and PH in that the attacks are much shorter, lasting from seconds to minutes, and can recur up to hundreds of times daily.
- The pain associated with HC is strictly unilateral and continuously present but fluctuating in intensity.
- HC responds to indomethacin.
- PSH is an indomethacin-responsive headache disorder.

Primary Headaches Associated With Specific Triggers

Cough Headache

Clinical Features

Cough headache is characterized by the abrupt onset of a severe, holocephalic or occipital explosive headache that lasts 5 to 30 minutes and is brought on by coughing, laughing, sneezing, and other maneuvers that increase intracranial pressure. Lifetime prevalence is 1%. Cough headache is more common in men than in women, typically has an onset after age 40, can go into spontaneous remission after 6 to 24 months, and is considered an indomethacin-responsive headache disorder.

Diagnosis

ICHD-III criteria for diagnosis are listed in Box 52.4. If cough headache is suspected, MRI of the brain with and without gadolinium (and other imaging studies if indicated) is important to rule out secondary causes. At least 50% of cases of cough headache are associated with a Chiari type I malformation; the differential diagnosis also includes disorders of cerebrospinal fluid pressure, third ventricle colloid cysts, sinusitis, and space-occupying lesions.

Treatment

Cough headache is an indomethacin-responsive headache disorder. Patients typically respond to prophylactic doses

Box 52.4 • *ICHD-III* Diagnostic Criteria for Cough Headache

A. At least 2 headache episodes fulfilling criteria B through D

B. Brought on by and occurring only in association with coughing, straining, or other Valsalva maneuver

C. Sudden onset

D. Lasting between 1 s and 2 h

E. Not better accounted for by another *ICHD-III* diagnosis

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of 25 to 75 mg 3 times daily. Other preventive options include topiramate or acetazolamide. Given the short duration of attacks, short-term therapy is not pragmatic. Also, spontaneous remission often occurs, generally after 6 to 24 months, and periodic attempts at medication tapers are beneficial.

Primary Exertional Headache

Epidemiology and Clinical Features

Primary exertional headache is characterized by headache occurring only during physical exertion. Lifetime prevalence is 1%. Primary exertional headache is more common in men than women, and it generally affects persons younger than 50 years. The headache can be bilateral or unilateral, and it can have migrainous features, including nausea, photophobia, phonophobia, and a pulsating quality.

Primary exertional headache is comorbid with migraine, but it differs from migraine in that exertion *precipitates* the onset of primary exertional headache, whereas migraine is *aggravated* by activity. Primary exertional headache also differs from cough headache in that prolonged physical exercise is needed to trigger this headache type. The headache associated with primary exertional headache usually occurs at the peak of exercise and subsides when the activity ceases, but it can sometimes persist up to 2 days. Contributing factors include heat, humidity, barometric pressure changes, high altitude, caffeine, hypoglycemia, and alcohol use. The diagnostic criteria are listed in Box 52.5.

Treatment

Treatment options include transient exercise moderation or abstinence, use of indomethacin before exercise, and propranolol. Ergotamine tartrate is effective in some patients. Given that this headache type tends to remit with time and rarely lasts longer than 6 months, the preventive treatment should be stopped after 3 to 6 months to check for headache remission.

Box 52.5 • *ICHD-III* Diagnostic Criteria for Primary Exertional Headache

A. At least 2 headache episodes fulfilling criteria B and C

B. Brought on by and occurring only during or after strenuous physical exercise

C. Lasting <48 h

D. Not better accounted for by another *ICHD-III* diagnosis

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

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Primary Headache Associated With Sexual Activity

Epidemiology and Clinical Features

Primary headache associated with sexual activity can occur in the context of sexual intercourse or masturbation. Lifetime prevalence is 1%. It most commonly occurs at orgasm (orgasmic subtype) and is usually described as a sudden onset of "the worst headache of my life" (thunderclap headache). This orgasmic subtype accounts for 80% of cases, is often associated with an increase in blood pressure, and lasts anywhere from 1 minute to 3 hours. A preorgasmic subtype also exists.

Differential Diagnosis

Given that the differential diagnosis for thunderclap headache includes many serious conditions, patients must undergo a comprehensive evaluation, particularly in the case of the first thunderclap headache occurring with sexual activity (see Chapter 53, "Secondary Headache Disorders").

Treatment

Patients with the orgasmic form can be treated either preemptively with indomethacin 30 to 60 minutes before sexual activity or prophylactically with a β-blocker or indomethacin on a daily basis. Vasoconstrictive medications, such as triptans and ergot derivatives, should be avoided in these patients.

- At least 50% of cases of cough headache are associated with a Chiari type I malformation; the differential diagnosis also includes disorders of cerebrospinal fluid pressure, third ventricle colloid cysts, sinusitis, and space-occupying lesions.
- Cough headache is an indomethacin-responsive headache disorder.
- Primary exertional headache is comorbid with migraine, but it differs from migraine in that exertion *precipitates* the onset of primary exertional headache, whereas migraine is *aggravated* by activity.

Other Primary Headache Disorders

Hypnic Headache

Epidemiology and Clinical Features

Hypnic headache is a rare primary headache disorder (prevalence, 0.07%) that occurs mainly in persons older than 50 years. Hypnic headache is characterized by the onset of a nocturnal headache, lasting 10 to 180 minutes,

that occurs exclusively during sleep and at least 15 nights per month. Attacks occur near the same time each night, generally 2 to 4 hours after falling asleep, and may recur up to 6 times during the night. Some patients may also experience attacks during daytime naps. Up to 75% of attacks occur during rapid eye movement sleep. The pain is more often mild to moderate and bilateral, and autonomic symptoms are rare. Patients uncommonly have migrainous features, including mild nausea, photophobia, and phonophobia.

Diagnosis

The differential diagnosis should include other TACs as well as secondary disorders. The evaluation should include MRI of the brain, with and without gadolinium, and dedicated imaging of the pituitary gland because pituitary and parasellar lesions can mimic hypnic headache. Patients should also undergo a sleep evaluation to exclude the possibility of a sleep-related breathing disorder or nocturnal hypertension.

Treatment

Hypnic headache can be treated with caffeine, either as a cup of coffee at bedtime or with caffeine tablets (60–200 mg). Other prophylactic options include melatonin (3–12 mg at bedtime), indomethacin (25–75 mg at bedtime), or lithium carbonate (300–600 mg).

New Daily Persistent Headache

Clinical Features

New daily persistent headache is a rare chronic headache disorder that begins spontaneously and becomes daily within 72 hours after onset. Its phenotype usually resembles that of either chronic tension-type headache or chronic migraine, but patients tend to recall the exact moment the headache began and can describe that moment, down to the date of onset, with clarity. The underlying cause is unknown, but in about a third of cases, it follows a recent infection or flulike illness. There are 2 subtypes: The first is a self-limited condition that can resolve without medical intervention; the second is highly resistant to medications or other therapy for chronic headache and can persist for years.

Diagnosis

Diagnostic criteria are listed in Box 52.6. New daily persistent headache is a diagnosis of exclusion. A workup to exclude secondary causes must include the following: complete blood cell count (to exclude anemia and chronic infection), thyrotropin level (to exclude hypothyroidism), erythrocyte sedimentation rate and C-reactive protein level for older patients, MRI of the brain with and without gadolinium (to exclude space-occupying lesions and spontaneous intracranial hypotension), magnetic resonance venography of the head (to exclude venous sinus thrombosis), and lumbar puncture (to exclude disorders of increased or decreased cerebrospinal fluid pressure and chronic meningitis).

Box 52.6 • *ICHD-III* Diagnostic Criteria for New Daily Persistent Headache

A. Persistent headache fulfilling criteria B and C
B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 h
C. Present for >3 mo
D. Not better accounted for by another *ICHD-III* diagnosis

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

Adapted from Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013 Jul;33(9):629–808. Used with permission.

Treatment

There is no known effective treatment for new daily persistent headache, but standard acute and prophylactic treatments for chronic migraine and chronic tension-type headache can be tried. Rarely, patients may also respond to doxycycline.

- Hypnic headache is a rare primary headache disorder (prevalence, 0.07%) that occurs mainly in persons older than 50 years.
- Hypnic headache is characterized by the onset of a nocturnal headache, lasting 10 to 180 minutes, that occurs exclusively during sleep and at least 15 nights per month.
- New daily persistent headache is a rare chronic headache disorder that begins spontaneously and becomes daily within 72 hours after onset.

53 Secondary Headache Disorders[a]

AMAAL J. STARLING, MD; DAVID W. DODICK, MD

Introduction

When encountering a patient with headache, the first task is to differentiate between a secondary headache and a primary headache. This step is essential because secondary causes of headache may require vastly different treatment and evaluation than primary headaches. Clues to the differentiation of headaches are discussed in Chapter 50, "Introduction and Approach to Headache." The present chapter discusses secondary causes of headaches.

Thunderclap Headache

Introduction and Definition

Thunderclap headache (TCH) is an acute, severe headache that reaches peak intensity at onset. TCH is a neurologic emergency and should immediately prompt an urgent evaluation for a secondary headache. Box 53.1 lists the differential diagnosis of TCH.

When a TCH is identified, standard of care mandates emergent computed tomography (CT) of the head followed by lumbar puncture if the CT is negative; however, depending on the clinical picture, magnetic resonance imaging (MRI) of the brain with or without additional neurovascular imaging may be needed for diagnosis and management. Management and treatment depend on the underlying cause.

Box 53.1 • Differential Diagnosis of Thunderclap Headache

- Subarachnoid hemorrhage
- Sentinel headache
- Reversible cerebral vasoconstriction syndrome
- Cervical artery dissection
- Cerebral venous sinus thrombosis
- Stroke (hemorrhagic or ischemic)
- Hypertensive crisis
- Spontaneous intracranial hypotension
- Pituitary apoplexy
- Retroclival hematoma
- Third ventricle colloid cyst
- Intracranial infection
- Primary thunderclap headache
- Primary cough, sexual, and exertional headache

Adapted from Schwedt TJ, Matharu MS, Dodick DW. Thunderclap headache. Lancet Neurol. 2006 Jul;5(7):621–31. Used with permission.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage is the most common cause of TCH and is present in 25% of patients with TCH. Since subarachnoid hemorrhage carries a poor overall outcome, with significant morbidity and mortality, the initial evaluation of a TCH should focus on ruling out a subarachnoid hemorrhage. Clinically, patients with TCH have a severe TCH described as "the worst headache of my life" that lasts for several days to weeks. Associated features may include nausea, vomiting, photophobia, neck stiffness, and altered mental status. Physical exertion, straining, or Valsalva

[a] Portions previously published in Schwedt TJ, Matharu MS, Dodick DW. Thunderclap headache. Lancet Neurol. 2006 Jul;5(7):621–31. Used with permission.

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; CVST, cerebral venous sinus thrombosis; GCA, giant cell arteritis; MRI, magnetic resonance imaging; PACNS, primary angiitis of the central nervous system; PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; TCH, thunderclap headache

maneuvers may precede headache onset; however, it can occur without any inciting event or exertion. See Chapter 4, "Nontraumatic Subarachnoid Hemorrhage," for further details.

Sentinel headaches are clinically similar to headaches from subarachnoid hemorrhages, except that patients with sentinel headaches should not have neck stiffness, altered mental status, or focal neurologic symptoms. Sentinel headaches are likely due to a small undetectable leak instead of a structural change in the aneurysm wall resulting in pain. Of the patients with aneurysmal subarachnoid hemorrhage, 10% to 43% have a history of a sentinel headache in the weeks before aneurysm rupture.

Diagnostic evaluation should include emergent, noncontrast CT of the head, and, if CT is negative, lumbar puncture should follow. The sensitivity of CT of the head nears 100% within the first 12 hours of symptom onset but decreases to 50% within 1 week. Routine cerebrospinal fluid (CSF) assessment, including cell counts and visual inspection for xanthochromia, should be performed. If available, mass spectrophotometry can be performed. Unlike the decreasing sensitivity of CT for detecting subarachnoid hemorrhage after 12 hours, the sensitivity of mass spectrophotometry after 12 hours is more than 95%.

If subarachnoid hemorrhage is identified, management includes identifying and repairing the source of bleeding and preventing complications. (See Chapter 4, "Nontraumatic Subarachnoid Hemorrhage.")

TCH is rarely a benign condition or primary TCH. Even if the evaluation described above is negative, further studies are indicated to evaluate the brain and neurovascular structures in more detail to rule out other conditions, which are noted below. Depending on the clinical picture, and if not contraindicated, 1 or more of the following should be performed: MRI of the brain with and without gadolinium, magnetic resonance angiography of the head and neck, and magnetic resonance venography.

Cervical Artery Dissection

Cervical artery dissection can present as a TCH, in isolation and without associated signs or symptoms, 20% of the time. Headache, regardless of onset, is common in cervical artery dissections (60%–95% of patients). Clinically, patients with carotid dissections present with a headache that is ipsilateral to the dissection, usually in the jaw, face, ear, and periorbital and frontal regions, and patients with vertebral dissections have pain localized to the occipital region. The pain is usually nonthrobbing and severe. Neck pain commonly accompanies headache in dissections. It is rare that headache and neck pain are the sole manifestations of cervical artery dissections; however, it is not uncommon for these symptoms to precede other neurologic symptoms and signs. A unilateral Horner syndrome is often present with carotid dissection.

A unilateral TCH secondary to subarachnoid hemorrhage is highly uncommon. Therefore, the unilateral characteristic of these headaches and the association with neck pain, with or without additional localizing neurologic symptoms or signs, should prompt a diagnostic evaluation that includes neurovascular imaging of the head and neck. Management of arterial dissection is covered in Chapter 10, "Ischemic Stroke: Common Causes and Diagnosis."

Reversible Cerebral Vasoconstriction Syndrome

Patients with reversible cerebral vasoconstriction syndrome (RCVS) present with a TCH, normal to near-normal CSF findings, and diffuse, segmental reversible cerebral vasoconstriction. They vary clinically with regard to the presence and severity of neurologic deficits and imaging abnormalities. RCVS has been described in the peripartum period and in patients exposed to sympathomimetic drugs and selective serotonin reuptake inhibitors.

The presence of diffuse, segmental cerebral vasoconstriction is key for diagnosis (Figure 53.1). MRI of the brain coupled with magnetic resonance angiography of the head is the diagnostic imaging of choice. Cerebral angiography, the gold standard for vessel imaging, allows for intra-arterial intervention if needed.

The imaging and angiographic findings with RCVS may be indistinguishable from those with primary angiitis of the central nervous system (PACNS), which is the main differential diagnosis. However, these 2 entities differ clinically. Headache in RCVS has a thunderclap onset; headache in PACNS has a subacute, gradually progressive onset. CSF in RCVS is normal or nearly normal; CSF in PACNS is abnormal in about 80% of patients. MRI of the brain can be normal in RCVS; MRI of the brain is not normal in PACNS but rather usually shows multifocal lesions

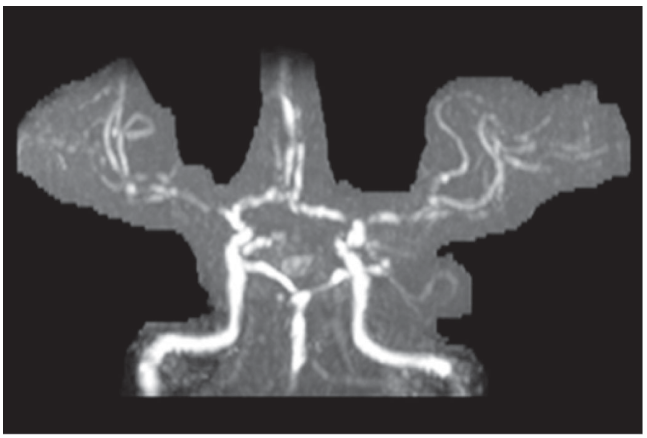

Figure 53.1 *Magnetic Resonance Angiography of the Brain Showing Diffuse, Segmental Vasoconstriction in Reversible Cerebral Vasoconstriction Syndrome.*

in both cortical and white matter. In RCVS, vasoconstriction largely normalizes in 12 weeks, although complete normalization may take several months; in PACNS, vasoconstriction rarely normalizes as quickly and completely.

Differentiating RCVS from PACNS is important because the management and prognosis are different. The mainstay of RCVS treatment is calcium channel blockers; for PACNS, treatment is immunosuppression. The prognosis for patients with RCVS is favorable with prompt diagnosis and management, although diagnostic delay can result in permanent neurologic sequelae. Complications can include subarachnoid hemorrhage, ischemic and hemorrhagic infarctions, or posterior reversible encephalopathy syndrome (PRES)-like changes on MRI. The prognosis for patients with PACNS is less favorable; even with prompt diagnosis and treatment, permanent neurologic deficits are common.

Posterior Reversible Encephalopathy Syndrome

Patients with PRES can present with a TCH or at least a severe, acute headache. PRES can occur in an acute hypertensive crisis, in eclampsia, or in the presence of specific drugs, most commonly immunosuppressants. Frequently, patients have global and focal neurologic symptoms and signs, such as altered mental status, visual loss, and seizures.

CT of the head and subsequent lumbar puncture will miss this diagnosis. However, MRI of the brain shows vasogenic edema most often in the posterior white matter and cortex, although more frontal areas can be involved (Figure 53.2). Although these areas of MRI abnormalities are usually due to edema alone, which is reversible, misdiagnosis or delay in treatment may lead to disease progression and infarction. PRES can occur in patients who present initially with RCVS, and vice versa. Vascular imaging of the head may show multifocal areas of stenosis or vasospasm. Identifying RCVS with PRES is important because its presence will change management.

After diagnosis, treatment depends on the underlying cause. Acute hypertensive crisis requires a graduated decrease in blood pressure. In some patients, contributing medications may be discontinued. If PRES is due to eclampsia, magnesium is commonly used. RCVS in association with PRES may require calcium channel blockers in addition to other measures to carefully lower the blood pressure without causing hypoperfusion in the presence of stenoses. Prognosis is favorable and the neurologic status of most patients returns to baseline in days to weeks.

Cerebral Venous Sinus Thrombosis

Up to 10% of patients with cerebral venous sinus thrombosis (CVST) present with a TCH without other neurologic signs or symptoms. Clinically, CVST headaches are persistent, progressive, and exacerbated by Valsalva maneuvers, such as coughing, heavy lifting, or bearing down (because of increased intracranial pressure). Lying down also increases intracranial pressure and can be painful for these patients. Although 15% to 30% of patients with a CVST can have an isolated headache, most have additional neurologic symptoms and signs, including papilledema, seizures, or focal neurologic signs. For diagnosis and treatment of CVST, see Chapter 11, "Ischemic Stroke: Uncommon and Special Situations."

Spontaneous Intracranial Hypotension

Spontaneous intracranial hypotension is often caused by a spontaneous CSF leak that results in sagging of the brain from reduced intracranial pressures. Traction on the innervated meninges due to the sagging of the brain results in headache most commonly, but other symptoms may occur.

Up to 15% of patients with spontaneous intracranial hypotension can present with a TCH without other neurologic signs or symptoms; however, postural aggravation is the most striking characteristic. An orthostatic headache resolves with recumbency and returns quickly with the upright position. These patients are usually young and have a possible history of minor trauma or connective tissue disorder (or both). Clinically, the headaches are bilateral not unilateral. Additional symptoms are often present, including neck stiffness or pain, auditory abnormalities or tinnitus, vertigo, diplopia, or upper extremity radicular

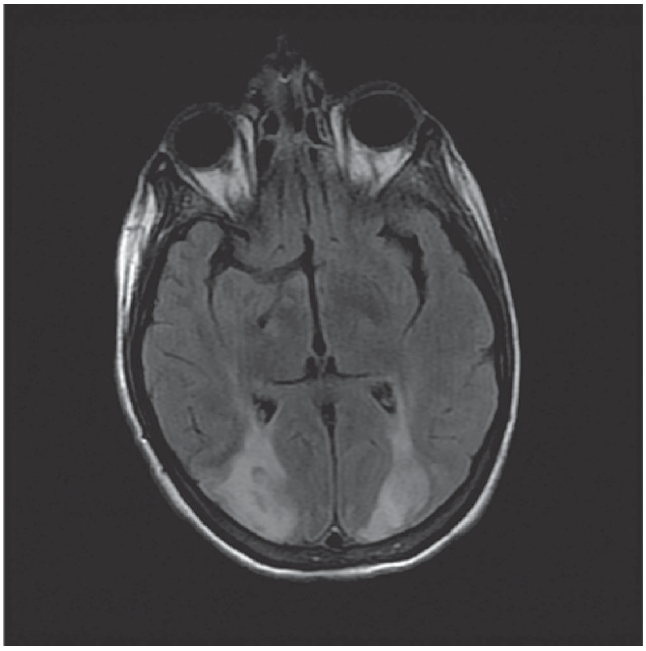

Figure 53.2 *Magnetic Resonance Imaging of the Brain Showing Vasogenic Edema in the Posterior White Matter and Cortex in Posterior Reversible Encephalopathy Syndrome.*

symptoms. The orthostatic characteristic of the headache may lessen with time; thus, it is important to ask whether the headaches ever had a postural trigger.

CT of the head may show low-lying cerebellar tonsils. Lumbar puncture commonly has a low opening pressure. MRI of the brain with and without a contrast agent as well as MRI of the spine may confirm the diagnosis of spontaneous intracranial hypotension, often showing diffuse pachymeningeal enhancement and extradural fluid collections. MRI of the brain may also show "brain sag," with low-lying cerebellar tonsils, crowding of the posterior fossa, subdural hematomas, effacement of the prepontine cistern and flattening of the pons, and descent of the optic chiasm (Figure 53.3). A CT myelogram is the best test for identifying the actual site of the leak.

When the diagnosis is confirmed, first-line treatment after conservative measurements have failed is a large-volume (20 mL) blind epidural autologous blood patch. This can be repeated 2 to 3 times if there is a partial response. If this fails, the site of the leak can be localized with a myelogram and treated with targeted epidural blood patches, fibrin glue injections, or, in refractory cases, neurosurgical intervention.

Stroke

Patients with stroke (ischemic or hemorrhagic) can present with a TCH. Headache, regardless of onset, occurs in 25% of patients with ischemic stroke and in up to 70% of patients with hemorrhagic stroke. CT of the head is diagnostic in a hemorrhagic stroke; however, CT can be normal in a recent, small, or posterior circulation ischemic stroke. Therefore, MRI is needed for all TCH patients.

Patients with retroclival hematoma can present with a TCH. Retroclival hematomas are a rare complication of severe head and neck injuries resulting in atlantoaxial dislocation. Spontaneous hemorrhage is even rarer but can occur from dural arteriovenous fistulas and tumors. Recommended imaging studies for diagnosis are MRI of the brain with and without a contrast agent and conventional cerebral angiography with selective external carotid artery injection.

Pituitary Apoplexy

Patients with pituitary apoplexy present with an acute, severe headache that can have a thunderclap onset. This occurs in patients with pituitary adenomas, known or unknown, and can occur with pregnancy, general anesthesia, bromocriptine therapy, or pituitary irradiation. Clinically, patients present with a holocranial headache with an acute or thunderclap onset, nausea, vomiting, constriction of visual fields, and ophthalmoplegia. Systemic symptoms vary widely but can be as severe as adrenal crisis and coma. MRI of the brain is the best diagnostic imaging for pituitary apoplexy.

Third Ventricle Colloid Cyst

Patients with third ventricle colloid cyst can present with a TCH. Headache, regardless of onset, is the most common

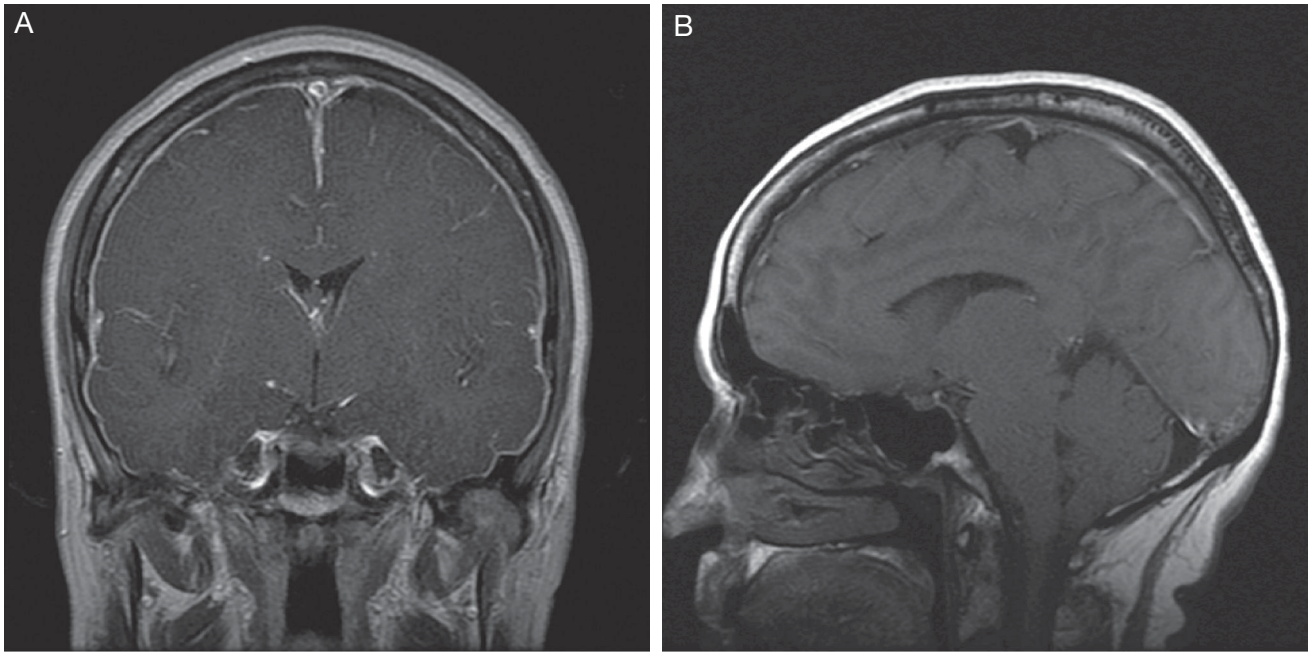

Figure 53.3 *Magnetic Resonance Imaging of the Brain in a Patient With Spontaneous Intracranial Hypotension. A, Diffuse pachymeningeal enhancement. B, "Brain sag" with low-lying cerebellar tonsils, crowding of the posterior fossa, effacement of the prepontine cistern, flattening of the pons, and descent of the optic chiasm.*

presenting symptom and is reported in 68% to 100% of patients. Third ventricle colloid cyst affects men more often than women and usually is diagnosed between the third and fifth decades of life. Clinically, the headache occurs suddenly, can last from seconds to hours, and is followed by rapid resolution. A positional component may be present as well. Patients may also have sudden drop attacks. Diagnosis can be made with CT of the head or MRI of the brain. When patients are symptomatic, treatment involves surgical resection.

Intracranial, Extracranial, and Systemic Infections

Intracranial, extracranial, and systemic infections can cause headache. Intracranial infections include acute or chronic meningitis, encephalitis, brain abscess, and empyema. Patients with meningitis or encephalitis can present with a TCH, although more often the headache is subacute and progressive. Extracranial infections include sinusitis, tooth abscesses, and orbital cellulitis.

- Subarachnoid hemorrhage is the most common cause of thunderclap headache (TCH) and is present in 25% of patients with TCH.
- Since subarachnoid hemorrhage carries a poor overall outcome, with significant morbidity and mortality, the initial evaluation of a TCH should focus on ruling out a subarachnoid hemorrhage.
- Patients with reversible cerebral vasoconstriction syndrome (RCVS) present with a TCH, normal to near-normal CSF findings, and diffuse, segmental reversible cerebral vasoconstriction.
- The mainstay of RCVS treatment is calcium channel blockers; for primary angiitis of the central nervous system (PACNS), treatment is immunosuppression.
- Posterior reversible encephalopathy syndrome (PRES) can occur in an acute hypertensive crisis, in eclampsia, or in the presence of specific drugs, most commonly immunosuppressants.
- Spontaneous intracranial hypotension is often caused by a spontaneous CSF leak that results in sagging of the brain from reduced intracranial pressures.
- In patients with spontaneous intracranial hypotension, an orthostatic headache resolves with recumbency and returns quickly with the upright position.
- MRI of the brain with and without a contrast agent as well as MRI of the spine may confirm the diagnosis of spontaneous intracranial hypotension, often showing diffuse pachymeningeal enhancement and extradural fluid collections. MRI of the brain may also show "brain sag," with low-lying cerebellar tonsils, crowding of the posterior fossa, subdural hematomas, effacement of the prepontine cistern and flattening of the pons, and descent of the optic chiasm.

Cranial Neuralgias

Trigeminal Neuralgia

Trigeminal neuralgia is the most common cranial neuralgia, with an incidence of 8 per 100,000 persons. Average age at onset is 50 years. Clinically, patients with trigeminal neuralgia have unilateral, severe, stabbing, lancinating (electric shock–like) pain in the distribution of the trigeminal nerve. These attacks last from seconds to 2 minutes. Attacks may be precipitated by mechanical factors, such as wind, touch, toothbrushing, eating, or drinking. Strength and sensation should remain intact. *International Classification of Headache Disorders*, 3rd Edition, criteria are listed in Box 53.2. The underlying pathophysiology is irritation of the trigeminal nerve, which is usually idiopathic; however, structural causes should be investigated. Compression or distortion of the trigeminal nerve by blood vessels is the most common structural cause, although more rarely, vascular malformation and tumors are implicated. Rarely, young patients with new-onset trigeminal neuralgia, usually bilateral, may have multiple sclerosis (2%–4% of patients with trigeminal neuralgia).

For patients with trigeminal neuralgia, MRI of the brain with and without a contrast agent should be performed to identify a structural lesion or multiple sclerosis. First-line therapy is pharmacologic treatment. Carbamazepine, initially at 200 mg daily and subsequently titrated up to 1,200

Box 53.2 • *ICHD-III* Criteria for Trigeminal Neuralgia

A. At least 3 attacks of unilateral facial pain fulfilling criteria B and C

B. Occurring in ≥1 divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution

C. Pain has ≥3 of the following 4 characteristics:
   1. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 min
   2. Severe intensity
   3. Electric shock–like, shooting, stabbing, or sharp in quality
   4. Precipitated by innocuous stimuli to the affected side of the face

D. No clinically evident neurological deficit

E. Not better accounted for by another *ICHD-III* diagnosis

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

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mg daily, can reduce the intensity of pain and the number of attacks. Oxcarbazepine, pregabalin, gabapentin, baclofen, and lamotrigine have also been found to be helpful. If a structural lesion is identified, a surgical approach may be considered if medical therapy has not been successful. Surgical options include neuroablative procedures and microvascular decompression. Neuroablative procedures include alcohol block, glycerol block, balloon compression, radiofrequency ablation, and Gamma Knife radiosurgery. These procedures are compared in Table 53.1. Microvascular decompression provides immediate pain relief in as many as 90% of patients, with a recurrence rate of 3.5% annually. In contrast to the ablative procedures, this preserves facial sensation. Complications of microvascular decompression include cranial nerve deficits, CSF leak, hemorrhage, and anesthesia dolorosa.

Geniculate Neuralgia

Patients with geniculate neuralgia present with unilateral, lancinating pain within the ear that lasts for seconds to minutes. It may occur several times a day, and it can develop into a chronic, dull pain within the ear. The underlying pathophysiology is facial nerve irritation that is idiopathic or secondary to a structural lesion. MRI of the brain with and without a contrast agent should be performed to identify a structural lesion. It is important to rule out herpes zoster oticus (Ramsay Hunt syndrome), which occurs from reactivation of varicella zoster virus. Patients with herpes zoster oticus present with vesicles in the external ear with or without facial paralysis in addition to the pain. Pharmacologic treatment of geniculate neuralgia is similar to that of trigeminal neuralgia. Surgical treatment is reserved for severe, refractory cases.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is a severe, lancinating pain in the throat and at the base of the tongue that can radiate to the ear. Besides the location of pain, glossopharyngeal neuralgia is similar to both trigeminal neuralgia and geniculate neuralgia. Diagnostic and therapeutic recommendations are also the same.

Occipital Neuralgia

Occipital neuralgia is unilateral or bilateral occipital pain that originates at the skull base and may or may not radiate to the vertex. The quality of pain varies. It can be lancinating but sometimes has a more continuous, dull, throbbing quality. Pain can be elicited or exacerbated by pressure or

Table 53.1 • Comparison of Ablative Therapies for Trigeminal Neuralgia

Procedure	Description	Efficacy	Side Effects
Alcohol block	Injection of alcohol into painful peripheral nerve branch	Temporary effect Duration of pain relief: 2–30 mo Recurrence rate: 50%	Numbness in trigeminal distribution Skin necrosis (rare)
Glycerol block	Percutaneous stereotactic delivery of glycerol to trigeminal ganglion via foramen ovale	Initial pain relief: 80%–96% of patients Recurrence rate: 10%–72%	Numbness in trigeminal distribution Meningitis (rare)
Balloon compression	Percutaneous stereotactic balloon compression of trigeminal ganglion via foramen ovale	Initial pain relief: 90%–100% of patients Recurrence rate: 10%–56%	Numbness in trigeminal distribution (less risk of facial or corneal anesthesia than with glycerol or radiofrequency ablation) Weakness of trigeminal motor root Bradycardia (trigeminal vagal reflex)
Radiofrequency ablation	Percutaneous stereotactic radiofrequency thermocoagulation of trigeminal ganglion via foramen ovale	Initial pain relief: 91%–99% of patients Recurrence rate: 10%–25%	Numbness in trigeminal distribution Motor weakness (rare) Diplopia (proximity of abducens nerve; rare) Ophthalmic division lesions carry risk of corneal anesthesia, which can lead to keratitis
Gamma Knife radiosurgery	Stereotactic radiosurgery with partial ablation of trigeminal nerve root	Onset of pain relief: within 3 mo after treatment Initial pain relief: 75% of patients Recurrence rate: 50% in 3 y	Numbness in trigeminal distribution (9%–16% of patients) May be useful if trigeminal neuralgia is associated with multiple sclerosis

Adapted from Flemming KD. Headache. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 693–717. Used with permission of Mayo Foundation for Medical Education and Research.

percussion over the occipital nerves. The underlying pathophysiology may be related to chronic and excessive contraction of the neck and scalp muscles. Trauma, compression, or entrapment of the greater or lesser occipital nerves (or both) can also cause occipital neuralgia. Nerve blocks may be diagnostic and therapeutic. Pharmacologic therapy is similar to therapy for the other neuralgias.

- Clinically, patients with trigeminal neuralgia have unilateral, severe, stabbing, lancinating (electric shock–like) pain in the distribution of the trigeminal nerve. These attacks last from seconds to 2 minutes.
- For patients with trigeminal neuralgia, MRI of the brain with and without a contrast agent should be performed to identify a structural lesion or multiple sclerosis.
- Patients with geniculate neuralgia present with unilateral, lancinating pain within the ear that lasts for seconds to minutes.
- Glossopharyngeal neuralgia is a severe, lancinating pain in the throat and at the base of the tongue that can radiate to the ear.

Miscellaneous Secondary Headaches

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Introduction and Epidemiology

Idiopathic intracranial hypertension, also called pseudotumor cerebri, is not uncommon. The annual incidence is 1 to 2 per 100,000 worldwide. It occurs in both adults and children. The most common patient scenario for idiopathic intracranial hypertension is an obese woman of childbearing age.

Pathophysiology

The underlying pathophysiology is controversial. The 2 leading hypotheses are increased brain water content or increased resistance to CSF outflow (or both). The mechanism for headache is either cerebral venous distention or meningeal irritation from increased CSF pressure.

Clinical Presentation

Clinically, headaches vary in onset from acute to subacute. The pain is constant, often worse with recumbency and exacerbated with Valsalva maneuvers. Although the location of pain can vary, commonly retro-ocular pain is reported. Transient visual obscurations provoked by postural changes occur in 50% to 75% of patients. Patients may also report visual blurring, visual field loss, double vision, or pulsatile tinnitus.

Although cases without papilledema have been reported in the literature, typically, bilateral papilledema is considered necessary for diagnosis. Ophthalmologic testing may document visual field loss. Visual loss can result in blindness if not treated promptly.

Diagnosis

MRI of the brain and lumbar puncture are the diagnostic tests of choice. The MRI findings should be normal. CSF analysis should be normal, with an elevated pressure of 250 mm H_2O or more. Magnetic resonance venography may also be considered to rule out venous thrombosis.

Treatment

Management depends on the severity of visual loss. Medical treatment with acetazolamide, a carbonic anhydrase inhibitor, in doses up to 4 g daily is first-line treatment. Therapeutic lumbar punctures can lower the intracranial pressure, but repeated taps are not ideal from a patient perspective and are not recommended because patient avoidance may result in visual loss from a lack of treatment. Neurosurgical intervention is indicated for patients with rapidly progressive visual loss refractory to medical treatment. Ventriculoperitoneal or lumboperitoneal shunts are effective for reducing CSF pressures. Optic nerve sheath fenestration is used for relief of papilledema and stabilization of visual loss.

Giant Cell Arteritis

Giant cell arteritis (GCA) is typically diagnosed in the elderly. The mean age at diagnosis is about 70 years, and GCA is at least twice as common in females as males. Clinically, scalp tenderness, jaw claudication, polymyalgia rheumatica, and constitutional symptoms may accompany headache. The head pain itself is usually constant and throbbing with associated scalp and temporal artery tenderness. Amaurosis fugax can occur and is a warning of permanent visual loss. Visual loss is end stage but can be prevented with prompt diagnosis and subsequent treatment. Ischemic stroke due to involvement of the extracranial cervical vessels is also a rare complication.

Because GCA is treatable, determination of erythrocyte sedimentation rate or C-reactive protein level (or both) should be considered for every elderly patient with new-onset headache. Elevated results for these 2 tests are the most frequent laboratory abnormalities. Granulomatous arteritis documented with biopsy is necessary for diagnosis. Histologic features include patchy, granulomatous inflammation involving the vessel media. The pathologic changes may be patchy (resulting in "skip lesions"), indicating that biopsy findings may be falsely negative. Bilateral temporal artery biopsies may be performed to increase sensitivity.

High doses of corticosteroids are recommended for the treatment of GCA. The headache responds very quickly to corticosteroids. During treatment, symptoms, signs, and the erythrocyte sedimentation rate or C-reactive protein

level should be monitored. Corticosteroid dosages can usually be tapered over 6 to 12 months. Reemergence of symptoms should prompt an increase in the corticosteroid dosage.

Neoplasm

Headache is present in up to 50% of patients with brain tumors. The pathophysiology is likely increased intracranial pressure, impingement of dural structures, hydrocephalus, or a combination of these. Clinically, these patients present with head pain that is unilateral, bilateral, or generalized. The degree of pain is moderate and constant. Headache in patients with brain tumors may be present upon awakening, it may be associated with nausea and vomiting, and it may worsen with Valsalva maneuvers. Examination may show papilledema or focal neurologic symptoms (or both) according to the tumor location. Treatment is individualized depending on the location and tumor type.

Chiari Type I Malformation

Chiari type I malformations can result in headache. The definition of a Chiari type I malformation is age-dependent tonsillar descent below the level of the foramen magnum: 1) first decade of life, 6 mm below the foramen magnum; 2) second and third decades, 5 mm; 3) fourth through eighth decades, 4 mm; and 4) ninth decade, 3 mm. Chiari type I malformations may be associated with syringomyelia or hydrocephalus (or both). The underlying pathophysiology leading to head pain is from the compression of neural tissues and the alteration in CSF dynamics. Clinically, Chiari type I malformation headaches are often precipitated by Valsalva maneuvers or cough. Head pain localizes occipitally, and brainstem compression may cause posterior fossa symptoms, including vertigo, ataxia, nystagmus, or hearing loss. MRI of the brain shows the Chiari type I malformation, particularly with sagittal views. Treatment of symptomatic patients is suboccipital craniectomy for decompression.

Obstructive Sleep Apnea

Fifty percent of patients with obstructive sleep apnea may have headaches (Box 53.3). The underlying pathophysiology is likely overnight fluctuations in oxygen saturation, which result in hypercapnia, vasodilation, and increased intracranial pressure. Clinically, patients with obstructive sleep apnea have headaches that are present upon awakening. The pain is typically a mild to moderate tight, squeezing pain that is variable in location and can last for hours.

Box 53.3 • *ICHD-III* Criteria for Headache Associated With Sleep Apnea

A. Recurrent headache with ≥1 of the following characteristics and fulfilling criteria C and D
   1. Occurs on >15 d monthly
   2. Bilateral, pressing quality and not accompanied by nausea, photophobia, or phonophobia
   3. Each headache resolves within 30 min

B. Sleep apnea (respiratory disturbance index ≥5) demonstrated by overnight polysomnography

C. Headache is present on awakening

D. Headache ceases within 72 h and does not recur after effective treatment of sleep apnea

Abbreviation: *ICHD-III, International Classification of Headache Disorders*, 3rd Edition.

Adapted from Flemming KD. Headache. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 693–717. Used with permission of Mayo Foundation for Medical Education and Research.

A polysomnogram aids in the diagnosis of obstructive sleep apnea, and treatment should relieve the headache.

- The most common patient scenario for idiopathic intracranial hypertension is an obese woman of childbearing age.
- In patients with idiopathic intracranial hypertension, CSF analysis should be normal, with an elevated pressure ≥250 mm H_2O. Medical treatment with acetazolamide, a carbonic anhydrase inhibitor, in doses up to 4 g daily is first-line treatment.
- Because giant cell arteritis (GCA) is treatable, determination of erythrocyte sedimentation rate or C-reactive protein level (or both) should be considered for every elderly patient with new-onset headache.
- Headache in patients with brain tumors may be present upon awakening, it may be associated with nausea and vomiting, and it may worsen with Valsalva maneuvers.
- The definition of a Chiari type I malformation is age-dependent tonsillar descent below the level of the foramen magnum.
- Chiari type I malformation headaches are often precipitated by Valsalva maneuvers or cough.
- Clinically, patients with obstructive sleep apnea have headaches that are present upon awakening.

54 Clinical Pain Disorders[a]

JAMES C. WATSON, MD

Introduction

The International Association for the Study of Pain defines *neuropathic pain* as pain that is initiated or caused by a lesion or disease affecting the somatosensory system in the peripheral or central nervous system. Several well-recognized descriptors for neuropathic pain suggest a neuropathic rather than nociceptive pathophysiology (*hot, burning, painful cold, freezing, prickling or tingling, pins and needles, electrical, shooting, stabbing, lancinating*, and *itching*). However, the sensitivity and specificity of pain descriptors are limited (generally 70%–85%) when used alone or when incorporated into questionnaires to identify neuropathic pain; therefore, verbal pain descriptors alone are insufficient to make the diagnosis of neuropathic pain. The exceptions to this are the clinical signs of allodynia (ie, pain caused by a non-noxious stimulus, such as light touch) and hyperalgesia (ie, an increased painful response to a normally painful stimulus, such as pinprick), which are highly specific for neuropathic pain although not common or sensitive.

- *Neuropathic pain* is initiated or caused by a lesion or disease affecting the somatosensory system in the peripheral or central nervous system.

Neuropathic Pain Syndromes

Postherpetic Neuralgia

Definition and Epidemiology

Shingles is the result of reactivation of the varicella zoster virus that had remained latent within neural and satellite cells within the dorsal root ganglion after a remote episode of chickenpox. The reactivation occurs in the presence of relative immunosuppression from stress, medications, or disease and leads to a dermatomal, painful, blistering rash. For most patients, the pain associated with shingles resolves over the course of 1 to 4 months. Neuropathic pain that persists beyond this is considered postherpetic neuralgia (PHN).

Risk factors for development of PHN include age (PHN is more likely to develop in older patients with shingles, including 40% to 60% of those older than 60 years), the severity of the acute shingles rash, and the distribution of involvement. The highest risk of PHN is with trigeminal involvement, followed by the thoracic dermatomes, and, with a lower risk, other regions.

Reducing Risk and Treatment

Several factors decrease the risk of PHN. The zoster vaccine has been approved by the US Food and Drug Administration (FDA) for all patients older than 50 (regardless of whether they have had shingles previously). It decreases the risk of shingles by 50% and, if shingles develops despite vaccination, the vaccine decreases the risk of PHN by 67%. Antivirals (acyclovir, valacyclovir, or famciclovir) used within 72 hours of the acute shingles rash or while new lesions are still appearing have modestly decreased the rate of PHN. The role of corticosteroids on the incidence of PHN is not proven; however, they are commonly used during the shingles eruption on the basis of limited evidence that they decrease the acute pain and duration of shingles. A small randomized controlled trial showed that amitriptyline may decrease the risk of PHN if

[a] Portions previously published in Watson JC. Central neuropathic pain: syndromes, pathophysiology, and treatments. In: Rice ASC, Sykes N, Bennett MI, Yuan C-S. Clinical pain management. 2nd ed. Vol. 3: Cancer pain. London (United Kingdom): Hodder & Stoughton; c2008. p. 374–87. Used with permission.

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; CPSP, central poststroke pain; CRPS, complex regional pain syndrome; FDA, US Food and Drug Administration; PHN, postherpetic neuralgia; SCI, spinal cord injury

the drug is administered when the shingles rash appears and is used for 3 months.

After PHN has developed, however, treatment is difficult. A general evidence-based approach to neuropathic pain management incorporates studies from all neuropathic pain types (Box 54.1). Topicals, including the lidocaine patch and a single application of a high-concentration (8%) capsaicin patch (after anesthetizing the region of PHN), are effective for PHN without the systemic side effects of oral medications. Oral neuropathic and analgesic medications are commonly used, although only gabapentin and pregabalin are FDA approved for PHN. Spinal cord stimulation has been used for refractory cases; however, it can be difficult to capture the affected areas on the torso with stimulation, and traditional spinal cord stimulation cannot be used to treat trigeminal PHN.

- Risk factors for development of PHN include age (PHN is more likely to develop in older patients with shingles, including 40%–60% of those older than 60 years), the severity of the acute shingles rash, and the distribution of involvement.
- The zoster vaccine has been approved by the FDA for all patients older than 50 (regardless of whether they have had shingles previously). It decreases the risk of shingles by 50% and, if shingles develops despite vaccination, the vaccine decreases the risk of PHN by 67%.

Box 54.1 • Evidence-Based Medicine Neuropathic Pain Ladder

Level I—Treat underlying disease and comorbidities
- Topicals
  - 5% lidocaine patch
  - 8% capsaicin patch
- Anticonvulsants
  - Gabapentin
  - Pregabalin
- Antidepressants
  - Tricyclic antidepressants
  - Duloxetine

Level II—If pain relief is partial but inadequate, add additional agents with distinct mechanism of action
- Anticonvulsants
  - Sodium channel blockers
  - Topiramate
  - Valproic acid
- Antidepressants
  - Venlafaxine
- Tramadol

Level III—Consider consultation with pain specialist
- Long-acting opioids
- Other drugs
- Interventional options
  - Neuromodulation
  - Injection therapy
  - Nerve blocks

Painful Peripheral Neuropathy

Definition and Classification

Painful peripheral neuropathies can be stratified several ways (see Chapter 40, "Peripheral Nerve Disorders") including by the affected modality (sensory, sensorimotor, motor, or autonomic) or distribution of findings (length dependent, diffuse, or multifocal). Sensory neuropathies can be stratified further by the type of nerve fiber affected. Large-fiber peripheral neuropathies can be diagnosed with electromyography and nerve conduction studies. When the disease is limited to A delta and unmyelinated C fibers, the sensory neuropathy is referred to as a small-fiber neuropathy. Results from electromyography and nerve conduction studies are normal in a small-fiber neuropathy. Both large- and small-fiber neuropathies can be painful, although small-fiber neuropathies are more frequently painful since those nerve fibers carry pain sensations. Patients who have small-fiber neuropathies frequently present with a symmetric (usually distal initially) neuropathic pain syndrome with burning feet and often an associated dysautonomia (early satiety, orthostatism, impotence, bowel or bladder difficulties, or sudomotor dysfunction).

Treatment

The primary treatment of painful peripheral neuropathies is to address the underlying cause of the neuropathy if possible (ie, treat the diabetes mellitus in a patient who has diabetic painful peripheral neuropathy). When the underlying cause of the neuropathy is treated, the hope is that the associated pain syndrome may improve; however, the primary goal is to prevent or slow further progression. Lingering symptoms are treated symptomatically.

Neuropathic pain is generally worse in the evenings when the distractions of the day are absent and the patient's positive sensory phenomenon and pain are no longer masked. This often disrupts sleep. Interventions (eg, soaking the feet, desensitizing massage, or medications) may be sufficient in some cases when used only in the evening. Most treatment studies of painful neuropathy have involved diabetic length-dependent neuropathies. Currently, pregabalin and duloxetine are FDA approved for the treatment of painful diabetic neuropathy, although

gabapentin and tricyclic antidepressants are also considered first-line treatment options (Box 54.1). Long-acting opioids have also been shown to be effective in carefully selected patients. Several meta-analyses and treatment guidelines have been published on the treatment of neuropathic pain and painful diabetic neuropathy (see Suggested Reading).

Chemotherapy-Induced Peripheral Neuropathy

Definition and Epidemiology

Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of many routinely used chemotherapeutic agents, including vinca alkaloids, taxanes, and platinum agents. It is estimated that CIPN may develop in 30% to 40% of patients receiving chemotherapy with these particular agents, although the incidence varies with the chemotherapy drug, dosing (cumulative dose and duration of dosing), background comorbidities that serve as a second hit to nerve function (eg, diabetes mellitus, thyroid disease, or vitamin B_{12} deficiency), and concomitant use of other neurotoxic agents. CIPN is most commonly a length-dependent (stocking-glove), sensory-predominant (although weakness can occur) neuropathy that is often painful. Pain symptoms are neuropathic and include burning, dysesthesias, and sometimes allodynia.

Pathophysiology

The pathophysiology of CIPN varies by drug class but includes disruption of axonoplasmic flow (necessary to maintain the axon) through microtubule disruption, mitochondrial dysfunction, or cytotoxic effects on DNA. The result is a dying back of the nerve, beginning with the most distal aspects. Once initiated, axonal wallerian degeneration progresses over several weeks, even after discontinuation of an offending chemotherapeutic agent, and CIPN symptoms may seem to continue to progress for several weeks. Progression should then cease. The clinical neuropathy and neuropathic pain may improve and in some cases resolve, but in most cases CIPN is only partially reversible and is often permanent.

Management and Treatment

Preventing CIPN would be ideal; however, in randomized controlled trials, amitriptyline, carbamazepine, and vitamin E were ineffective when they were administered prophylactically during chemotherapy.

Common practice is to extrapolate evidence-based recommendations for the treatment of other neuropathic pain conditions (eg, painful diabetic neuropathy and PHN) to painful CIPN. This approach is rational, but well-designed randomized controlled trials of commonly used neuropathic agents (gabapentin, amitriptyline, nortriptyline, and lamotrigine) have not shown efficacy in patients with painful CIPN.

Erythromelalgia

Definition and Clinical Presentation

Erythromelalgia is a rare disorder affecting females more commonly and occurring in all age groups, including pediatric populations. It consists of a clinical symptom triad of erythema, heat (reported subjectively and objectively), and severe pain usually affecting the distal limbs (feet more commonly than hands), although more proximal involvement, including the face and ears, has been described (Figure 54.1). The symptoms are intermittent, often precipitated by heat or exercise, and the patient may be asymptomatic at the time of evaluation.

An autosomal dominant inherited form of erythromelalgia results from an *SCN9A* gene mutation of the sodium channel protein Nav1.7 subunit. This is a toxic gain-of-function mutation that is expressed in dorsal root ganglia and sympathetic ganglia neurons.

Diagnostic Testing

Diagnostic testing has shown that erythromelalgia is a form of peripheral neuropathy, with predominantly distal small-fiber features (and postganglionic sudomotor failure as the most consistent component). Vascular testing characteristically confirms evidence of a vasculopathy (perhaps related to altered neural control of vascular tone) with an increase in temperature, an increase in blood flow as measured by laser Doppler, and, paradoxically, no increase in skin oxygenation (some cases show a frank paradoxical decrease) as measured by transcutaneous oxygen pressure in affected distal limb sites during symptoms. Smoking

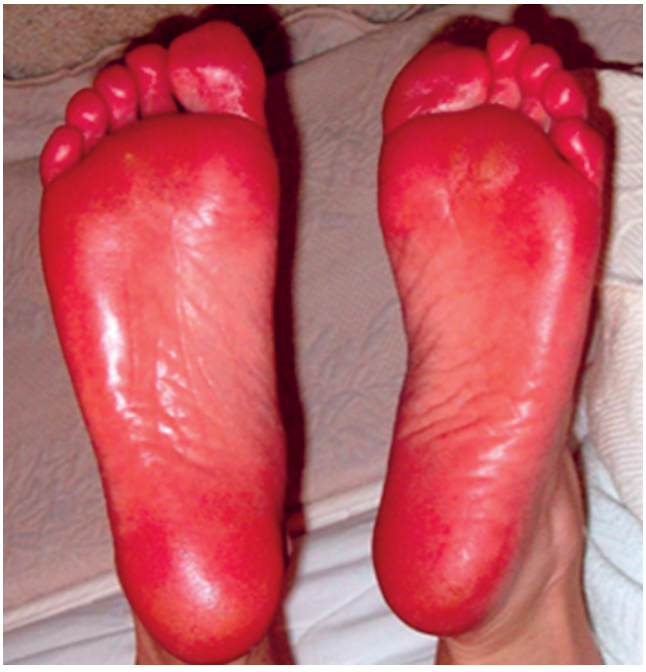

Figure 54.1 *Erythromelalgia.*

and myeloproliferative disorders are overrepresented as comorbidities and should be screened for. Patients find relief with cooling of the limbs in ice water and should be counseled as to the risk of thermal injury. Kaplan-Meier survival curves show a decrease in expected survival among patients with erythromelalgia, in part related to an increased rate of suicide among these patients.

Treatment

The treatment of erythromelalgia is challenging and primarily defined by case and cohort reports. Treatment options include aspirin, anticonvulsants and antidepressants typically used for neuropathic pain, calcium channel blockers and β-blockers, topical lidocaine or compounded creams of amitriptyline and ketamine, and oral magnesium.

Complex Regional Pain Syndrome

Definition and Clinical Criteria

Complex regional pain syndrome (CRPS) is a neuropathic pain disorder in which pain is within a region (eg, foot or leg) but outside an individual nerve territory. An identifiable initiating injury or period of immobilization is evident in most cases; however, the pain is disproportionate to the inciting injury. The clinical criteria (Box 54.2) require clinical symptoms (from patient history) in 3 or 4 of the 4 categories and clinical signs (from physical examination) in 2 or more of the 4 categories.

CRPS can be stratified into CRPS type 1 (previously referred to as reflex sympathetic dystrophy), with no specific identifiable nerve injury, and CRPS type 2 (previously referred to as causalgia), with an identifiable nerve injury.

Box 54.2 • Clinical Criteria for Complex Regional Pain Syndrome[a]

Sensory
- Hyperesthesia (symptom)
- Allodynia or hyperalgesia

Vasomotor
- Temperature asymmetry (>1°C)
- Skin color change or asymmetry

Sudomotor or edema
- Sweat change or asymmetry
- Edema

Motor or trophic change
- Decreased range of motion
- Motor dysfunction (weakness, tremor, or dystonia)
- Trophic change (hair, nail, or skin)

[a] Required clinical criteria: clinical symptoms (from patient history) in 3 or 4 of the 4 categories and clinical signs (from physical examination) in 2 or more of the 4 categories.

Diagnosis

CRPS is a clinical diagnosis. Objective measurement of temperature and peripheral sudomotor function (with quantitative sudomotor axon reflex testing) to identify asymmetries can help in confirming clinical signs that are challenging to assess definitively at the bedside but are not required for the diagnosis. Similarly, depending on the chronicity of CRPS, characteristic changes of CRPS may appear on bone scan. However, these changes are not specific for CRPS and, while providing supportive evidence when CRPS is suspected, should not be used to definitively make or exclude the diagnosis of CRPS.

Treatment

The key to the treatment of CRPS is mobilization of the affected limb through physical therapy. All other treatments are symptomatic and aimed at facilitating mobilization of the affected limb. Desensitization of the allodynic limb is important. Sympathetic blocks (lumbar sympathetic blocks for the lower extremities and stellate ganglion blocks for the upper extremities) may provide temporary improvement in CRPS-associated pain and can be repeated if they are facilitating the physical therapy program. Contrary to early theories on the cause of CRPS (ie, reflex sympathetic dystrophy), not all cases of CRPS have sympathetic overactivity or respond to sympathetic block. Traditional topical and oral neuropathic and analgesic pain medications are necessary in almost all cases. For refractory cases, spinal cord stimulation can be an effective treatment in appropriately selected patients.

- CRPS is a neuropathic pain disorder in which pain is within a region (eg, foot or leg) but outside an individual nerve territory. An identifiable initiating injury or period of immobilization is evident in most cases; however, the pain is disproportionate to the inciting injury.
- CRPS can be stratified into CRPS type 1 (previously referred to as reflex sympathetic dystrophy), with no specific identifiable nerve injury, and CRPS type 2 (previously referred to as causalgia), with an identifiable nerve injury.

Central Neuropathic Pain Syndromes

Definition

Central neuropathic pain syndromes are some of the most challenging neuropathic pain syndromes to treat. Although central neuroplastic changes ("central sensitization" or "windup") may occur with sustained peripheral nociceptive input into central nervous system pain pathways, *central neuropathic pain* refers to processes in which the

primary lesion or dysfunction (not the secondary effects of it) occurs within the central nervous system.

Pathophysiology

The injury associated with a central neuropathic pain syndrome can occur at any level of the central nervous system. Although ventroposterior thalamic strokes are the quintessential central neuropathic pain syndrome, strokes elsewhere can have the same consequences. Patients who have lateral medullary infarctions (ie, Wallenberg syndrome), for example, have one of the highest incidences of central poststroke pain (CPSP)—25% within 6 months after the stroke. Even higher incidences of central neuropathic pain syndromes occur with spinal cord injury (SCI). The critical factor for the development of a central neuropathic pain syndrome is that the neurologic lesion causes dysfunction of spinal-thalamic-cortical pathways, which is clinically evident as impaired pain (pinprick) and temperature sensation. Some studies have found that abnormal thermal sensation (cold especially) is more critical and that pain (pinprick) pathway dysfunction may not be useful for discriminating between poststroke pain and no-pain groups. The integrity (or lack thereof) of the lemniscal (large-fiber, posterior column) sensory pathway (carrying the modalities of light touch, vibration, and proprioception) does not appear to be fundamentally involved in or vital to the development of CPSP.

Given that spinothalamic tract dysfunction appears necessary, although not necessarily sufficient independently, to cause central neuropathic pain, the concept of an associated denervation hypersensitivity has been proposed to be the required cofactor for the development of central neuropathic pain. Spontaneous pain in CPSP is linked to hypersensitivity or spontaneous discharges in thalamic and central neurons that have lost part of their normal (inhibitory) input.

Clinical Presentations

The 3 most common central neuropathic pain syndromes are CPSP, SCI-related pain, and multiple sclerosis–related pain. It is estimated that a secondary pain syndrome may develop in up to 40% to 80% of patients with SCI or multiple sclerosis. Some series do not adequately discriminate central pain from other pain types, however.

By definition, patients with central neuropathic pain syndromes have neurologic deficits. The functional limitations and anesthetic regions in these patients may cause common musculoskeletal and visceral pain types to be overlooked because the discriminatory clinical features of neuropathic, musculoskeletal, and visceral pain types are often blurred. Additionally, functional limitations from neurologic injury predispose patients to musculoskeletal pains from disuse, overuse, or altered mechanics of use. In fact, in neurologically injured patients, these musculoskeletal pains are more prevalent than central neuropathic pain; however, when present, central neuropathic pain is more severe, limiting, and refractory to treatment.

After injury, the temporal onset of a central neuropathic pain syndrome is variable. SCI-related central neuropathic pain can be classified as below the level of injury or at the level of injury. Neuropathic pain below the level of injury may take a few years to become evident, whereas pain at the level of injury or radicular SCI-related pain is usually evident within months after the injury. CPSP is usually evident within the first month, although for some patients the pain begins later, even a year after the original stroke. Multiple sclerosis–related central neuropathic pain is more variable but occurs more commonly with the presentation of the demyelinating plaque. The classic example is trigeminal neuralgia in a young patient with paroxysmal neuralgiform pain that heralds a pontine demyelinating plaque.

Treatment

A few randomized controlled trials have examined the treatment of central pain. The only drug that is FDA approved for a central neuropathic pain syndrome is pregabalin, which is approved for SCI-related neuropathic pain. Other treatments include typical oral neuropathic and analgesic medications (Box 54.1). The medical literature is evolving on the role of cannabinoids in the treatment of central neuropathic pain syndromes. The role of neuromodulation—spinal cord, motor cortex, and deep brain stimulation—is also expanding as a treatment option for these challenging pain syndromes.

- The critical factor for the development of a central neuropathic pain syndrome is that the neurologic lesion causes dysfunction of spinal-thalamic-cortical pathways.
- The 3 most common central neuropathic pain syndromes are CPSP, SCI-related pain, and multiple sclerosis–related pain.
- The only drug that is FDA approved for a central neuropathic pain syndrome is pregabalin, which is approved for SCI-related neuropathic pain.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

IX.1. Which of the following is a basic principle to be considered when prescribing an acute migraine medication?
a. Treat late in the attack
b. Use the correct dose and formulation
c. Limit use of the medication to 5 days weekly
d. If the patient has early or severe nausea and vomiting, if the patient wakes up with migraine, or if severe migraine develops rapidly, always use an oral medication
e. Some patients respond to 1 drug and not another; try an individual drug for 12 headaches before trying another

IX.2. Which of the following is a recommended first-line agent for the short-term treatment of migraine?
a. Hydrocodone by mouth
b. Rizatriptan by injection
c. Isometheptene by mouth
d. Butalbital-acetaminophen-caffeine by mouth
e. Sumatriptan by mouth

IX.3. Which of the following is a basic principle to be considered when prescribing a migraine preventive medication?
a. The goal is to completely eliminate the headaches
b. Start with a low dose and increase it slowly until therapeutic effects develop, side effects develop, or the ceiling dose is reached
c. Preventive medication should be continued for approximately 2 weeks at the target dose or the maximal tolerated dose before determining utility
d. If 1 preventive agent fails, continue its use
e. Daily use of abortive agents is a mainstay of chronic headache management

IX.4. Which of the following preventives has the best evidence for efficacy in chronic migraine?
a. Amitriptyline
b. Topiramate
c. Zonisamide
d. Tizanidine
e. Divalproex sodium

IX.5. A 32-year-old woman presents with a 6-month history of unilateral headache around the left eye. The headaches occur 10 times daily, and each headache lasts 20 minutes. Between attacks she has no pain. The headaches are associated with ipsilateral conjunctival injection and tearing. Neurologic examination findings are normal, as are the findings from magnetic resonance imaging (MRI) of the brain with gadolinium. She has tried short-term subcutaneous sumatriptan and oxygen, but neither seemed to help. She took verapamil at a maximal dosage of 720 mg daily for 3 months, but that did not help. What is the most likely diagnosis?
a. Hemicrania continua
b. Primary stabbing headache
c. Paroxysmal hemicrania
d. Cluster headache
e. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome)

IX.6. A 38-year-old woman presents with a 12-month history of continuous unilateral pain around the left eye. She rates the baseline pain as 6 out of 10. She describes the sensation as feeling as if a tiny piece of metal is in her left eye, but the opthalmologist reports normal findings on examination. The patient has unilateral headache pain exacerbations lasting a few hours, when the pain increases to 9 out of 10. During these headache exacerbations she notes mild left conjuctival injection. Neurologic examination findings are normal, as are the findings from MRI of the brain with gadolinium. She has no pain on palpation of the left trochlea. What medication should be tried in this patient, barring contraindications?
a. Melatonin
b. OnabotulinumtoxinA
c. Verapamil
d. Lamotrigine
e. Indomethacin

IX.7. Which of the following preventives is most useful in patients with cluster headache?
a. Verapamil
b. Propranolol
c. Amitriptyline
d. *Petasites hybridus* plant extract (butterbur)
e. Hydrocodone

IX.8. When a patient presents with a thunderclap headache, which of the following disorders should you be most concerned about?
a. Migraine
b. Subarachnoid hemorrhage
c. Cluster headache
d. Headache secondary to brain tumor
e. Tension-type headache

IX.9. A 76-year-old man presents with a 1-month history of daily, continuous, bitemporal headache. He has not had many headaches before. He complains of mild fever and significant night sweats. He notes aching and stiffness in the morning in the neck, shoulder, and pelvic girdles. He has lost about 4.5 kg in the past month. His notes tenderness when he combs his hair.

Neurologic examination findings are normal. What disease should you be most concerned about?
a. Headache secondary to brain tumor
b. Hypnic headache
c. Giant cell arteritis
d. Chronic tension-type headache
e. Carotid dissection

IX.10. A 72-year-old man presents with a 6-week history of daily headaches. They are moderately severe and bilaterally diffuse with a steady, nonpulsatile character. He notes scalp pain with washing his hair and aching in his masseteric regions after chewing meat for a while. Three days previously he had a 10-minute episode of right eye visual loss with recovery. Neurologic examination findings are normal. The erythrocyte sedimentation rate was 105 mm/h. Which of the following should be the next step in care?
a. Carotid ultrasonography
b. Computed tomography of the head
c. Initiation of aspirin therapy
d. Initiation of corticosteroid therapy
e. MRI of the brain

IX.11. A 26-year-old man presents with unilateral pain in the left periorbital and frontal regions. The pain began 4 days ago, after a mild motor vehicle accident. The patient reports that he had mild "whiplash" after his car was hit from behind while he was at a stoplight. On examination you notice that he has Horner syndrome on the left. He tells you that he was always able to "gross out" his friends with his double-jointed fingers (he has hyperextensible joints). What disorder should you be most concerned about?
a. Cluster headache
b. Carotid dissection
c. Vertebral dissection
d. Reversible cerebral vasoconstriction syndrome
e. Hemicrania continua

IX.12. Which of the following is a first-line neuropathic pain treatment?
a. Gabapentin
b. Topiramate
c. Venlafaxine
d. Tramadol
e. Long-acting opioids

Answers

IX.1. Answer b.
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IX.2. Answer e.
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IX.7. Answer a.
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IX.8. Answer b.
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IX.9. Answer c.
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IX.10. Answer d.
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IX.11. Answer b.
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IX.12. Answer a.
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Section

X

Neuro-oncology and Paraneoplastic Disorders

Alyx B. Porter, MD, *editor*

55 Introduction to Neoplastic Disease

KELLY D. FLEMMING, MD; ALYX B. PORTER, MD

Introduction

With advanced imaging readily available in most places, neoplastic disease of the nervous system is more easily identified. Despite earlier detection, nervous system neoplasms remain a significant cause of neurologic morbidity and mortality.

This chapter broadly reviews the clinical manifestations and general approach to diagnosis and management of nervous system tumors. Subsequent chapters review individual types of tumors, complications of therapy for tumors, and finally paraneoplastic diseases.

Epidemiology and Statistics

Neoplasms of the nervous system may occur in childhood or adulthood. It is useful to consider which neoplasms are most common by age group because this may influence the diagnostic evaluation. In adults, the most common intracranial tumors are metastases from a primary solid tumor (non–small cell lung carcinoma, breast cancer, and small cell lung carcinoma, followed by melanoma, renal cell carcinoma, and gastrointestinal tumors). Meningioma is the most common extra-axial brain tumor and has benign features. Glioblastoma is the most common malignant primary brain tumor in adults.

In children, the most common brain tumors, in descending order, are astrocytoma, medulloblastoma, and ependymoma.

- In adults, the most common intracranial tumors are metastases from a primary solid tumor.
- Glioblastoma is the most common malignant primary brain tumor in adults.
- In children, the most common brain tumors, in descending order, are astrocytoma, medulloblastoma, and ependymoma.

Clinical Manifestations

Neoplasms of the nervous system generally present in a subacute to chronic, progressive manner. In some cases, an acute change in neurologic status occurs because of hemorrhage into a neoplasm.

Patients with neoplasms may present with focal neurologic symptoms relevant to the location of the tumor, seizures, headaches, localized pain (if peripheral or spine tumor), and/or signs and symptoms of increased intracranial pressure. In some cases, the neoplasm may be found incidentally in the evaluation for another symptom.

Increased intracranial pressure may result from development of hydrocephalus or localized edema with mass effect surrounding the tumor. Increased intracranial pressure often results in headaches that are worse in the morning with coughing, sneezing, or straining. Associated nausea and/or vomiting may be present. Patients may develop papilledema, and in some cases, patients develop false localizing symptoms such as a sixth nerve palsy.

Neoplasms by Location Predilection

It is useful to have a working knowledge of the differential diagnosis of individual tumors by location (Figure 55.1). This knowledge aids in making decisions on diagnostic testing and the approach to management.

General Approach to Diagnosis

A careful history can help elucidate important risk factors, genetic predispositions, and associated conditions. Some tumors may be associated with other diseases or conditions, including genetic conditions, and screening should be done as appropriate (Table 55.1).

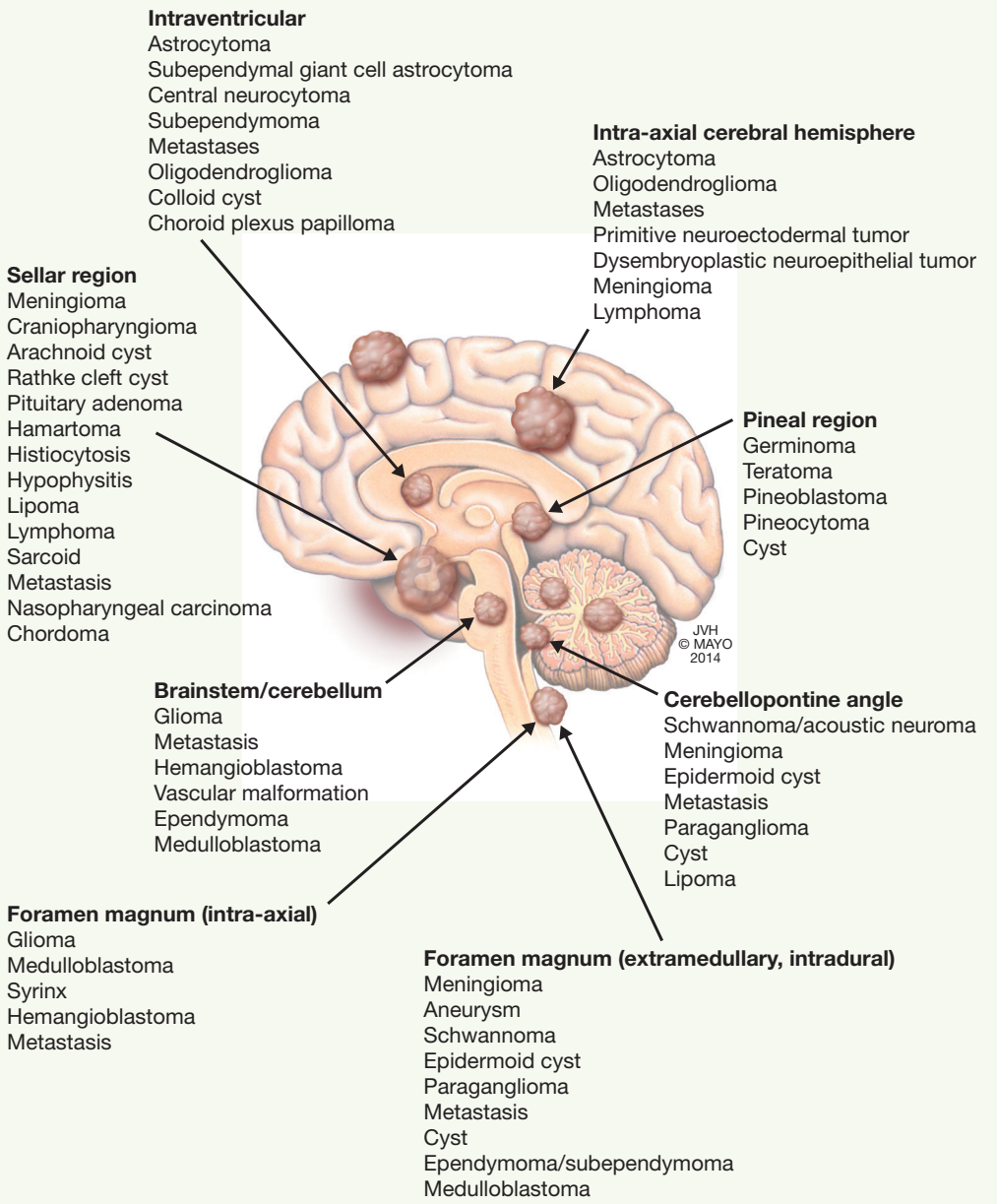

Figure 55.1 *Differential Diagnosis of Central Nervous System Masses by Location.*
(Used with permission of Mayo Foundation for Medical Education and Research.)

In most cases of suspected intracranial disease, a contrast-enhanced magnetic resonance imaging scan of the brain is the most valuable test. It aids in localization and characterization and, in some situations, can make the diagnosis without further testing. Functional magnetic resonance imaging may also be useful in presurgical planning.

Tumors affecting the pituitary or hypothalamus may require testing of hormones, and tumors near the optic chiasm require visual field testing.

In patients with midline, pineal-based tumors raising radiographic concern for germ cell tumors, additional workup should include serum and cerebrospinal fluid investigation for carcinoembryonic antigen and α-fetoprotein. Depending on those results, biopsy may not be necessary to elucidate the pathologic diagnosis.

In suspected metastatic disease, a careful history and physical examination may identify a possible malignancy. In the setting of intracranial metastases, common screening might include computed tomography of the chest, abdomen, and pelvis. Mammography should be considered in women and testicular ultrasonography in men.

Table 55.1 • Conditions With Associated Nervous System Tumors

Condition	Type of Tumor Associated With Condition
Neurofibromatosis 1	Neurofibroma Optic glioma
Neurofibromatosis 2	Schwannoma Meningioma
Tuberous sclerosis	Subependymal giant cell astrocytoma
von Hippel-Lindau syndrome	Hemangioblastoma, pheochromocytoma, renal cell carcinoma
Turcot syndrome	Basal cell carcinoma and medulloblastoma
Li-Fraumeni syndrome	Brain tumors, leukemia, sarcoma, breast cancer
Human immunodeficiency virus infection	Central nervous system lymphoma
Prior history of radiation	Meningioma Malignant peripheral nerve sheath tumors Astrocytoma
Multiple endocrine neoplasia type I	Pituitary adenoma

Ultimately, in some patients, biopsy or resection of the tumor may be required to secure the pathologic diagnosis and grade of the tumor, which aids in treatment planning. A multidisciplinary team approach is useful to determine which patients require biopsy and the manner in which it is performed.

- Some tumors may be associated with other diseases or conditions, including genetic conditions, and screening should be done as appropriate.
- In most cases of suspected intracranial disease, a contrast-enhanced magnetic resonance imaging scan of the brain is the most valuable test.

56 Glial Tumors[a]

DEREK R. JOHNSON, MD

Introduction

Glial tumors are primary brain and spinal cord tumors arising from supporting cells of the central nervous system, including oligodendrocytes, astrocytes, microglia, and ependymal cells. Collectively, glial tumors are the most common category of primary brain tumor. They may be infiltrative or well circumscribed, and prognosis ranges from surgical cure to survival of less than 2 years, depending on tumor type.

Epidemiology

Incidence/Prevalence

The overall incidence of glioma in the United States is approximately 6.6 per 100,000 person-years. The most common glioma by far is glioblastoma, with an incidence of 3.2 per 100,000 person-years. The incidence of glial tumors is approximately 40% higher in men than in women, in contrast to meningiomas, which are more common in women. Age is the strongest risk factor for glioma in adults, with incidence rates rising from a low of 3.2 per 100,000 person-years in those aged 20 to 34 to a high of 19.3 per 100,000 person-years in those aged 75 to 84.

Risk Factors

No strong environmental risk factors have been identified for glioma. While exposure to ionizing radiation has been convincingly linked to glioma incidence, available data suggest that significant radiation doses are required, such as those received as part of therapeutic radiation for another tumor. No conclusive evidence currently exists linking glioma and cellular telephone use, and this is an area of ongoing controversy. A few genetic syndromes are associated with increased glioma risk (Table 56.1).

Tumor Grading

The World Health Organization (WHO) tumor classification and grading system is used to categorize tumors by their cell type of origin and microscopic features (Table 56.2). Tumors may be classified as WHO grade I, II,

Table 56.1 • Genetic Syndromes With an Increased Risk of Glioma

Li-Fraumeni syndrome (AD) p53 gene or *CHEK2* gene	Soft tissue and bone sarcoma, breast carcinoma, acute leukemia, and brain tumors (astrocytoma, glioblastoma, medulloblastoma, choroid plexus carcinoma)
Neurofibromatosis 1 (AD)	Propensity for optic gliomas, infiltrating astrocytomas
Neurofibromatosis 2 (AD)	Schwannomas and meningiomas, but also propensity for glial tumors such as spinal ependymoma
Turcot syndrome	Adenomatous colon polyps and increased risk of glioblastoma and medulloblastoma

Abbreviation: AD, autosomal dominant.

[a] Portions previously published in Johnson DR, Jaeckle KA. Low grade gliomas and oligodendrogliomas in adulthood. In: Packer RJ, Schiff D, editors. Neuro-oncology. 1st ed. Oxford (United Kingdom): Wiley-Blackwell; c2012. p. 76–85. Used with permission.

Abbreviations: CT, computed tomography; DNET, dysembryoplastic neuroepithelial tumor; GBM, glioblastoma; IDH, isocitrate dehydrogenase; MRI, magnetic resonance imaging; NF1, neurofibromatosis 1; PA, pilocytic astrocytoma; PXA, pleomorphic xanthoastrocytoma; WHO, World Health Organization

Table 56.2 • WHO Classification and St. Anne/Mayo Grading of Astrocytic Tumors

WHO		St. Anne/Mayo	
Designation	**Classification**	**Grade (Based on Criteria)[a]**	**Criteria[a]**
Pilocytic astrocytoma	I	1 (no criteria)	No criteria
Astrocytoma	I, II	1 (no criteria, WHO I) 2 (1 criterion)	No criteria Nuclear atypia
Anaplastic astrocytoma	III	3 (2 criteria)	Nuclear atypia Mitosis
Glioblastoma	IV	4 (3 criteria)	Nuclear atypia Mitosis Endothelial proliferation and/or necrosis

Abbreviation: WHO, World Health Organization.

[a] St. Anne/Mayo criteria: nuclear atypia, mitosis, and capillary endothelial proliferation and/or necrosis. Grade = number of criteria + 1; maximum grade, 4.

Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.

III, or IV, with higher grade generally correlating with greater tumor aggressiveness, greater tendency for infiltration of surrounding brain, and poorer prognosis. The most important clinical characteristic of WHO grade I gliomas is the tendency of these tumors to be well circumscribed, and thus potentially surgically curable if they occur in a location where complete resection is possible. The tumors discussed in this chapter are outlined in Table 56.3 by their WHO grading classification.

- The most common glioma by far is glioblastoma.

Astrocytic and Oligodendroglial Tumors

WHO Grade I

Pilocytic Astrocytoma

Pilocytic astrocytoma (PA) is the most common WHO grade I glioma. PA can occur at any age, but it is far more common in childhood and is often diagnosed in the first decade of life. PAs are often located in the cerebellar hemispheres, particularly in children, but are also often found in the optic chiasm, hypothalamus region, and periventricular areas of the third and fourth ventricles. PA in the brainstem can present as posterior exophytic brainstem glioma or focal tectal plate mass, though higher-grade glioma can present in a very similar way. The cerebral hemispheres are more commonly involved with PA in adults than in children.

Table 56.3 • WHO Grading Classification of Glial Tumors

WHO I	Pilocytic astrocytoma Subependymal giant cell astrocytoma Subependymoma Ganglioglioma Dysembryoplastic neuroepithelial tumor
WHO II and III	Astrocytoma Oligodendroglioma Oligoastrocytoma Gliomatosis cerebri Brainstem glioma Pleomorphic xanthoastrocytoma Ependymoma and anaplastic ependymoma Neurocytoma
WHO IV	Glioblastoma

Abbreviation: WHO, World Health Organization.

The characteristic imaging appearance of PA is an enhancing mural nodule, often with a heterogeneous enhancement pattern, contiguous with a fluid-filled cyst (Figure 56.1). Not all PAs have a cystic component, and those occurring in the optic pathways, brainstem, and spinal cord are particularly likely to present as a solid enhancing mass.

Microscopically, PAs are characterized by compact pilocytic arrangements of elongated (sometimes stellate) cells admixed with microcytic areas. Slight nuclear pleomorphism and rare mitoses may be seen. Rosenthal fibers, which are elongated eosinophilic intracytoplasmic inclusions, are a classic feature of PA, but they can also be seen in other processes, such as long-standing gliosis, and they should not be considered diagnostic of PA.

Treatment of PA begins with maximal surgical resection. Even in cases of subtotal resection, postoperative observation is reasonable. Radiation therapy is typically reserved for symptomatic cases in which only biopsy is possible or for recurrent PA after resection.

Optic nerve gliomas are a subset of PA that occur within the optic nerve and are often associated with neurofibromatosis 1 (NF1). Although only 1% to 7% of children with NF1 have optic gliomas, approximately half of all optic gliomas occur in patients with NF1. Optic gliomas present with visual loss and painless proptosis, or with

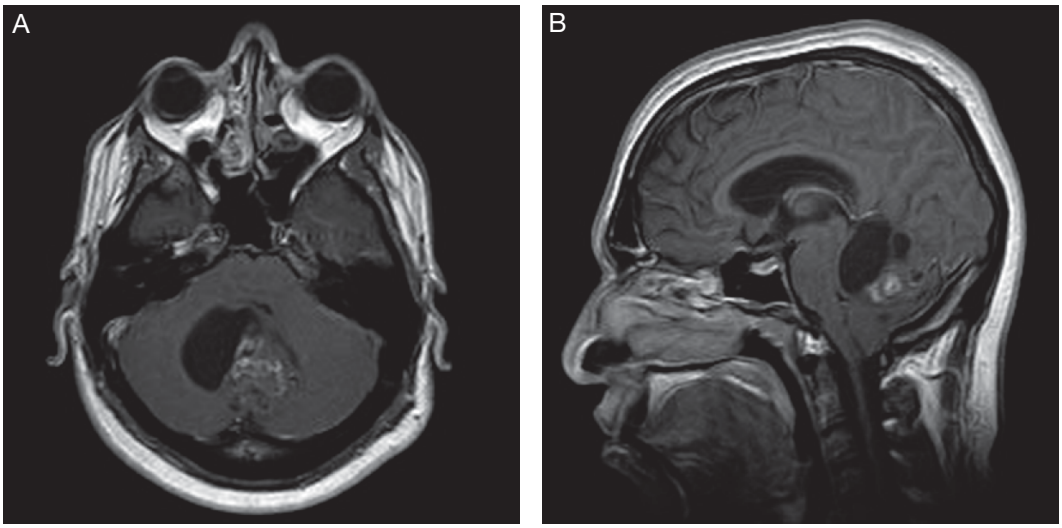

Figure 56.1 *Magnetic Resonance Images of Pilocytic Astrocytoma.*
T1-weighted images with contrast in axial (A) and sagittal (B) planes show an enhancing mural nodule with adjacent cyst located within the cerebellum.

endocrinopathy in the case of hypothalamic involvement. Optic nerve gliomas are typically slow growing and may either directly infiltrate the optic nerve or spread in the subarachnoid space with minimal involvement of the nerve itself (Figure 56.2). Treatment is not always necessary, but it should be considered in the case of progressive visual deterioration. If resection is not possible, radiation therapy is preferred in older children and adults, whereas chemotherapy is more often used in children younger than 5 years.

Subependymal Giant Cell Astrocytoma

Subependymal giant cell astrocytoma is a WHO grade I tumor that arises beneath the ependymal cell layer lining

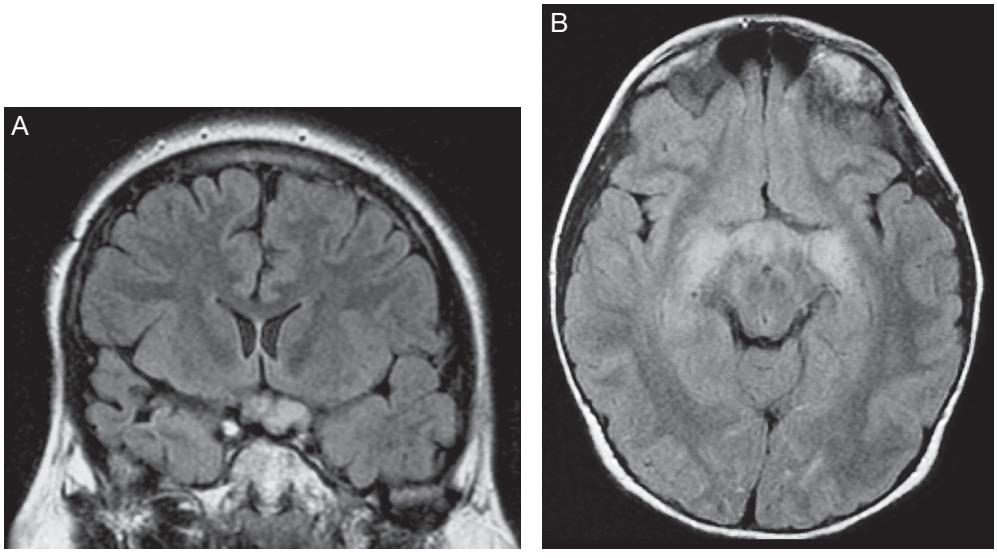

Figure 56.2 *Magnetic Resonance Images of Optic Glioma.*
A, Coronal FLAIR image of an 18-year-old girl shows a multilobular mass centered on the optic chiasm. B, Axial FLAIR image of a 5-year-old boy with neurofibromatosis 1 shows bilateral optic nerve gliomas extending along the optic tracts to the lateral geniculate bodies and further posteriorly along the optic radiations.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

a ventricle and typically grows into the ventricle before presenting as obstructive hydrocephalus. Subependymal giant cell astrocytoma is almost exclusively seen in patients with tuberous sclerosis and is often diagnosed in the first or second decade of life. The rate of tumor recurrence after resection is low, and tumors that cannot be resected or recur after resection can be treated with focal stereotactic radiosurgery. Mammalian target of rapamycin inhibitors such as everolimus may lead to tumor shrinkage, but they are not a first-line therapy at this time.

- Pilocytic astrocytomas are often located in the cerebellar hemispheres, particularly in children.
- The characteristic imaging appearance of pilocytic astrocytomas is an enhancing mural nodule, often with a heterogeneous enhancement pattern, contiguous with a fluid-filled cyst.
- Optic gliomas present with visual loss and painless proptosis, or with endocrinopathy in the case of hypothalamic involvement.
- Subependymal giant cell astrocytoma is almost exclusively seen in patients with tuberous sclerosis and is often diagnosed in the first or second decade of life.

WHO Grade II and III: Astrocytoma, Oligodendroglioma, and Oligoastrocytoma

Overview

WHO grade II and III gliomas may be composed almost purely of astrocytes (astrocytomas) or oligodendrocytes (oligodendrogliomas), or they may contain a mixture of the 2 cell types (oligoastrocytomas). They are generally tumors of young and middle adulthood. In contrast to WHO grade I glioma, WHO grade II, III, and IV glial tumors have an infiltrating nature with tumor projections extending through otherwise normal brain tissue and reaching well beyond the region of abnormality seen on magnetic resonance imaging (MRI). Because of this fact, these are not surgically curable tumors and the likelihood of tumor recurrence after initial treatment approaches 100%.

WHO grade II and III tumors should be thought of as existing on a spectrum rather than as distinct diagnostic entities. Grade II tumors have a natural tendency to progress to grade III tumors over time, and both can evolve to grade IV tumors. Likewise, tumors that have morphologic characteristics of a single cell type at diagnosis may appear morphologically mixed at recurrence. Generally speaking, WHO grade II tumors are less aggressive than grade III tumors, and tumors with a significant oligodendroglial component are less aggressive than pure astrocytic tumors.

Clinical Presentation

The clinical presentation is strongly dependent on tumor location, but seizure is by far the most common presenting symptom. Less frequent presenting symptoms include headache, hemiparesis, and cognitive/behavioral changes. Because tumors with an oligodendroglial component are more likely to involve the cortex, patients with these tumors are more likely to present with seizure or experience seizure at some point in the course of disease.

Diagnosis

Because the presenting symptoms of glioma are nonspecific, imaging is important for accurate diagnosis. WHO grade II tumors are typically isointense on computed tomography (CT) but visible on MRI as hyperintense abnormalities on T2-weighted images that are hypointense on T1-weighted images. Tumors with an oligodendroglial component often appear more heterogeneous than pure astrocytomas because of internal cysts and calcification. WHO grade II gliomas classically do not enhance on postgadolinium MRI imaging, whereas grade III tumors do; however, exceptions exist to both of these rules. CT scans remain useful for the detection of tumor calcification, which is more frequent in oligodendroglial tumors than in pure astrocytic tumors (Figure 56.3 and Figure 56.4).

Microscopically, WHO grade II fibrillary astrocytoma, the most common subtype of astrocytoma, is characterized by well-differentiated astrocytes with scant cytoplasm, atypical and hyperchromatic nuclei, and fine fibrillary processes (Figure 56.5). Mitoses are very rare or absent. Grade III astrocytomas share many of the characteristics of grade II tumors, but they show greater cellularity, more prominent nuclear atypia, and mitotic activity, but no necrosis or microvascular proliferation. Oligodendroglioma is microscopically characterized by homogeneous-appearing cells with sparse cytoplasm and round uniform nuclei. A fixation artifact results in clearing of the cytoplasm around the nuclei, creating a "fried egg" appearance (Figure 56.6).

Most WHO grade II and III gliomas contain somatic point mutations within the genes for isocitrate dehydrogenase 1 (IDH1) or less frequently isocitrate dehydrogenase 2 (IDH2). This mutation is thought to occur very early in tumorigenesis. Astrocytomas often contain somatic mutations in the tumor suppressor gene p53. Tumors with a significant oligodendroglial component often contain coexistent deletions of portions of chromosomes 1 and 19, referred to as 1p/19q codeletion. The presence of 1p/19q codeletion is prognostic of longer survival in WHO grade II and III tumors as well as predictive of chemotherapy response in WHO grade III tumors.

Treatment

Treatment of WHO grade II and III astrocytoma, oligodendroglioma, and oligoastrocytoma begins with surgery for definitive diagnosis and tumor debulking. Gross total resection, defined as complete removal of T2/FLAIR abnormality in nonenhancing tumors and complete removal of the contrast-enhancing region of enhancing tumors, is

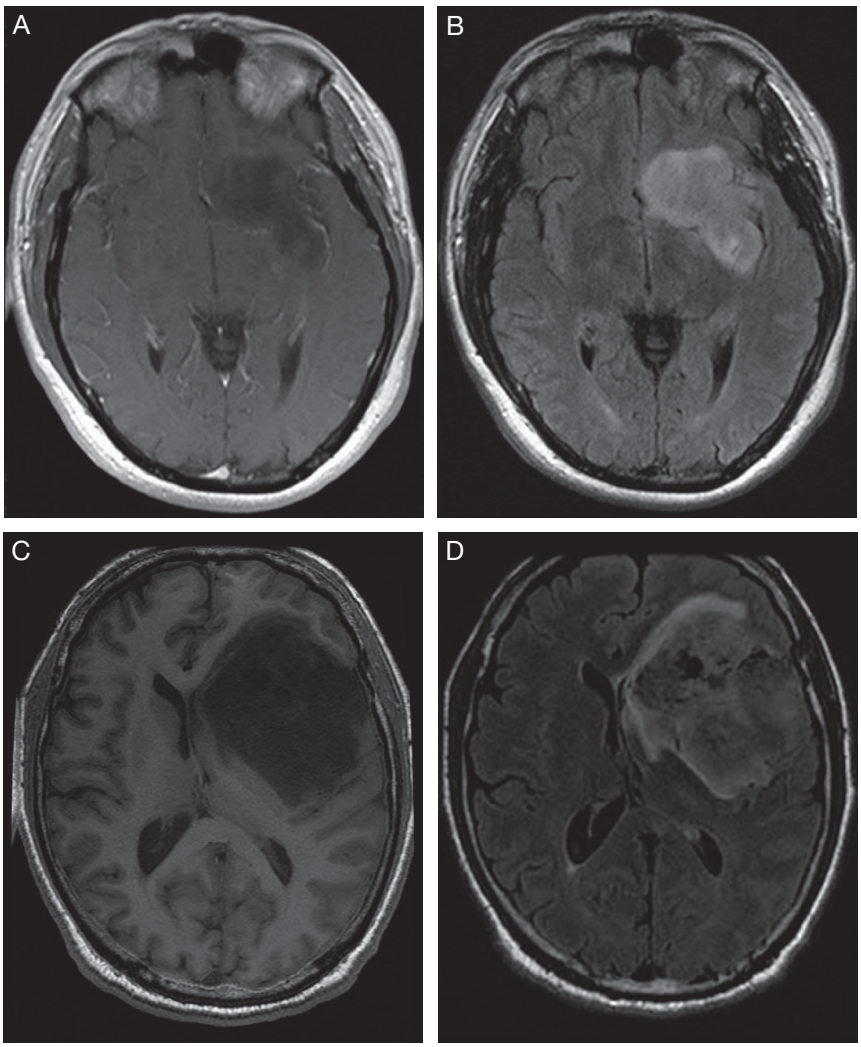

Figure 56.3 *Magnetic Resonance Images of World Health Organization Grade II Astrocytoma.*
A, Postgadolinium T1-weighted image and, B, FLAIR image. C, Pregadolinium T1-weighted image and, D, FLAIR image.

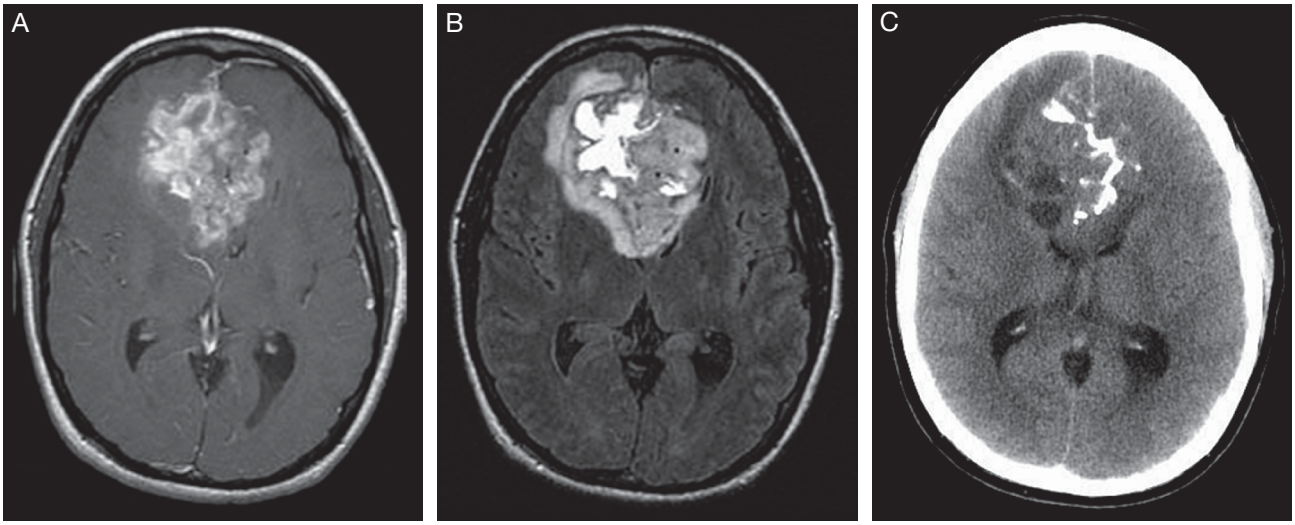

Figure 56.4 *Magnetic Resonance Images and Computed Tomography Scan of Anaplastic Oligodendroglioma.*
A, Postgadolinium T1-weighted image shows contrast enhancement without the presence of a ring-enhancing lesion. B, FLAIR image shows heterogeneous appearance characteristic of anaplastic oligodendroglial tumors. C, Computed tomography scan shows calcification within the tumor.

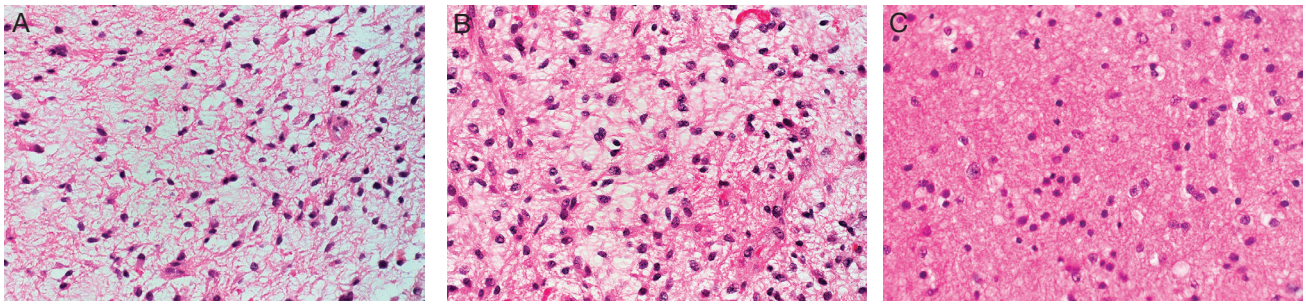

Figure 56.5 *Fibrillary Astrocytoma.*
A and B, Fibrillary astrocytomas are characterized by well-differentiated astrocytes with hyperchromatic nuclei and scant cytoplasm; fine fibrillary processes make up the background. C, The fibrillary background is often interrupted by microcysts.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

associated with prolonged survival if it can be achieved without negatively affecting patient performance status. Extensive subtotal resection is also associated with improved survival, but studies differ with respect to what proportion of tumor must be removed to yield survival benefit, with most studies suggesting a threshold near 80%. Radiation therapy is the cornerstone of postsurgical treatment of WHO grade II and III infiltrating glioma and is usually delivered 5 days a week for 6 weeks. Radiation therapy may be deferred until time of progression in the case of WHO grade II tumors after successful gross total resection, but it is typically administered as part of the initial treatment plan for grade II tumors that cannot be resected and grade III tumors regardless of resection status. The role of chemotherapy in the treatment of WHO grade II and III gliomas remains controversial. Recent data suggest that the addition

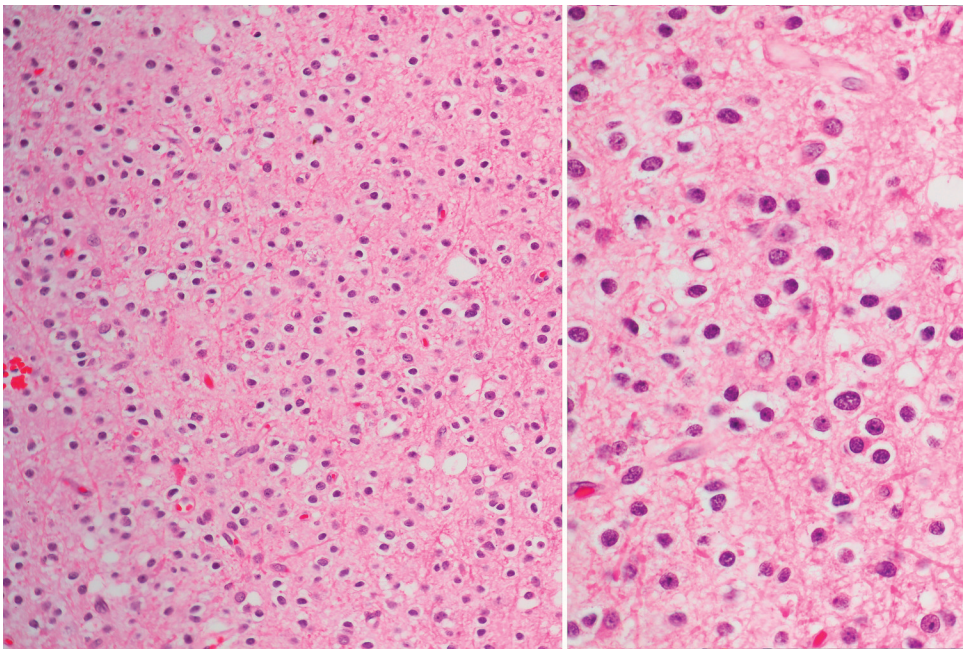

Figure 56.6 *Oligodendroglioma.*
Sheets of uniform cells with "fried egg" appearance due to artifactual clearing of the cytoplasm (best seen in higher magnification on the right).
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

of chemotherapy with a combination of procarbazine, lomustine (also called CCNU), and vincristine, collectively known as PCV, to radiation therapy at time of diagnosis improves survival in WHO grade III oligodendrogliomas and oligoastrocytomas that are 1p/19q codeleted. In practice, PCV therapy has been largely displaced by the use of the oral alkylating agent temozolomide, given perceived similar efficacy and greater tolerability of temozolomide, despite the absence of a comparative efficacy trial.

- In oligodendroglioma, a fixation artifact results in clearing of the cytoplasm around the nuclei, creating a "fried egg" appearance.
- Treatment of WHO grade II and III astrocytoma, oligodendroglioma, and oligoastrocytoma begins with surgery for definitive diagnosis and tumor debulking.
- Radiation therapy is the cornerstone of postsurgical treatment of WHO grade II and III infiltrating glioma.

Other WHO Grade II and III Tumors

Gliomatosis Cerebri

The term *gliomatosis cerebri* describes a pattern of infiltrating glioma growth involving multiple lobes of the brain rather than a biologically distinct tumor. Imaging is characterized by T2 hyperintensity involving 3 or more cerebral lobes, often with extension across the corpus callosum, without the presence of a dominant tumor mass (Figure 56.7). Faint areas of contrast enhancement may be present.

Pathologically, gliomatosis cerebri is more often astrocytic than oligodendroglial in composition and is more often WHO grade II than higher grade. Biopsy is necessary for diagnosis, but there is no role for more extensive tumor resection. Treatment is controversial and may involve radiation therapy, chemotherapy, or both.

Brainstem Glioma

Like gliomatosis cerebri, brainstem glioma is a variant of infiltrating glioma defined by location and behavior. Diffuse infiltrating gliomas are much more common in children than adults and may be either WHO grade II or higher grade. Children present with the subacute onset of multiple cranial neuropathy, ataxia, and long-tract signs. MRI reveals expansion of the brainstem and T2/FLAIR hyperintensity usually without enhancement on T1-weighted postgadolinium images (Figure 56.8). Biopsy is usually not required for treatment in children but should be considered in adults. When tissue is obtained, WHO grade II astrocytoma is the most common pathologic diagnosis in adults, whereas children often have higher-grade tumors. Radiation therapy is the treatment of choice for brainstem glioma. Prognosis is very poor in children and somewhat better in adults.

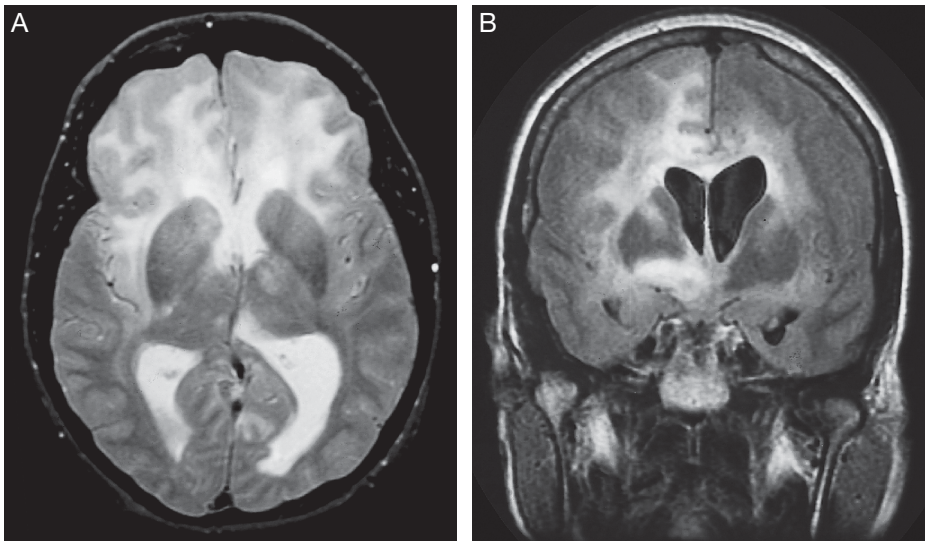

Figure 56.7 *Magnetic Resonance Images of Gliomatosis Cerebri.*
A, Axial T2-weighted image and, B, coronal FLAIR image show extensive confluent abnormal nonenhancing increased T2 signal involving white matter of both frontal lobes, notably the corpus callosum anteriorly. Additional abnormal signal is seen in the hypothalamus (B), notably in the region of the anterior commissure on the right. Obstructive hydrocephalus of the lateral ventricles and severe mass effect are present.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

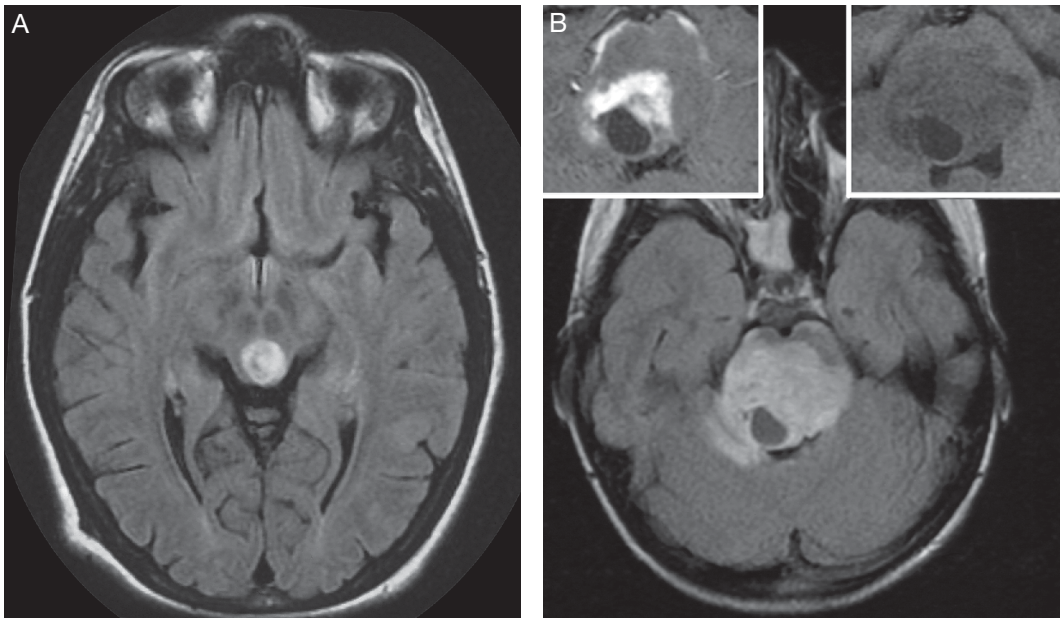

Figure 56.8 *Magnetic Resonance Images of Brainstem Glioma.*
A, Axial FLAIR image shows a tectal plate mass that is likely low-grade glioma. B, Axial FLAIR image of a 7-year-old girl with brainstem glioma shows a cystic enhancing expansive mass (upper left inset, contrast-enhanced T1-weighted image) in the posterior fossa extending from pons to midbrain, abutting the anterior surface of the fourth ventricle and cerebral aqueduct, causing moderate noncommunicating hydrocephalus (not shown). The large tumor appears to be of high T2 and low T1 signal (upper right inset, T1-weighted image). Although the radiographic appearance of this lesion is suggestive of pilocytic astrocytoma, biopsy showed high-grade brainstem glioma.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

Pleomorphic Xanthoastrocytoma

Pleomorphic xanthoastrocytoma (PXA) is a rare slow-growing WHO grade II astrocytic tumor most often found in children and young adults. PXAs are typically located in the supratentorial compartment and tend to occur along the surface of the brain, often contacting the leptomeninges. Seizure activity is by far the most common symptomatic presentation of PXA.

On imaging, PXA shares several characteristics with PA. Both most commonly present as an enhancing mural nodule with an adjacent cyst and less commonly present as a solid enhancing nodule. Distinguishing characteristics include location, often supratentorial for PXA and infratentorial for PA, and the superficial location of PXA. On CT, remodeling of the inner table of the skull is sometimes visible.

Surgical resection may be curative and is also associated with greater likelihood of long-term seizure control. The prognosis of PXA is notably better than that of other WHO grade II astrocytic tumors.

- Most often found in children and young adults, pleomorphic xanthoastrocytomas are typically located in the supratentorial compartment and tend to occur along the surface of the brain, often contacting the leptomeninges.

WHO Grade IV: Glioblastoma

Overview

Glioblastoma (GBM), also known as WHO grade IV astrocytoma, is the most common and most aggressive infiltrating glioma. GBM may arise de novo as a grade IV tumor (ie, primary GBM), or it may result from progression of a lower-grade glioma, in which case it can be referred to as a secondary GBM. Median age at diagnosis is 64 years, but the incidence rate continues to rise with age, peaking in the 75- to 84-year-old age group. Despite recent advances in therapy, the median survival time after diagnosis remains less than 2 years in most clinical trials and closer to a year in the population at large. Gliosarcoma is sometimes considered another WHO grade IV tumor, but it is best thought of as a morphologic subtype of GBM, sharing the same risk factors, prognosis, and treatment plan.

Diagnosis

The typical MRI appearance of a GBM is a solitary heterogeneously enhancing lesion on T1 post-contrast imaging with a surrounding region of T2 hyperintensity that represents vasogenic edema (Figure 56.9). On CT, the enhancing lesion is surrounded by a region of hypodensity. GBM is highly infiltrative and may cross the corpus callosum.

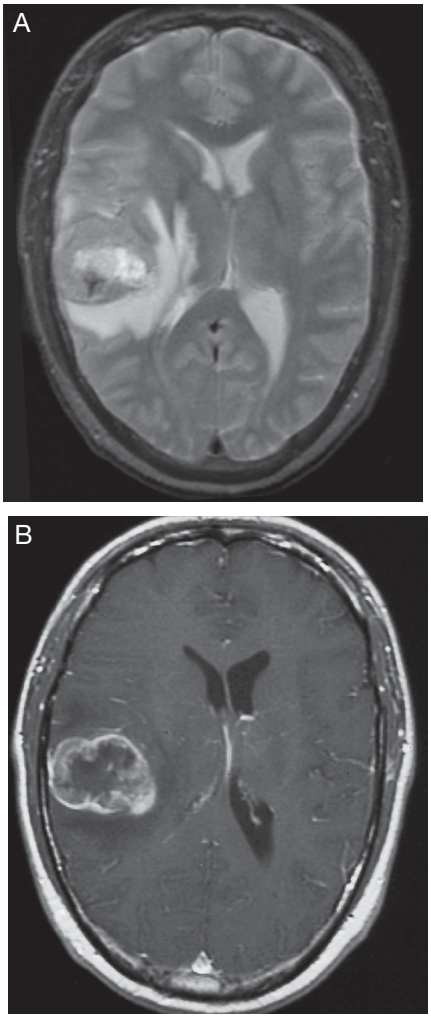

Figure 56.9 *Magnetic Resonance Images of Glioblastoma Multiforme.*
A, T2-weighted image and, B, contrast-enhanced T1-weighted image of a 33-year-old patient show a peripherally enhancing mass with a heterogeneous signal within the lesion, situated in the junction of the right posterior frontotemporal operculum and insula. Note vasogenic edema in the white matter surrounding the lesion, associated with mass effect and right-to-left midline shift.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

Microscopically, GBM is a highly cellular and mitotically active tumor composed of poorly differentiated astrocytes. Microvascular proliferation, necrosis, or both are required for diagnosis. Areas of necrosis are often surrounded by pseudopalisading cells (Figure 56.10). Two important molecular prognostic factors in GBM are IDH mutation and MGMT methylation. IDH mutation, which is rare in primary GBM but much more frequent in secondary GBM, is associated with a good prognosis relative to IDH wild-type tumors. Epigenetic silencing via methylation of the O6-methylguanine–DNA methyltransferase DNA-repair gene (*MGMT*) within a tumor is also associated with a better prognosis in patients with GBM and may even be predictive of response to chemotherapy in elderly patients.

Treatment

As with other gliomas, treatment of GBM begins with maximum safe resection, which is followed by radiation therapy and chemotherapy. The current standard-of-care regimen at the time of this writing involves 6 weeks of radiation therapy with daily oral temozolomide chemotherapy during radiation therapy, followed by 6 to 12 monthly cycles of oral temozolomide chemotherapy. Despite aggressive treatment, tumor recurrence is universal, and a variety of treatments may be employed for recurrent disease. The only medication approved by the US Food and Drug Administration for recurrent GBM is bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor A.

- Glioblastoma is highly infiltrative and may cross the corpus callosum.
- Microvascular proliferation, necrosis, or both are required for diagnosis of glioblastoma. Areas of necrosis are often surrounded by pseudopalisading cells.
- As with other gliomas, treatment of glioblastoma begins with maximum safe resection, which is followed by radiation therapy and chemotherapy.

Ependymal Tumors

Subependymoma

Overview

Subependymoma is a rare slow-growing WHO grade I ependymal tumor that most often occurs in the fourth ventricle arising from the medulla or the lateral ventricles attached to the septum pellucidum. Subependymoma is a tumor of adulthood, typically presenting between the ages of 40 and 60 years.

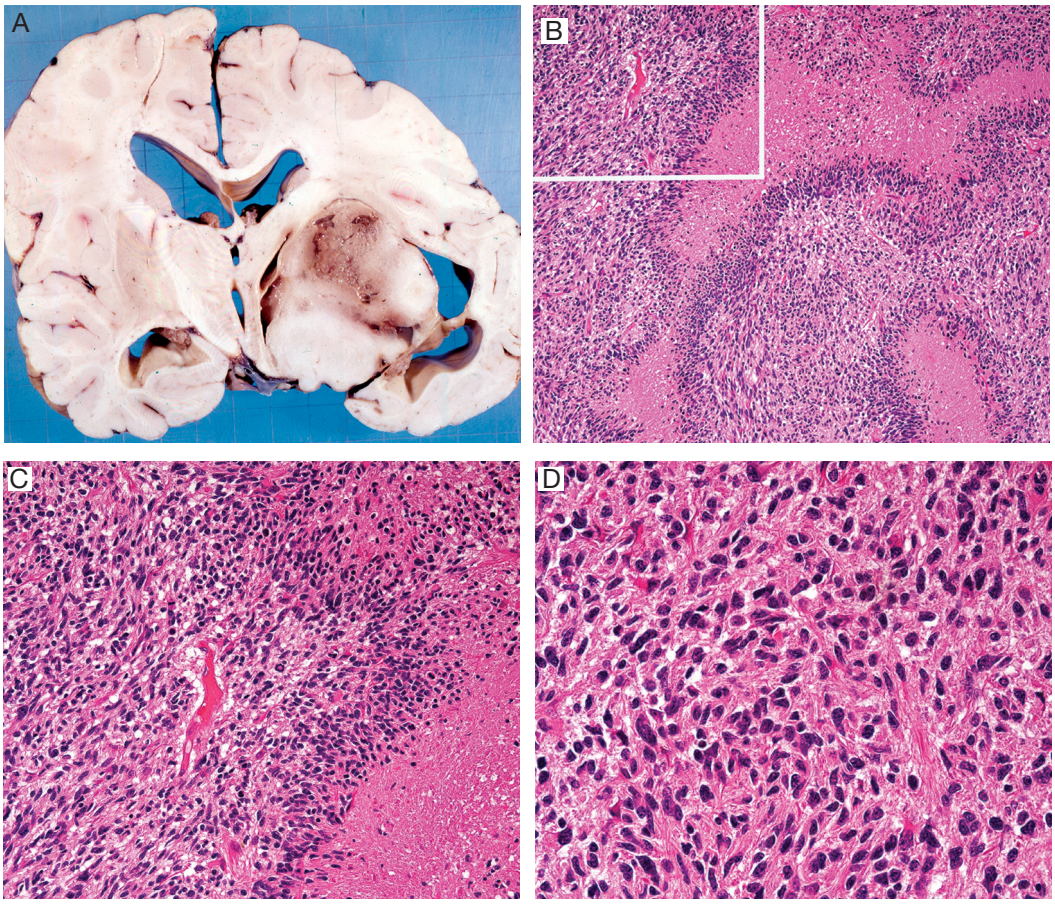

Figure 56.10 *Glioblastoma Multiforme.*
A, Coronal section shows a large tumor involving deep gray matter in the left hemisphere, with a large heterogeneous central area of cystic necrosis. Histopathologic characteristics of glioblastoma multiforme include pseudopalisading cells around necrotic regions (B), neovascularization, cellular pleomorphism (C and D), and mitotic figures. (C is higher magnification of inset in B.)
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

Diagnosis and Treatment

Radiographically, subependymoma appears as a heterogeneous intraventricular mass that is mildly hyperintense on T2-weighted MRI with little or no enhancement on T1-weighted postgadolinium images. Histologically, subependymomas consist of microcystic spaces and bland-appearing cells without appreciable nuclear atypia or mitoses. Surgery is curative.

Ependymoma and Anaplastic Ependymoma

Overview

Ependymoma (WHO grade II) and anaplastic ependymoma (WHO grade III) are glial tumors of ependymal origin. Ependymomas can occur at any age but are far more common in children. In children, the vast majority of ependymomas are intracranial, specifically intraventricular, typically in the infratentorial compartment. In adults, ependymomas typically occur in the spine, and when they do develop intracranially, the supratentorial compartment is a more frequent site than the infratentorial compartment. Most ependymomas are sporadic, but they are a common feature of neurofibromatosis 2.

Clinical Presentation

Clinical presentation is a function of tumor location. In children, infratentorial intracranial tumors often fill or obstruct the fourth ventricle and lead to hydrocephalus. These tumors often arise from the floor of the fourth ventricle, in contrast to medulloblastoma, a nonglial childhood tumor that tends to arise from the roof the fourth ventricle. Symptoms may include lethargy, nausea, vomiting, headache, or enlarging head circumference in children

in whom the cranial sutures have not closed. Multiple cranial neuropathy and ataxia are other common presentations. Spinal ependymoma may present with long-tract signs localizing to or below the level of the lesion and/or radiculopathy and back pain at the level of the tumor. Ependymoma can seed the cerebrospinal fluid, and imaging of the entire neuraxis and lumbar puncture should be obtained for treatment planning.

Diagnosis

On MRI imaging, intracranial ependymomas are T2-hyperintense intraventricular tumors with minimal to moderate enhancement on post-contrast sequences. Extension through the intraventricular foramina is common. Ependymomas may appear heterogeneous in consistency because of cysts, foci of necrosis, and areas of calcification. Most spinal intramedullary ependymomas are based in the midline of the spinal cord and extend symmetrically bilaterally. They may display minimal contrast enhancement, but T2-weighted imaging is more sensitive for the detection of these tumors. Hemosiderin caps are often seen on the superior and inferior margins of spinal ependymomas and are highly suggestive of the diagnosis.

Histologically, ependymomas are characterized by ependymal pseudorosettes with glial fibrillary acidic protein–positive processes extending toward blood vessels.

Treatment

Treatment of ependymoma begins with surgery. While removal of all visible tumor does not guarantee cure, if any residual tumor is left behind, recurrence is extremely likely. For children younger than 3 years with intracranial ependymoma, postoperative chemotherapy is typically used to improve tumor control while avoiding the cognitive adverse effects of radiation. In older children and adults, postoperative radiation therapy is preferred, though observation alone after surgery can be considered in cases of supratentorial WHO grade II ependymoma after complete resection. In cases of spinal WHO grade II ependymoma, no adjuvant therapy is typically recommended after complete resection, whereas radiation therapy is preferred for subtotal resection or WHO grade III (anaplastic) tumors.

- Ependymomas can occur at any age but are far more common in children. In children, the vast majority of ependymomas are intracranial, specifically intraventricular, typically in the infratentorial compartment.
- Infratentorial intracranial ependymomas often arise from the floor of the fourth ventricle, in contrast to medulloblastoma, a nonglial childhood tumor that tends to arise from the roof the fourth ventricle.

Neuronal and Mixed Glial/ Neuronal Tumors

Dysembryoplastic Neuroepithelial Tumor

Overview

Dysembryoplastic neuroepithelial tumor (DNET) is a WHO grade I glial-neuronal neoplasm of children and young adults. DNET typically involves the cerebral cortex and exhibits a predilection for the temporal lobes, particularly the mesial portions of the temporal lobes. Focal or secondarily generalized seizures, which are often refractory to antiepileptic therapy, are by far the most common presenting symptom of DNET.

Diagnosis and Treatment

On MRI, DNETs appear as well-circumscribed lesions involving the cerebral cortex that are hyperintense on T2-weighted sequences and hypointense on T1, frequently with a pseudocystic appearance. Approximately one-third of DNETs display contrast enhancement, often due to tumor ischemia or hemorrhagic changes.

The goals of surgery for DNET are tissue diagnosis and seizure control. Even subtotally resected tumors may be observed postoperatively, because recurrence or progression risk is very low.

Ganglioglioma

Overview

Ganglioglioma is a rare tumor composed of neoplastic mature ganglion cells in combination with neoplastic glial cells. The vast majority of gangliogliomas are WHO grade I, but WHO grade III (anaplastic) gangliogliomas can occur and are associated with more aggressive behavior. Ganglioglioma can occur at any age, but it is far more common in children and young adults. Like DNET, ganglioglioma has a predilection for the temporal lobes and often presents clinically with seizure activity.

Diagnosis and Treatment

On MRI, ganglioglioma may appear as either a solid T2-hyperintense, T1-hypointense mass or as a cyst with a mural nodule. Contrast enhancement is more common in ganglioglioma than in DNET but may be absent. The key microscopic diagnostic feature of ganglioglioma is the presence of irregular groups of large dysplastic multipolar neurons (Figure 56.11).

Treatment is surgical, with a low risk of recurrence after complete surgical resection.

Neurocytoma

Overview

Neurocytoma is a rare WHO grade II neuronal tumor of young adults. Neurocytoma is often located

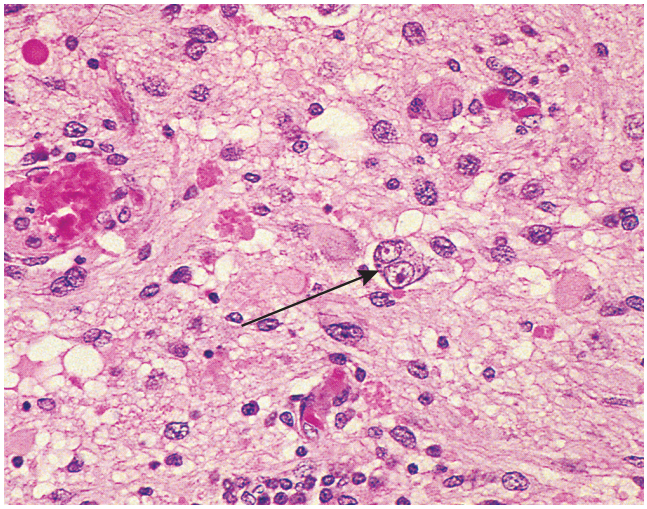

Figure 56.11 *Ganglioglioma.*
Binucleated ganglion cells (arrow) are a characteristic feature and pathognomonic of gangliogliomas, but not always present.
(Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 103. By permission of Mayo Foundation for Medical Education and Research.)

within a ventricle, in which case it is referred to as central neurocytoma. The most frequent location of central neurocytoma is the anterior portion of one of the lateral ventricles near the foramen of Monro. Much less frequently neurocytoma occurs in the brain parenchyma, in which case the term *extraventricular neurocytoma* is used. Central neurocytoma often presents with symptoms of elevated intracranial pressure.

Diagnosis and Treatment

On MRI, central neurocytoma appears as a well-demarcated T2-hyperintense intraventricular mass, often with heterogeneous signaling characteristics due to internal cysts or calcification, or both. Neurocytomas typically enhance on postgadolinium images (Figure 56.12).

Treatment of neurocytoma is surgical. Although these tumors are WHO grade II, they do not share the infiltrating nature of WHO grade II astrocytoma or oligodendroglioma. Radiation therapy can be effective for recurrent or progressive tumor if additional surgery is not an option.

- Dysembryoplastic neuroepithelial tumor typically involves the cerebral cortex and exhibits a predilection for the temporal lobes, particularly the mesial portions of the temporal lobes.
- Like dysembryoplastic neuroepithelial tumor, ganglioglioma has a predilection for the temporal lobes and often presents clinically with seizure activity.
- The key microscopic diagnostic feature of ganglioglioma is the presence of irregular groups of large dysplastic multipolar neurons.

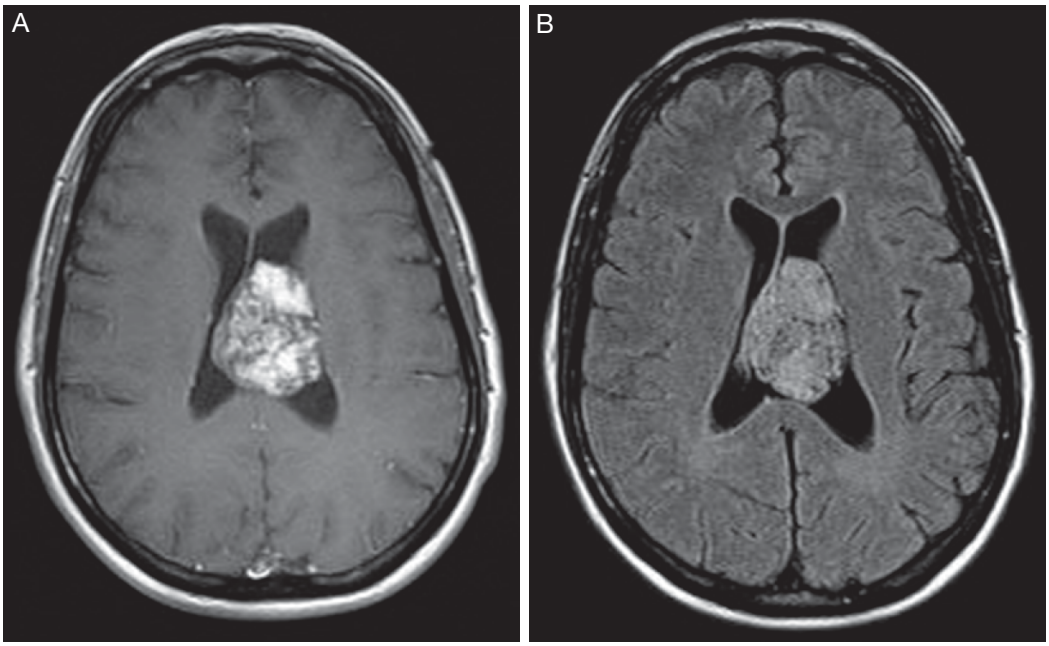

Figure 56.12 *Magnetic Resonance Images of Central Neurocytoma.*
Heterogeneous, complex mass involves the lateral ventricles. A, Axial T1-weighted gadolinium-enhanced image shows enhancement of the tumor. B, Axial FLAIR image demonstrates lack of peritumoral edema.

- Neurocytoma is often located within a ventricle, in which case it is referred to as central neurocytoma.

Glioma Symptom Management

Seizure

Antiepileptic therapy is warranted in patients with brain tumor who experience even a single seizure. Duration of therapy is controversial; some neurologists advocate lifelong therapy, and others routinely attempt to discontinue antiepileptic drug therapy after tumor resection and a seizure-free period of variable length. The American Academy of Neurology has issued a practice guideline stating that prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors, because of lack of efficacy in preventing first seizures and the potential for anticonvulsant-related adverse effects.

Peritumoral Edema

Patients with WHO grade III and IV glioma often develop significant peritumoral vasogenic edema, visible as T2/FLAIR signal abnormality surrounding the region of contrast enhancement on MRI. The edema itself may cause neurologic symptoms, or even herniation when severe. In the case of life-threatening symptoms, emergent treatment with intravenous corticosteroids such as dexamethasone is indicated. Osmotic therapy with mannitol or hypertonic saline solution is not the preferred choice, given that peritumoral edema is vasogenic rather than cytotoxic. When edema is symptomatic but not life-threatening, oral corticosteroid therapy is indicated. Occasionally, tumors may cause obstructive hydrocephalus requiring a cerebrospinal fluid diversion procedure. Either ventriculoperitoneal shunting or third ventriculostomy can be considered, depending on the tumor location and the preference of the surgeon.

57 Nonglial Central Nervous System Tumors

HEATHER E. LEEPER, MD; ALYX B. PORTER, MD

Introduction

A wide variety of primary tumors affect the central nervous system (CNS). Chapter 56, "Glial Tumors," reviewed common glial tumors of the CNS. This chapter reviews additional types of primary CNS tumors common in clinical practice and the approach to their management.

Primary CNS Lymphoma

Overview and Epidemiologic Factors

Primary CNS lymphoma (PCNSL) is a rare variant of extranodal non-Hodgkin lymphoma that may involve the brain, leptomeninges, eyes, or spinal cord and accounts for up to 5% of all adult primary brain neoplasms. Age-adjusted incidence has increased in the past 3 decades. Infection with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome increases the risk of PCNSL by 3,600-fold, but with highly active antiretroviral therapy, the frequency of immune system compromise sufficient for HIV-associated PCNSL (CD4 count ≤50) is dramatically reduced, along with the risk of this disorder.

Although the lower age in the presentation range is as low as the third decade, roughly 50% of cases arise in persons aged 60 years or older, with more than 15% in persons aged 80 years or older. Epstein-Barr virus is highly associated with lymphoma occurring with HIV infection and other immunocompromised states.

Clinical Presentation

PCNSL has a predilection for periventricular regions and diencephalon. Neurologic symptoms are commensurate with tumor location. Encephalopathy is common. Up to 20% of patients can have concurrent ocular involvement at presentation, yet only 50% of patients report visual symptoms. As the disease progresses, 18% of cases have involvement of the leptomeninges. Rarely, PCNSL presents only as leptomeningeal disease. Another rare form of extranodal lymphoma may present in the eye and at recurrence presents in the brain or leptomeninges.

Diagnosis

On magnetic resonance imaging (MRI), PCNSL in immunocompetent patients shows diffuse, generally congruent T2 and T1 enhancement, often with restricted diffusion (Figure 57.1). Mass effect is modest. A single lesion is present in 60% to 70% of cases; multiple lesions are present in 30% to 40%. Immunocompromised patients are more likely to have multiple lesions, ringlike or irregular enhancement, and central necrosis. Hemorrhage is uncommon, but when present, it is more likely in immunocompromised patients.

The major histological feature is polymorphous large cells resembling immunoblasts and smaller cells resembling lymphocytes arranged in sheets, perivascularly or in a cluster (Figure 57.2). The neoplastic cells are derived from germinal center B cells and nearly all express the pan-B-cell markers CD 4, CD 19, CD 20, CD 22, and CD 79a.

Diagnosis is most commonly achieved through stereotactic-guided biopsy. Surgical resection provides no

Abbreviations: AFP, α-fetoprotein; β-hCG, β-human chorionic gonadotropin; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DWI, diffusion-weighted imaging; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; PCNSL, primary central nervous system lymphoma; PNET, primitive neuroectodermal tumor; WHO, World Health Organization

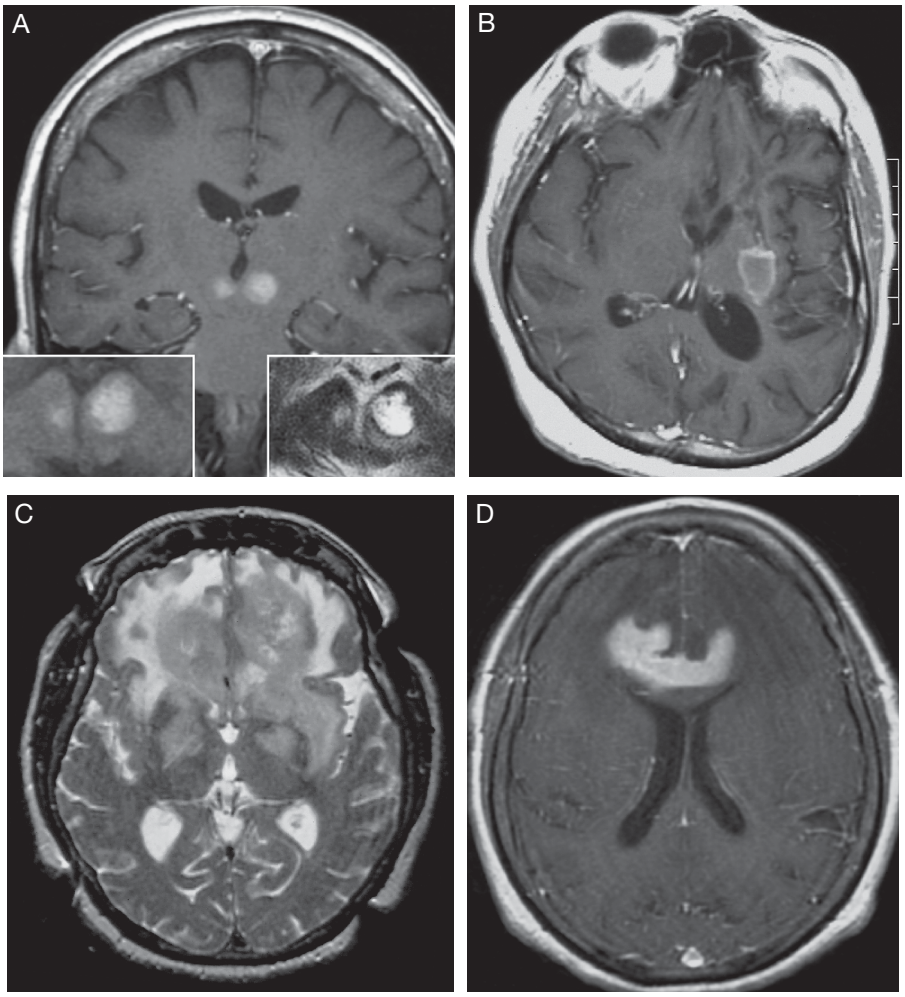

Figure 57.1 *MRI of Primary Central Nervous System Lymphoma.*
A, A 64-year-old woman with diffuse large B-cell lymphoma presented with worsening mental status. Gadolinium-enhanced T1-weighted image shows lesions in deep gray matter appearing as mirror images. Both pregadolinium T1- (left inset) and T2- (right inset) weighted images showed increased signal, suggestive of subacute hemorrhage into the mass. B, Gadolinium-enhanced T1-weighted image of an 18-year-old girl with diffuse large B-cell lymphoma shows ring enhancement outlining the lesion in deep gray matter (common location for lymphoma). C, T2-weighted image and, D, gadolinium-enhanced T1-weighted image of a different patient with diffuse large B-cell lymphoma show large intraparenchymal mass in frontal lobes bilaterally, extending through genu of corpus callosum and involving deep gray matter. There appears to be extensive perilesional vasogenic edema and mass effect on the frontal horns of the lateral ventricles.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

discernible disease control and therefore is not recommended.

Treatment

Treatment has centered on high-dose methotrexate therapy, with consideration of the addition of rituximab and temozolomide in some cases. Many centers also are incorporating induction chemotherapy, followed by autologous stem cell transplant after the disease appears to be in remission. Whole-brain radiation is often withheld until a time of recurrence because of severe neurologic morbidity related to leukoencephalopathy. Prognosis continues to be highly dependent on age and performance status.

- Infection with human immunodeficiency virus and acquired immunodeficiency syndrome increases the risk of primary central nervous system lymphoma (PCNSL) by 3,600-fold.

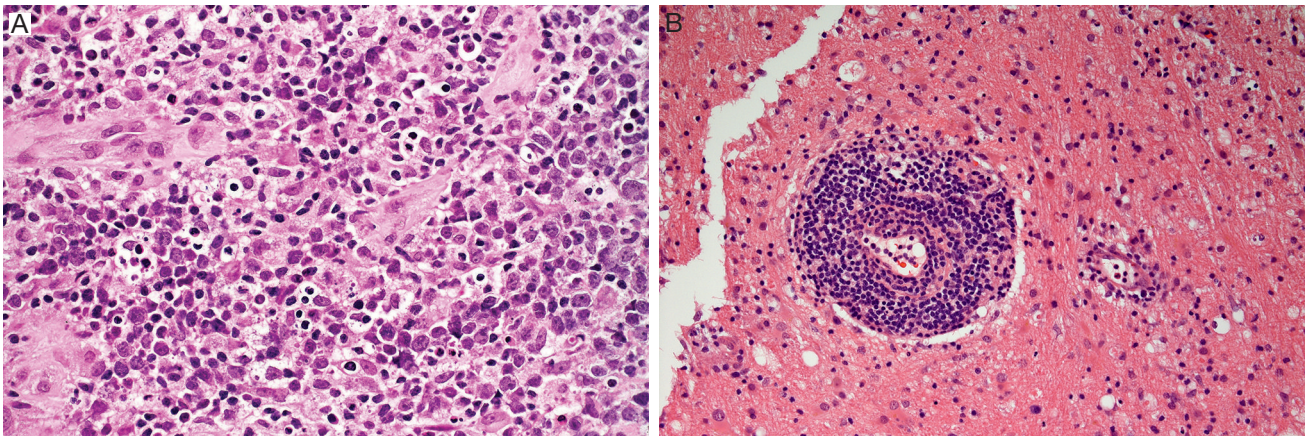

Figure 57.2 *Primary Central Nervous System Lymphoma.*
A, Sheets of polymorphous large cells resembling immunoblasts are admixed with smaller cells resembling lymphocytes and are interrupted by areas of necrosis. B, Typical angiocentric pattern due to propensity of angioinvasive cells to accumulate in perivascular spaces and invade vascular walls.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

- PCNSL has a predilection for periventricular regions and diencephalon.
- A single lesion is present in 60% to 70% of PCNSL cases; multiple lesions are present in 30% to 40%.
- In PCNSL, immunocompromised patients are more likely to have multiple lesions, ringlike or irregular enhancement, and central necrosis.

Systemic Lymphoma With CNS Metastasis

Aggressive variants of non-Hodgkin lymphoma, such as Burkitt and lymphoblastic lymphomas, have potential to involve the CNS. Approximately 5% to 10% of patients with these variants have CNS involvement, but extensive-stage disease with any form of high-grade lymphoma can involve the CNS at any level. In contrast, low-grade disease, such as follicular and mantle cell lymphomas, rarely involves the CNS. Leptomeningeal spread causing cranial nerve palsies, polyradiculopathy, and communicating hydrocephalus due to impaired cerebrospinal fluid (CSF) resorption by the arachnoid villi is the most common manifestation of this CNS involvement. Dural pachymeningeal patterns can present with regional mass effect.

Primitive Neuroectodermal Tumors

Medulloblastoma

Overview

The most common primitive neuroectodermal tumor (PNET) is medulloblastoma, arising from the cerebellar external granular layer precursor cells. They are World Health Organization (WHO) grade IV neoplasms because of their invasive, aggressive nature and high rate of CSF seeding. Medulloblastoma accounts for 20% of all intracranial tumors in children.

Clinical Presentation

Medulloblastoma is a predominantly childhood-onset tumor, with 70% occurring before age 16 years. The peak age at presentation is 7 years. Among adults with medulloblastoma, 80% of cases occur between 21 and 40 years of age. Male patients comprise 60% of patients with medulloblastoma. Patients present for medical attention with reports of headache, nausea, vomiting, visual disturbance, and incoordination resulting from mass effect and obstructive hydrocephalus.

Diagnosis

On MRI, the tumor appears hyperintense on T2 with heterogeneous enhancement and signal pattern. Complete evaluation requires MRI of the entire neuraxis for screening of drop metastases. Three-quarters of medulloblastomas arise at the midline cerebellum or vermis; the other one-quarter of medulloblastomas arise in the cerebellar hemispheres, which is the more common location in young adults. Grossly, medulloblastoma often appears as soft but firm pink to dark gray masses. Foci of necrosis and calcification are uncommon, and small but widespread hemorrhage may be present. Histologically, the most common characteristics are small, round, blue cells with scant cytoplasm; dark nuclei with nuclear molding or wrapping; and

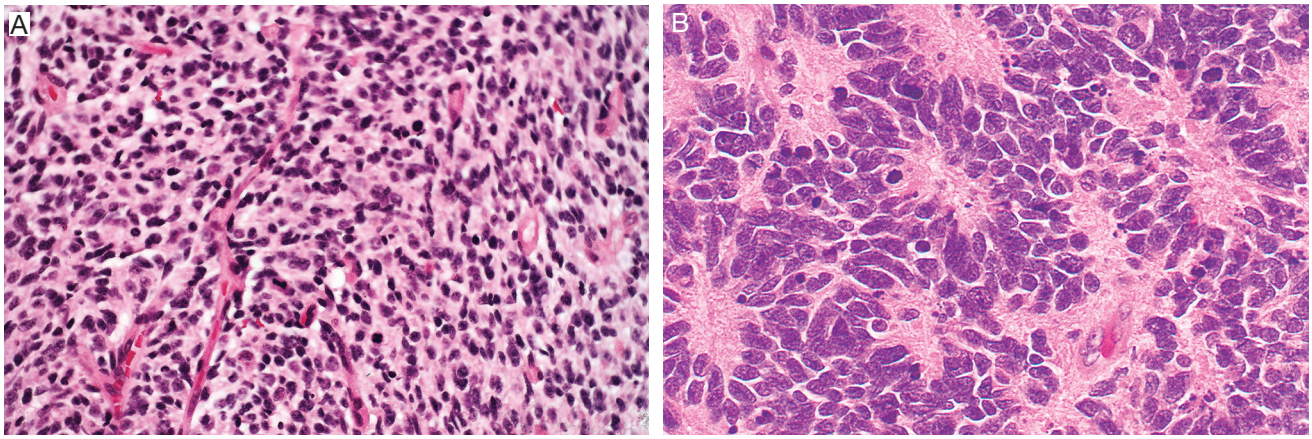

Figure 57.3 *Medulloblastoma.*
A, Densely packed, undifferentiated cells with hyperchromatic pleomorphic nuclei and sparse cytoplasm. B, Neuronal differentiation into neuroblastic Homer (Wright) rosettes (lacking a central vascular component) is common.
(A, Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research. B, Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 111. Used with permission of Mayo Foundation for Medical Education and Research.)

neuroblastic rosettes with fibrillary centers (Figure 57.3). Some medulloblastoma tumors also contain ependymal perivascular rosettes. Among the 4 variants of medulloblastoma—classic, desmoplastic/nodular, large cell/anaplastic, and medulloblastoma with extensive nodularity—the desmoplastic/nodular variant may be seen more frequently in adults and persons with Gorlin syndrome, also known as *nevoid basal cell carcinoma syndrome*.

Treatment and Prognosis

Surgical resection is followed by craniospinal radiation. The 5-year survival rate differs by age of presentation, extent of surgical resection, presence or absence of disseminated disease, and histological subtype. However, it ranges from 30% to 80%.

Other PNETs

Other types of PNETs are less common and include ependymoblastoma, esthesioblastoma, pineoblastoma, retinoblastoma, and cerebral neuroblastoma. Cerebral neuroblastomas typically occur in the first decade before age 5 years. This type is less common than neuroblastoma arising from the sympathetic chain. Patients often present with increased intracranial pressure, opsoclonus, myoclonus, and encephalopathy. Cerebral neuroblastoma has a predilection for the frontal lobes and[Q*] parietal lobes, and prognosis is poor.

- The most common primitive neuroectodermal tumor is medulloblastoma, arising from the cerebellar external granular layer precursor cells.
- Complete evaluation of medulloblastoma requires magnetic resonance imaging of the entire neuraxis for screening of drop metastases.

Pituitary Adenoma

Overview

Pituitary adenomas account for approximately 17% of all intracranial neoplasms. Despite this prevalence, the majority are asymptomatic, with 25% found incidentally at autopsy. Girls and women are more commonly affected than boys and men, except in the case of growth hormone–secreting adenoma.

Clinical Presentation

In adults, pituitary adenomas are usually diagnosed between the third and sixth decades. These tumors can be classified as *functional* (Table 57.1) and *nonfunctional* depending on whether the lesion is the primary source of a hormone produced in excess. Nonfunctional adenomas present with symptoms from the regional mass effect, most notably bitemporal superior visual field deficits, as well as mass effect on the pituitary stalk or hypothalamus. The latter may result in

Table 57.1 • Symptoms of a Functional Pituitary Adenoma

Hormone in Excess	Clinical Delineation
Growth hormone	Acromegaly, gigantism
Corticotropin/ACTH	Cushing disease
Prolactin	Gynecomastia, galactorrhea, hypogonadism (infertility)

Abbreviation: ACTH, adrenocorticotropic hormone.

hypothyroidism, hypogonadism, or hyperprolactinemia (anterior pituitary dysfunction), or diabetes insipidus (posterior pituitary dysfunction or a combination). Hyperprolactinemia results from compression of the pituitary stalk due to reduction in the hypothalamic dopaminergic inhibition of prolactin-producing cells.

Pituitary apoplexy may be a neurologic emergency that presents with sudden-onset headache, alteration of consciousness, cavernous sinus hypertension (eg, proptosis, chemosis), ophthalmoplegia, and facial pain. The cause of the apoplexy, or hemorrhage within the gland, is thought to be a high metabolic demand of the adenoma in the setting of marginal blood supply, although apoplexy can occur in normal pituitary or pharyngeal recess cysts (ie, Rathke cleft cysts). Sheehan syndrome is apoplexy at childbirth, thought to be secondary to transient hypotension and hypoperfusion of the physiologically hypertrophied pituitary during gestation. Computed tomography (CT) or MRI, or both, provided acutely is important in diagnosing the cause of this emergency (Figure 57.4).

Diagnosis

MRI of the brain with close attention to the pituitary gland and hypothalamus can identify the adenoma. Hormone levels can help distinguish functional from nonfunctional adenoma. Commonly, assessment is performed of the concentration of prolactin, insulinlike growth factor–1 levels, thyrotropin, free thyroxine, and morning cortisol. In addition, testosterone level is tested in men. Visual field testing is often performed to detect any subtle visual field abnormalities, such as a bitemporal hemianopsia.

Plasma prolactin levels can be useful in differentiating whether the hyperprolactinemia is primary (tumor secreting) or secondary (related to stalk compression). Plasma prolactin values greater than 200 ng/mL are diagnostic of primary hyperprolactinemia. An important diagnostic consideration with hypothyroidism resulting from dysfunction of the hypothalamic or pituitary axis, or both, is that it is not associated with increased thyrotropin levels. In contrast, hypothyroidism resulting from primary thyroid gland dysfunction does affect the thyrotropin levels.

Grossly, pituitary adenomas are categorized as *microadenoma* when the tumor diameter is 1 cm or less and as

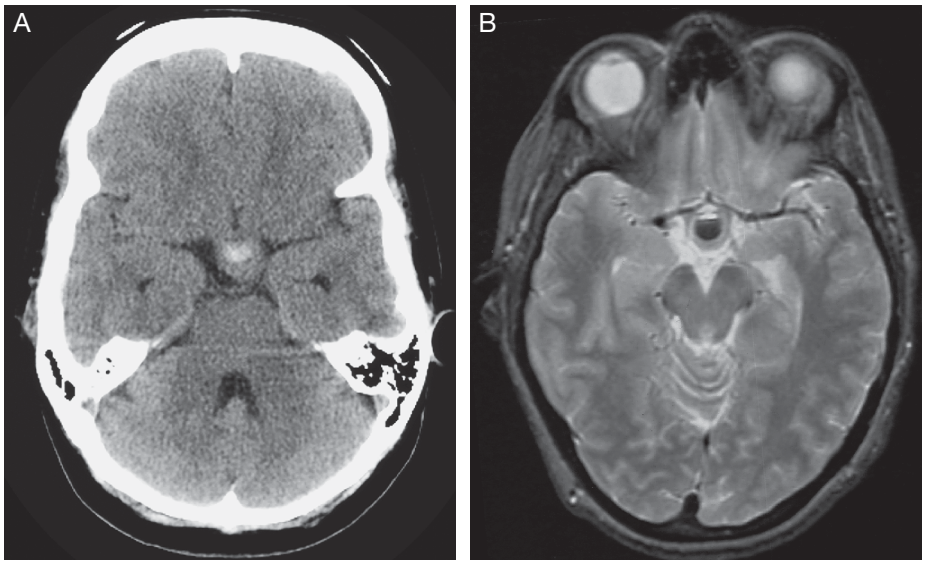

Figure 57.4 *A, Nonenhanced CT of a 37-year-old woman with history of sudden-onset headache, nausea, and vomiting shows area of high attenuation in sella turcica. The presentation is that of pituitary apoplexy, and the area of hyperintensity is actual hemorrhage into pituitary macroadenoma. B, T2-weighted MRI shows "level" of decreased T2 signal within pituitary gland consistent with the hemorrhage.*
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

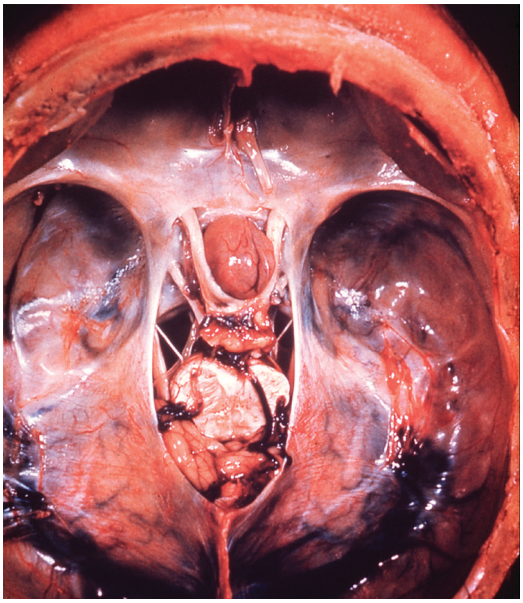

Figure 57.5 *Pituitary Macroadenoma In Situ (Postmortem Examination).*
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

macroadenoma when the tumor is greater than 1 cm (Figure 57.5). Adenomas have multiple patterns on histological examination, ranging from sheets to acini to perivascular arrangements. Usually, the tissue appears blue microscopically because of a high nucleus to cell ratio.

Treatment

Operation is indicated for pituitary apoplexy, symptomatic functioning microadenoma, and macroadenoma, such as prolactinoma **not** responding to dopamine agonists and associated with symptomatic regional mass effect. For residual or recurrent tumor, neurosurgery may be followed with stereotactic radiosurgery to control tumor growth. The most common risks associated with transsphenoidal resection include CSF leak and panhypopituitarism. Adrenal support is recommended in the perioperative and postoperative periods.

- Pituitary adenomas can be classified as *functional* and *nonfunctional* depending on whether the lesion is the primary source of a hormone produced in excess.
- Operation is indicated for pituitary apoplexy, symptomatic functioning microadenoma, and macroadenoma, such as prolactinoma **not** responding to dopamine agonists and associated with symptomatic regional mass effect.

Meningioma

Overview and Classification

Meningiomas, which arise from arachnoid cap cells of the meninges, account for approximately 30% of primary intracranial tumors and are the most common primary tumor affecting the CNS in adults. Most are WHO grade I, but WHO grade II and grade III meningiomas can occur as well. Meningiomas most frequently occur in middle age and peak in the sixth to seventh decades. A distinct female predominance exists, with the female to male ratio reaching 3.5:1 in the age range of 40 to 44 years. Spinal meningiomas are exceedingly more common in women than men; anaplastic and atypical meningiomas are more common in men.

Meningiomas are known to express receptors for estrogen, progesterone, and androgen. Their most common (40%–70%) cytogenic alteration is deletion of chromosome 22, although multiple other allelic gains and losses have been identified in association with meningioma. *NF2* gene mutations have been found in as many as 60% of sporadic meningiomas, resulting in a nonfunctional form of the merlin protein. Meningioma incidence has been linked closely to radiation exposure from the treatment of other primary tumors, especially when the radiation is delivered at high doses (>2,000 rad). Radiation-induced meningiomas tend to be multifocal high grade and to occur at an age younger than the general population, usually within 20 to 30 years after the radiation exposure.

Clinical Presentation

Patients may be asymptomatic or may present with long-term, progressive focal signs relevant to the location (intracranial vs spine). Occasionally, patients may present with seizure in addition to focal signs.

Diagnosis

The locations of meningiomas within the calvarium, in order of decreasing frequency, are parasagittal, cerebral convexities, sphenoid wing, olfactory groove, petrous ridge, tentorium, and optic nerve sheath. Anaplastic and atypical meningiomas arise most commonly from the cerebral convexities and falx. Spinal meningiomas are most commonly found at the thoracic level. MRI is most useful in diagnosis.

Meningiomas are dural-based and usually well circumscribed, and they avidly enhance with contrast medium on imaging. They are most often associated with a dural tail of enhancement extending from the tumor

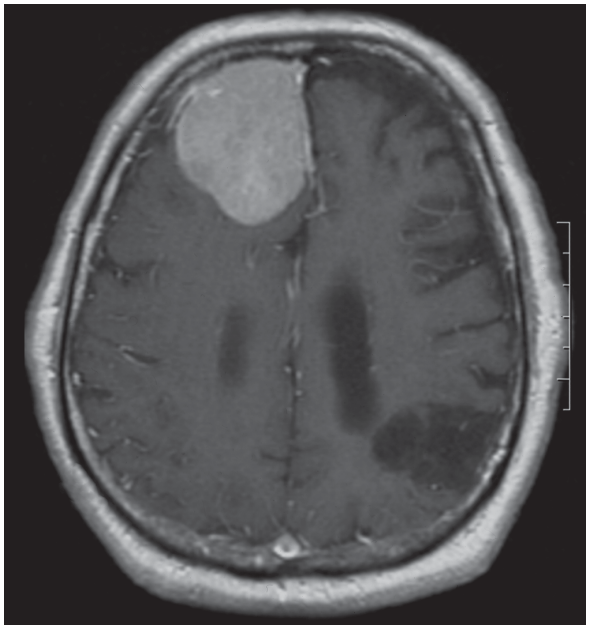

Figure 57.6 *MRI of a Large Right Frontal Meningioma With Characteristic Dural Tail and Near Homogeneous Enhancement (Gadolinium-Enhanced Axial T1-Weighted Sequence).*

(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

base laterally along adjacent dura. This characteristic is an important imaging feature useful in the radiologic differential diagnosis for extra-axial tumors. On MRI without contrast medium, meningiomas are T1 isointense to gray matter. T2 signal from the lesion differs considerably from 1 case to another (Figure 57.6). T2 signal change in the surrounding brain is seen occasionally and reflects some combination of chronic reactive gliosis to frank vasogenic edema. CT is useful for showing calcification within the lesion when diagnostic uncertainties exist.

Most meningioma subtypes are benign, with low risk of aggressive growth or recurrence after complete resection, and hence they are classified as *typical/WHO grade I*. Those with certain histologic features, such as brain invasion and mitotic activity, have greater likelihood of recurrence and aggressive growth and are classified as *atypical/WHO grade II* or *anaplastic/WHO grade III*. Of the many subtypes within each WHO grading classification, meningiomas of meningothelial, fibrous, and transitional characteristics are the most common, and all are grade I. Common histopathologic features of several meningioma subtypes are whorls and psammoma bodies interspersed among arachnoid-derived epithelioid cells, with pseudoinclusions created through nuclear membrane invagination (Figure 57.7). Grade III meningioma subtypes include papillary, rhabdoid, and anaplastic. Gross or microscopic invasion of brain is associated with lesions of WHO grades II and III, but involvement of dura and adjacent bone occurs frequently irrespective of subtype or grade, sometimes seen with overt bony destruction or, conversely, a pattern of marked hyperostosis.

Treatment

For all meningiomas, treatment options include surgical resection, fractionated external beam radiation, and stereotactic radiosurgery. The treatment choice depends on the tumor size and location and, when observation with serial imaging is not prudent, on such patient factors as age and overall health.

- Meningiomas, which arise from arachnoid cap cells of the meninges, account for approximately 30% of primary intracranial tumors and are the most common primary tumor affecting the central nervous system in adults.
- Common histopathologic features of several meningioma subtypes are whorls and psammoma bodies interspersed among arachnoid-derived epithelioid cells, with pseudoinclusions created through nuclear membrane invagination.

Hemangioblastoma

Overview

Hemangioblastoma, a rare neoplasm representing 1% of all primary CNS tumors, occurs sporadically. However, approximately 10% occur in the clinical context of von Hippel-Lindau disease, in which case the patient is more likely to be a child or young adult with more than 1 tumor, particularly in the cerebellum. Sporadic tumors usually arise in adulthood between the second and fifth decades, with equal incidence in women and men.

Clinical Presentation

Hemangioblastomas can arise in any part of the nervous system, but typically they occur within the cerebellar hemispheres, causing symptoms because of a posterior fossa mass effect. In extreme cases, the symptoms result from obstructive hydrocephalus and increased intracranial pressure. Because of the capacity of hemangioblastomas to produce erythropoietin, secondary polycythemia may occur.

Diagnosis and Treatment

A hemangioblastoma appears as a cystic mass in about three-quarters of cases. It is highly vascularized and

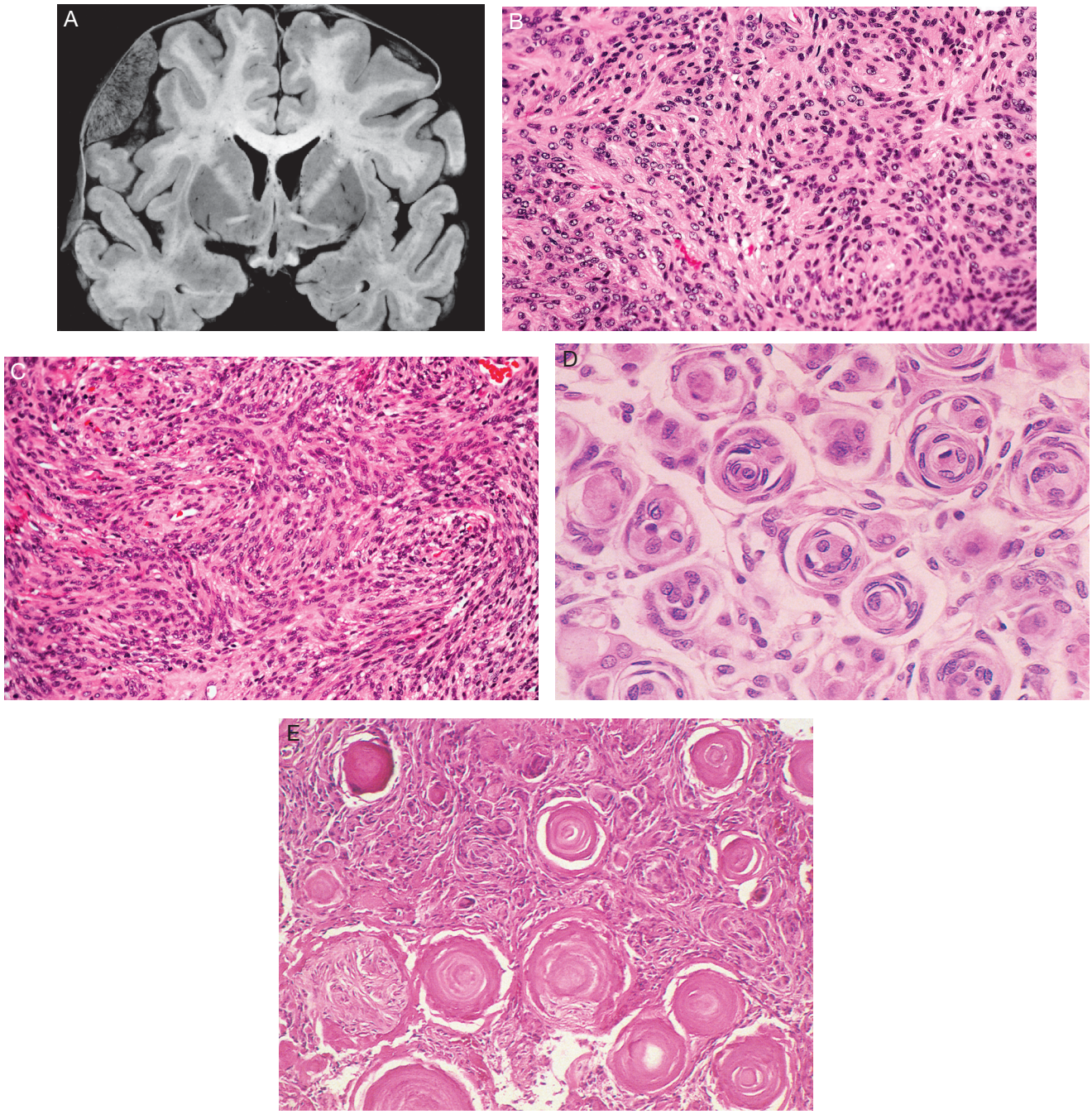

Figure 57.7 *A, Well-circumscribed meningioma attached to dura mater overlying left cerebral convexity. B and C, Meningothelial meningioma consisted of sheets of cells, some with pseudoinclusions that are nuclear membrane invaginations of the cytoplasm. D, An abundance of whorls is seen with transitional meningioma. E, Psammomatous meningioma is characterized by abundant psammoma bodies on a background filled with whorls.*

(A, Adapted from Okazaki H. Fundamentals of neuropathology: morphologic basis of neurologic disorders. 2nd ed. New York [NY]: IGAKU-SHOIN; c1989. p. 203–74. Used with permission. B and C, Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research. D and E, Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 131. Used with permission of Mayo Foundation for Medical Education and Research.)

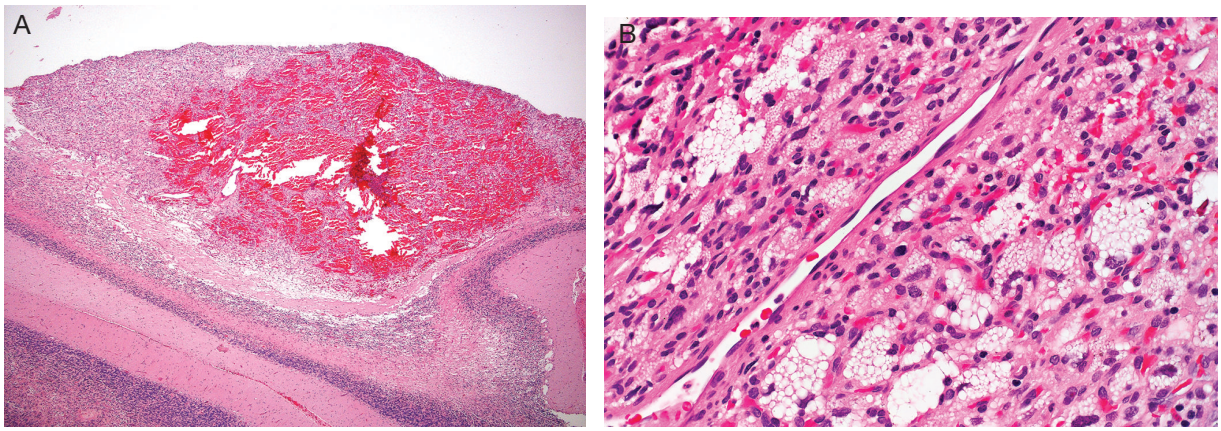

Figure 57.8 *Hemangioblastoma.*
A, Low-power view showing profoundly vascular tumor overlying the cerebellum. B, Fine vascular network of small capillaries and arterioles make this a vascular tumor. In the space between vascular channels are stromal cells with hyperchromatic nuclei and abundant cytoplasm containing lipids and glycogen.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

appears as a T2 hyperintense mass with an avidly contrast medium–enhancing mural nodule. The enhancing nodule is nearly always seen in some relation to a pial surface. Flow voids depicting enlarged feeding and draining vessels are frequently seen in association with the lesion. In the other cases, the tumor appears solid but retains an association with enlarged feeding and draining vessels.

Microscopically, the reticulin-containing vascular channels are intermixed among large, vacuolated stromal cells containing hyperchromatic nuclei and abundant lipid- and glycogen-filled cytoplasm (Figure 57.8).

Treatment is surgical resection of the mural nodule, which is curative of this WHO grade I tumor.

- Approximately 10% of hemangioblastomas occur in the clinical context of von Hippel-Lindau disease.

Hemangiopericytoma

Overview

Hemangiopericytoma is both highly vascular and cellular and is a rare, aggressive mesenchymal tumor classified as WHO grade II or as WHO grade III in the case of anaplastic hemangiopericytomas. Adherent to the dura of the skull or, rarely, the spine, hemangiopericytomas are solid lesions with a subtle predilection for the more posterior dura and venous confluences. For this reason, they are considered a mimic of meningioma. Hemangiopericytomas tend to arise in men more frequently than in women at a ratio of 1.4:1 and during the second to fourth decades.

Diagnosis

On MRI, hemangiopericytomas appear as T2 hyperintense and T1 isointense and as masses with intense contrast medium enhancement, often with flow voids depicting associated vessels (Figure 57.9). Histologically, they are composed of a monomorphous population of densely packed cells with scant cytoplasm interspersed among staghorn-shaped vessels (Figure 57.9).

The mainstay of treatment is surgical resection, with limited clinical response to radiation therapy. Screening for extracranial metastases is recommended, given the predilection for lung involvement. Their aggressiveness is reflected in recurrence rates as high as 90%.

Cystic Lesions of the CNS

Dermoid and Epidermoid

Overview

Dermoid and epidermoid tumors are slow-growing lesions that result from incidental inclusion of squamous epithelium in the leptomeninges, ventricles, or CNS parenchyma at the time of neural tube closure during gestation weeks 3 to 5. Both these entities are rare: Epidermoid tumors account for less than 1% of primary intracranial tumors, and dermoid tumors are even less common. Epidermoid tumors have rarely been documented to occur in the setting of repeated lumbar punctures causing traumatic penetration of skin fragments into the thecal sac.

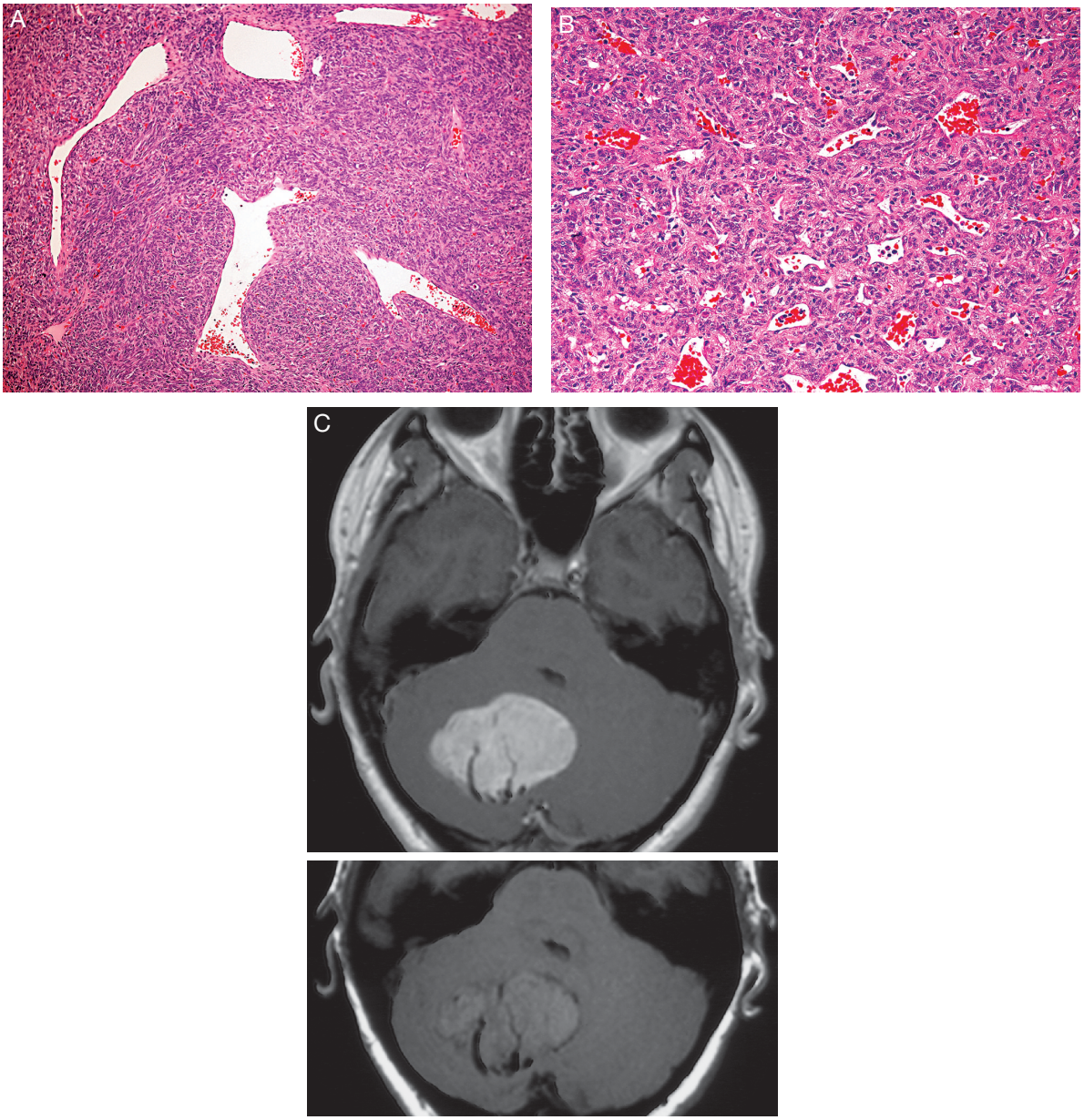

Figure 57.9 *Hemangiopericytoma.*
A, Sheets of densely packed cells with little cytoplasm are interrupted by small vascular (capillary) channels and larger vascular channels that have a branching "stag-horn" appearance, characteristic of this tumor. B, Higher magnification showing small vascular structures interrupting sheets of neoplastic cells. C, Well-circumscribed cerebellar tumor appearing isointense with the cerebellar cortex on nonenhanced T1-weighted image (bottom) and displaying intense enhancement on enhanced T1-weighted image (top), with prominent flow voids representing vascular channels.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

Dermoid lesions that are truly cystic are usually located at the midline, in association with some identifiable defect of the adjacent bone; when at the lumbosacral level, some identifiable defect may be present in the adjacent skin. Consequently, dermoid tumors most commonly occur at the conus medullaris, but parasellar, midline posterior fossa, and the fourth ventricle locations are well documented. Epidermoid tumors have a predilection for intracranial involvement of paramidline areas, such as the cerebellopontine angle, parasellar region, and cranial diploe.

Diagnosis

The MRI characteristics of a dermoid cyst reflect its contents: T1 hyperintense due to high lipid content with heterogeneous T2 hyperintensity. Epidermoid tumors are usually isointense on T1 and T2 but can have foci of T1 hyperintensity that correspond to areas of high cholesterol content. The marked hyperintensity seen in diffusion-weighted imaging (DWI) is notably diagnostic.

Epidermoid tumors are differentiated histologically from dermoid cysts in their sole composition of keratinized, stratified squamous epithelium with crystalized cholesterol. By comparison, the lining of dermoid cysts includes adnexa, such as sebaceous glands or sweat glands, or both, and hair follicles, in addition to calcifications and stratified squamous epithelium (Figures 57.10 and 57.11).

The treatment of both entities is surgical resection. At operation for dermoids, the inadvertent disruption of the cyst and spillage of contents into the subarachnoid space can result in severe aseptic meningitis. Malignant degeneration is rare.

Colloid Cyst

Colloid cysts arise at the foramen of Monro, between the columns of the fornix at the level of the anterior third ventricle (Figure 57.12). The gelatinous material in the round cyst is capsulated by cuboidal or columnar epithelium.

Colloid cysts occur in the third to fifth decades and have clinical presentations that can vary from acute-onset headaches exacerbated by bending over and Valsalva maneuver, drop attacks, abrupt intermittent mental status changes, or, rarely, sudden death. These symptoms are precipitated by hydrocephalus due to cyst blockage of the foramen of Monro in a ball-valve manner.

The MRI characteristics of the cyst differ on the basis of the density of its gelatinous contents, but its location establishes its diagnosis.

Surgical resection is curative.

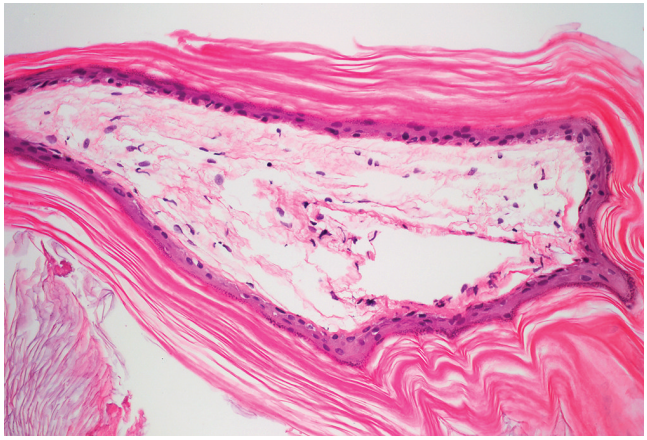

Figure 57.10 *Epidermoid Cyst.*
Note the characteristic keratinizing squamous epithelium lining the cyst.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

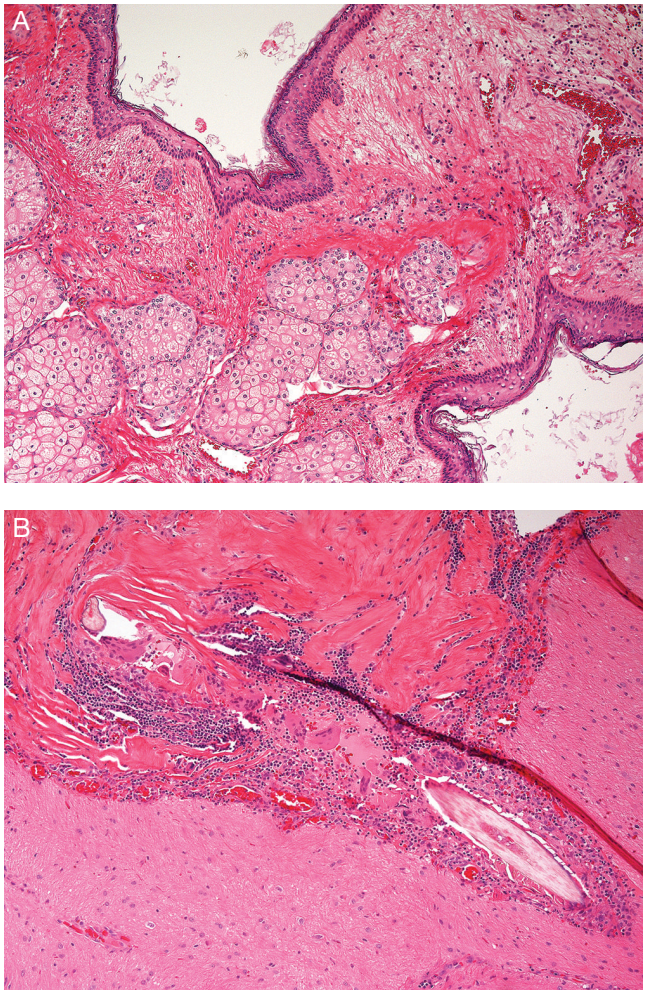

Figure 57.11 *Dermoid Cysts Are Lined With Stratified Squamous Call Epithelium (A), as Are Epidermoid Cysts. However, the distinguishing histological features of dermoid cysts are the presence of sebaceous glands (A) and hair follicles (B, oblique section of hair follicle).*
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

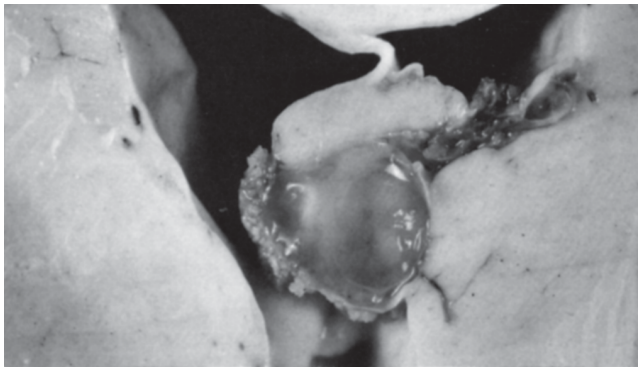

Figure 57.12 *Colloid Cyst of Third Ventricle.*
(Adapted from Okazaki H. Fundamentals of neuropathology: morphologic basis of neurologic disorders. 2nd ed. New York [NY]: IGAKU-SHOIN; c1989. p. 203–74. Used with permission.)

Arachnoid/Leptomeningeal Cyst

Arachnoid/leptomeningeal cysts are benign congenital anomalies secondary to cleavage of arachnoid membrane layers, comprised of thin walls not in communication with the subdural or subarachnoid space, and filled with clear fluid. Arachnoid cysts are more common in men.

Most arachnoid/leptomeningeal cysts are found incidentally, although some cause such symptoms and signs as headache, megaencephaly, and seizure or focal neurologic deficits due to compression of adjacent structures. Rarely, rupture may cause subdural hygroma.

A thin arachnoid layer comprising the cyst wall is appreciated microscopically. On MRI and CT, the clear fluid in the smooth cyst has density equivalent to CSF and does not enhance.

Treatment, if needed, is surgical resection, marsupialization, or shunting.

Pineal Cyst

Pineal cysts are benign, non-neoplastic, fluid-filled cavities within the gland. The contents can be proteinaceous or hemorrhagic fluid with compressed cords of normal pinealocytes encased by reactive astrocytes with Rosenthal fibers. These characteristics substantiate the chronicity.

These cysts are most commonly found in women 20 to 30 years of age and are rare before puberty or after menopause. They almost always are an incidental finding, and observation with serial MRI is the most common management approach.

- Colloid cysts occur in the third to fifth decades and have clinical presentations that can vary from acute-onset headaches exacerbated by bending over and Valsalva maneuver, drop attacks, abrupt intermittent mental status changes, to, rarely, sudden death.

Skull-Base Tumors

Chordoma

Chordoma is a rare, malignant tumor derived from remnants of the primitive notochord, thus arising in the axial skeleton within the clivus, vertebral bodies, or sacrum. The clival location is equally predominant in males and females, whereas the male to female predominance ratio is 2:1 for the sacral location.

Clinical Presentation

The peak incidence occurs in the fifth to sixth decades. Commensurate with involvement of the clivus and adjacent skull base, patients may report headaches, neck pain, and cranial nerve symptoms.

Diagnosis

On CT, bony destruction with abnormal calcifications is found. On MRI, the chordoma appears as a heterogeneous mass with nonuniform enhancement that is hyperintense on T2 and fluid-attenuated inversion recovery. On microscopic examination, the characteristic of vacuolated physaliphorous cells on a mucinous background is pathognomonic for chordoma (Figure 57.13).

Treatment

Treatment is en bloc surgical resection followed by radiation therapy, particularly proton therapy where feasible. The malignant nature of chordomas is reflected in their high recurrence rate and predilection for invading the adjacent skull base and its associated structures, such as the pituitary gland and the cavernous sinus.

Craniopharyngioma

Overview

Craniopharyngiomas are slow-growing tumors of WHO grade I, derived from the epithelium of the pharyngeal recess (Rathke pouch). Hence, they arise as a suprasellar mass from the superior aspect of the pituitary gland.

These tumors represent 1.2% to 4.6% of all intracranial neoplasms. They are the most common non-neuroepithelial intracranial tumor in children, representing 5% to 10% of intracranial neoplasms. The incidence of adamantinomatous craniopharyngioma occurs in 2 peaks: the first in children between ages 5 and 15 years and the second in adults between ages 45 and 60 years. The papillary variant incidence peaks between 40 and 55 years of age and is exceedingly uncommon in children.

Clinical Presentation

Because of its suprasellar location posterior or superior to the optic chiasm, a craniopharyngioma may first compress the crossing nasal fibers traveling superiorly within the optic nerve and chiasm, resulting in bitemporal lower

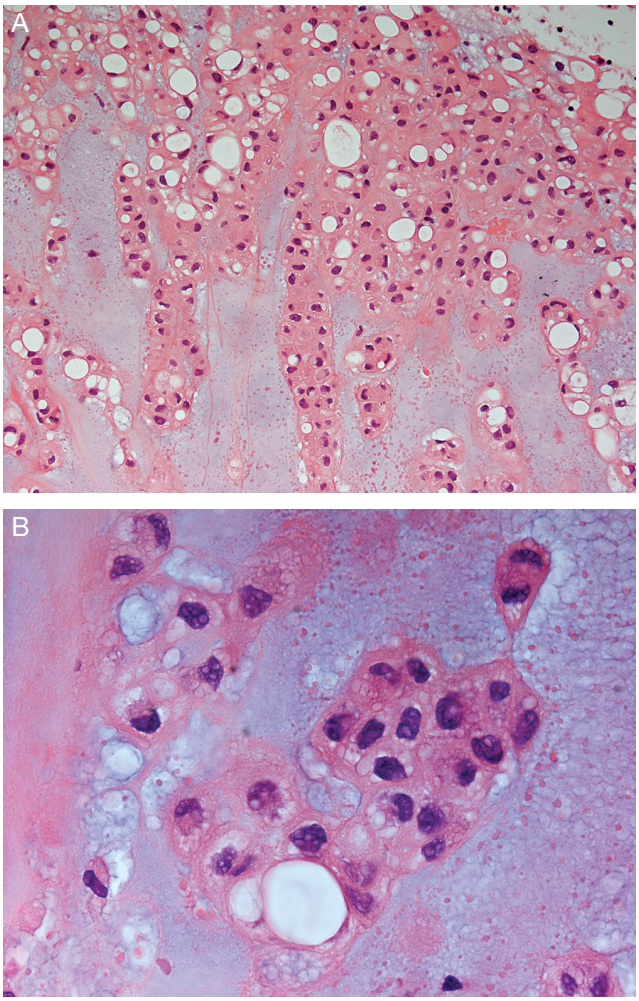

Figure 57.13 *A, Chordoma consists of strands of physaliphorous cells within a basophilic mucinous background.*
B, The cell cytoplasm contains vacuoles of various sizes.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

quadrantanopia with potential to progress to include the superior temporal quadrants. This progression of visual field loss is in contrast to the pattern incurred by an enlarging mass inferior to the optic nerve and chiasm, which causes compression on the inferiorly crossing nasal fibers and manifests as a bitemporal upper quadrantanopia, evolving to include the lower temporal quadrants. Other secondary clinical signs include headache, especially when obstructive hydrocephalus at the level of the third ventricle, and endocrinopathies due to compression of the pituitary stalk or gland, or both.

Diagnosis

With MRI, this suprasellar tumor typically appears hyperintense on T2-weighted images, with marked variation in patterns of enhancement (Figure 57.14). On T1-weighted images, cysts with a high cholesterol level may appear hyperintense.

Microscopically, craniopharyngiomas have 2 variants: adamantinomatous and papillary. The adamantinomatous variant is much more common and is composed of cords of stratified squamous epithelium bordered by palisading columnar epithelium in irregular trabeculae and formations of anuclear keratinocytes referred to as *wet keratin*. Although this variant typically appears to be a lobulated solid mass, it frequently is seen microscopically infiltrating into adjacent brain and firmly adherent to underlying nerves and vessels.

Craniopharyngiomas are mixed tumors with both solid and cystic components. The solid component may contain calcifications, especially of the outer rim; the cystic component contains a viscous, dark fluid referred to as *crankcase oil*. Inspection under polarized light allows visualization of the cholesterol crystals pathognomonic for adamantinomatous (*classic*) craniopharyngiomas. The papillary variant differs grossly by being well

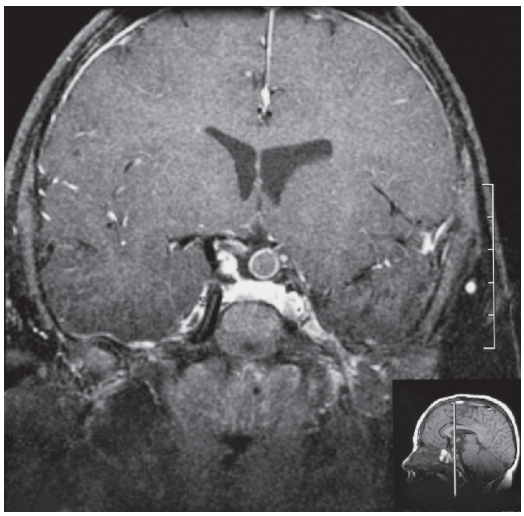

Figure 57.14 *Craniopharyngioma. Gadolinium-enhanced T1-weighted MRI shows ring-enhancing, partially cystic soft tissue nodule in left lateral aspect of suprasellar cistern. Pathologic features were consistent with craniopharyngioma. The ring enhancement may be due to peritumoral inflammatory response to cholesterol-rich cystic fluid.*
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

circumscribed without infiltrating borders and lacking cholesterol-rich, fluid-containing cysts and superficial calcifications. Microscopically, papillary craniopharyngiomas feature well-differentiated squamous epithelium without a palisading basal layer and no foci of wet keratin.

Treatment

Treatment is surgical resection, not only for definitive diagnosis and treatment but also to treat the obstructive hydrocephalus and secondary compressive symptoms. As with dermoid cysts, careful removal of the cyst contents is required to avoid chemical meningitis. Stereotactic radiosurgery can be considered for unresectable residual tumor.

- Chordoma is a rare, malignant tumor derived from remnants of the primitive notochord, thus arising in the axial skeleton within the clivus, vertebral bodies, or sacrum.
- Because of its suprasellar location posterior or superior to the optic chiasm, a craniopharyngioma may first compress the crossing nasal fibers traveling superiorly within the optic nerve and chiasm, resulting in bitemporal lower quadrantanopia with potential to progress to include the superior temporal quadrants.
- Craniopharyngiomas are mixed tumors with solid and cystic components. The solid component may contain calcifications, especially of the outer rim; the cystic component contains a viscous, dark fluid, referred to as *crankcase oil*. Inspection under polarized light allows visualization of cholesterol crystals pathognomonic for adamantinomatous (*classic*) craniopharyngioma.

Pineal Region Masses

Tumors that arise in the pineal gland and its vicinity are categorized into those arising from pineocytes (accounting for roughly 14%–27%) and those arising from embryologic remnants of primordial germ cells located in the axial skeleton and midline CNS (comprising the other 73%–86%).

Pineal region neoplasms are rare and account for less than 1% of all intracranial tumors. Germinoma is the most common tumor of the pineal region and represents approximately 60% of all CNS germ cell neoplasms. These prevalence data are different in Far Eastern Asia, where CNS germ cell tumors comprise 2% to 3% of all primary intracranial neoplasms. CNS germ cell tumors are most common in children and young adults, with 90% occurring in persons younger than 20 years at a male to female ratio of 2.0–2.5:1.0.

For any pineal region mass accompanied by hydrocephalus, a coordinated surgical approach is required because a third ventriculostomy may relieve hydrocephalus, averting the need for a shunt while affording an opportunity to biopsy and, possibly, to resect the mass in the same procedure.

Pineocytoma

Pineocytomas are rare, benign, slow-growing neoplasms composed of well-differentiated cells resembling pineocytes arranged in rosettes, highly reminiscent of normal pineal gland histologic characteristics. They are categorized as WHO grade I tumors.

Age at presentation is commonly between third and fourth decades and without sex predilection. Patients come to medical attention with reports of headache and visual or gait disturbance due to compression of the tectal plate and cerebral aqueduct.

On MRI, pineocytomas appear as hypodense or isodense on T1 and hyperintense on T2 with avid, homogeneous enhancement. Treatment is surgical resection and therapy for the obstructive hydrocephalus.

Pineoblastoma

In contrast to pineocytomas, pineoblastomas are highly malignant WHO grade IV tumors, derived from primitive embryonal cells. They are rare, accounting for approximately 40% of all pineal parenchymal tumors, which in and of themselves account for only one-quarter of the less than 1% incidence of pineal region tumors.

Pineoblastomas may arise at any age, but the majority of patients present in their first 2 decades, usually in childhood. There is no sex predilection. Symptoms are similar to other pineal region tumors, again due to local mass effect.

On MRI, the tumor appears isodense on T1 with heterogeneous enhancement.

Treatment is surgical resection followed by radiation and chemotherapy. Because of the potential for metastases within the CNS and spinal column, radiation of the entire neuraxis is indicated. Projected 5-year survival rates have been as high as 58%.

- In contrast to pineocytomas, pineoblastomas are highly malignant World Health Organization grade IV tumors, derived from primitive embryonal cells.

CNS Germ Cell Tumors

Germinoma

Overview

Germinomas occur most commonly in peripubescent males. The peak incidence is between 10 and 14 years old. They arise in the midline, in the vicinity of the third ventricle.

Clinical Presentation

Diabetes insipidus is the rule when germinoma involves the suprasellar region and is a helpful differential diagnostic clue when evaluating lesions in this region. Obstructive hydrocephalus, or at minimum ventriculomegaly, is also

exceedingly common because of cerebral aqueduct obstruction with pineal lesions. Oculomotor and pupillary symptoms and signs due to tectal region dysfunction or to compression of the optic nerve or chiasm, or both, may also present with pineal or suprasellar lesions, respectively. Involvement of the tectal plate can cause superior colliculus dysfunction leading to paralysis of upward gaze and convergence known by the eponym *Parinaud syndrome*.

Diagnosis

Germinomas may contain components of choriocarcinoma or endodermal sinus tumor, thus testing for placental alkaline phosphatase, β-human chorionic gonadotropin (β-hCG), and α-fetoprotein (AFP) can be useful diagnostically, albeit with low yield. CSF testing results are more sensitive and reliable, but in cases when CSF cannot be obtained safely, serum testing may be substituted. When present, these hormone levels are only mildly elevated, compared with nongerminomatous germ cell tumors.

Macroscopically, the tumor is soft and well circumscribed with occasional cystic features. Microscopically, sheets of large cells contain prominent nucleoli and glycogen-rich cytoplasm, with reactive lymphocytes intermixed. Imaging characteristics are strong enhancement on both MRI and CT; the tumor is isodense to cortex. A focus of central calcification can sometimes be appreciated, likely representing the engulfed pineal gland.

Treatment

Surgical intervention should be restricted to definitive tissue diagnosis through biopsy and, when needed, CSF diversion. High cure rates with radiation and chemotherapy of nearly 100% avert the need for resection. In 10% of cases, the presence of syncytiotrophoblastic cells, detected by β-hCG level, portends a slightly worse prognosis.

Teratoma

Teratomas occur as 2 variants: immature, containing at least in part poorly differentiated tissue, and mature, containing fully differentiated tissue. Teratomas consist of structures derived from ectoderm, endoderm, and mesoderm, thus mature teratomas may include skin, brain, bone, cartilage, fat, and muscle, in addition to cysts lined with respiratory or enteric epithelium, or both. Immature teratoma is diagnosed when the mass has any component of incompletely differentiated elements, most commonly mitotically active cells within hypercellular fields containing rosettes.

Serum AFP and carcinoembryonic antigen levels may be elevated. Those teratomas that are intra-axial occur more frequently supratentorially and typically present either antenatally or in the newborn period. These teratomas are large and result in an increasing head circumference and therefore cause difficulty at delivery.

Extra-axial teratomas are smaller and present in childhood or early adulthood. They occur at the same sites as germinomas—pineal and suprasellar regions—and thus can cause similar signs and symptoms related to compression, mass effect, and CSF flow obstruction. The incidence of teratomas in boys is even greater than germinomas. Radiographic features are variable because of the wide range of histological components of different densities and signal intensity.

Other Germ Cell Tumors

Other germ cell tumors, such as yolk sac/endodermal sinus tumors and choriocarcinoma, arise from extraembryonic tissue. They arise in structures surrounding the third ventricle, especially the pineal gland, and in the suprasellar region.

Yolk Sac Tumor

Yolk sac tumor, also known as *endodermal sinus tumor*, is composed of poorly differentiated epithelial cells in a loose, lacy structure. It contains Schiller-Duval bodies, eponymous for fibrovascular papillae surrounded by embryonal cells. Serum AFP and placental alkaline phosphatase testing can be purposeful for both diagnosis and monitoring treatment response. Endodermal sinus tumors are highly malignant and aggressive, occurring most frequently in girls and women within the first 3 decades. Typically, the tumor is large at presentation and predominantly solid, with extensive necrosis and hemorrhage. Treatment is surgical resection or debulking followed by chemotherapy.

Choriocarcinoma

Choriocarcinomas also arise from nonembryonic trophoblastic tissue, thus histologically, they are composed of malignant cytotrophoblasts and intermediate trophoblasts surrounded by multinucleated syncytiotrophoblasts. Only syncytiotrophoblasts are immunoreactive for β-hCG, the serum marker useful in diagnosis and treatment response or tumor recurrence. These cells frequently occur in association with other germ cell tumors. Choriocarcinomas are highly vascular, frequently with hemorrhage and necrosis. An aggressive and malignant tumor, choriocarcinoma is known for early hematogenous spread to the lungs. When it occurs as a systemic primary tumor, hemorrhagic metastasis to the brain is common.

Diagnostic Approach and Treatment in Germ Cell Tumors

Complete CNS staging is mandatory in all cases of CNS germ cell tumors because they have a predilection for CSF dissemination to all levels of the neuraxis, even at early disease stages. The CNS staging is to include MRI of the head and total spine with contrast medium, CSF cytologic evaluation, measurement of AFP and β-hCG levels in both serum and CSF, and laboratory studies of pituitary or hypothalamic hormones, or both. Obtaining CSF through

lumbar puncture may not be safe in all cases because of obstructive hydrocephalus.

The role of surgical operation is to provide adequate tissue for diagnostic confirmation, especially when laboratory levels are increased but not diagnostic. However, the value of gross total resection has yet to be proven because of the high risk of surgical morbidity in many cases. Treatment modalities include craniospinal radiation and chemotherapy. Nongerminoma and nonteratoma CNS germ cell tumors have a poor prognosis due to the high resistance to these modalities compared with the excellent prognosis for germinoma.

- Germinomas occur most commonly in peripubescent males and arise in the midline, in the vicinity of the third ventricle.

Miscellaneous Intracranial Tumors

Choroid Plexus Tumors

Overview

Primary neoplasms of the choroid plexus are choroid plexus papilloma (WHO grade I), atypical choroid plexus papilloma (WHO grade II), and choroid plexus carcinoma (WHO grade III). As a group, choroid plexus tumors account for 0.3% to 0.6% of all intracranial tumors across all age-groups; however, they account for 2% to 4% of all intracranial tumors in children younger than 15 years and 10% to 20% in infants up to 12 months of age. Papillomas occur 5 times more often than carcinomas.

Clinical Presentation

The majority (80%) of choroid plexus carcinomas occur in children. Although fourth ventricle tumors are evenly represented in all age-groups, approximately 80% of lateral ventricle tumors arise in persons younger than 20 years. Patients present with signs and symptoms related to CSF flow obstruction: megacephaly, decreased level of alertness, nausea, vomiting, headache, and visual impairment.

Diagnosis

On MRI, choroid plexus tumors usually are T1-isointense, T2-hyperintense, irregularly enhancing masses within the ventricles. Choroid plexus carcinomas are more likely to be associated with edema of adjacent brain; have foci of hemorrhage or necrosis, or both; and show evidence of disseminated tumor. Both on imaging and grossly, choroid plexus tumors have a cauliflowerlike appearance. Histologically, choroid plexus papillomas are comprised of thin fibrovascular cords bordered by uniform cuboidal cells with oval-to-round, basally situated nuclei (Figure 57.15).

Mitoses are rare, and necrosis brain invasion does not occur in choroid plexus tumors. By comparison, choroid plexus carcinomas histologically are densely cellular with loss of papillary arrangement replaced by sheetlike morphologic characteristics. Malignant features include necrosis, brain invasion, prominent nuclear pleomorphism, and brisk mitotic activity. Atypical choroid plexus papilloma is defined as choroid plexus papilloma with increased mitotic activity.

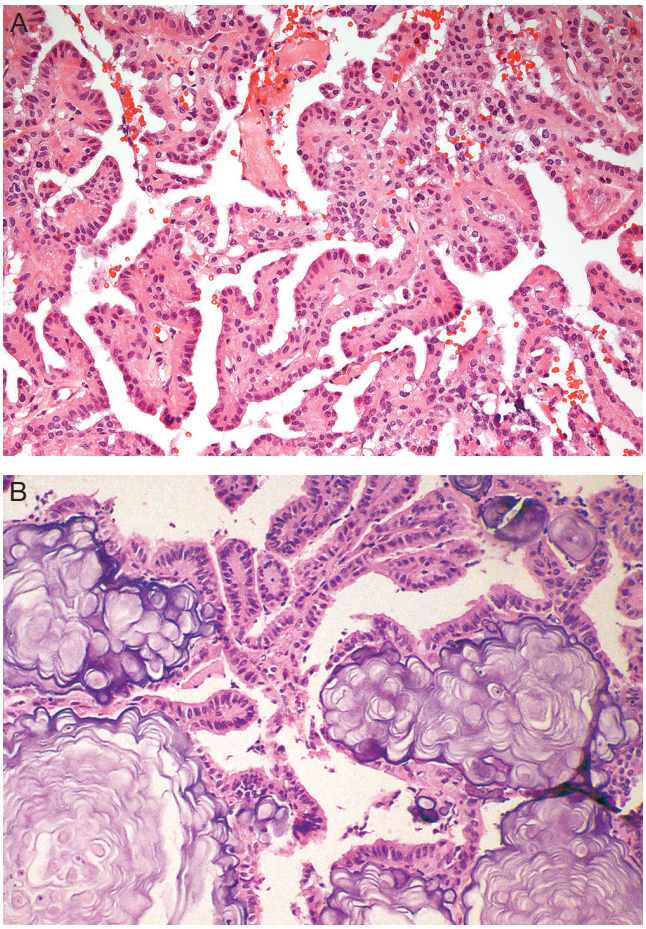

Figure 57.15 *Choroid Plexus Papillomas.*
A, Fibrovascular papillary structures characteristic of choroid plexus papilloma are lined with columnar epithelium. B, Stroma often contains foci of calcification, which is also observed on CT.
(A, Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research. B, Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 99. Used with permission of Mayo Foundation for Medical Education and Research.)

Treatment

Surgery for papillomas is curative. Five-year survival rates approach 100% with local control through gross total resection.

58 Spinal Cord Tumors

JOON H. UHM, MD

Introduction

Spinal tumors can be broadly classified on the basis of the anatomical compartment that they occupy. Regardless of location, because of the small confines of the spinal canal, significant neurologic morbidity can occur as a result of expansion of the cord, cauda equina, or both. Spinal cord neoplasms can be extradural, intradural extramedullary, or intramedullary (Table 58.1). In this chapter, each tumor will be summarized in regard to its pathophysiology, clinical features, imaging, and treatment.

Table 58.1 • Common Spinal Cord Tumors

Extradural	Intradural/ Extramedullary	Intramedullary
Metastatic disease (lung, breast, prostate) Rare: chordoma, sarcoma, lymphoma	Peripheral nerve sheath tumors Schwannoma Neurofibroma Meningioma Filum ependymoma	Astrocytoma Ependymoma Hemangioblastoma Metastases (lung, breast, melanoma)

Intramedullary Tumors

Ependymoma

Overview and Epidemiology

Ependymomas account for approximately 5% of all central nervous system tumors, with a much higher incidence in children than in adults. They can arise anywhere along the neural axis, but location is often predicted by age. In children, 90% of the tumors are intracranial and 10% affect the spine; of the intracranial tumors, two-thirds are infratentorial. In adults, approximately 75% of ependymomas affect the spinal canal. Ependymoma can sometimes be associated with neurofibromatosis 2 (NF2).

Clinical Presentation and Diagnosis

Clinical symptoms vary by tumor location. Infratentorial tumors can cause obstructive hydrocephalus, leading to symptoms of increased intracranial pressure, such as nausea, vomiting, and headaches. Tumors affecting the spinal cord parenchyma are often associated with pain, as the tumor's location along the central canal leads to pressure on decussating spinothalamic fibers. With progressive concentric growth, descending motor pathways can be affected, leading to paraparesis and bowel or bladder dysfunction.

The imaging method of choice is magnetic resonance imaging (MRI) with and without contrast. Tumors often appear to be well demarcated and have heterogeneous enhancement (Figure 58.1). In the posterior fossa, a characteristic feature is the extension of the tumor through the foramen of Magendie into the central canal and lateral extension through the foramen of Luschka into the cerebellopontine angle. In the spine, the tumors cause fusiform expansion of the cord. A mass along the filum terminale always raises suspicion of myxopapillary ependymoma. Regardless of tumor location, the entire neural axis should be imaged, as these tumors can (albeit rarely) seed distant spine or brain structures, given their proximity to the cerebrospinal fluid compartment. Imaging is best done preoperatively so as to avoid enhancement of the meninges, which can occur in the postoperative setting.

Abbreviations: MPE, myxopapillary ependymoma; MRI, magnetic resonance imaging; NF2, neurofibromatosis 2; PNST, peripheral nerve sheath tumor; VEGF, vascular endothelial growth factor; VHL, von Hippel-Lindau syndrome

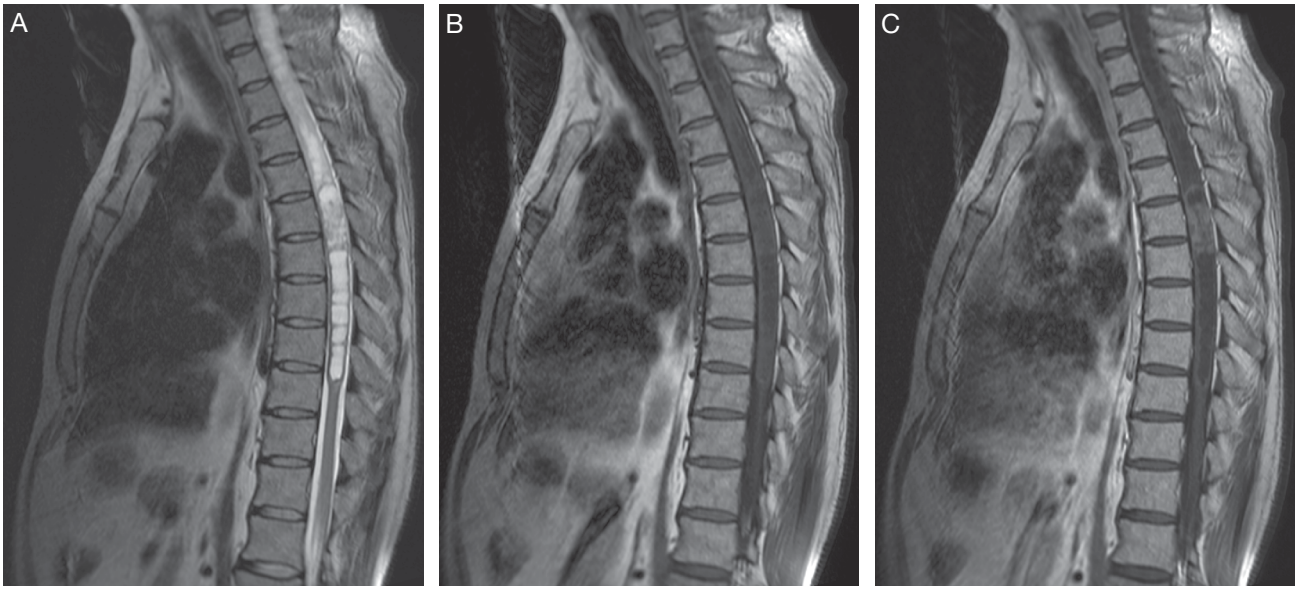

Figure 58.1 *Spinal Cord Ependymoma.*
Magnetic resonance imaging scan of the thoracic spine including T2 (A), T1 (B), and T1 with contrast (C) sagittal images shows an enhancing intramedullary mass at T5-T6 with cord expansion and associated syrinx.

On microscopy, tumors form sheets of uniform cells that radiate fibrillary processes toward blood vessels (forming pseudorosettes).

Treatment

Surgical resection constitutes the mainstay of therapy, as gross total resection offers chance of potential cure and avoids need for radiation. For residual and/or anaplastic ependymomas, radiation therapy prolongs survival. The role of chemotherapy is not established, but clinical trials are evaluating angiogenesis inhibitors; chemotherapy is reserved for patients in whom surgery and radiation options have been exhausted.

Astrocytoma

Histologically, astrocytomas that affect the cord are indistinguishable from those that affect the brain. Clinical symptoms are those of myelopathy of progressive onset. Imaging findings reflect the infiltrative behavior, with the tumor margins feathering into the cord parenchyma.

Unlike ependymomas that are well-demarcated tumors and amenable to gross total resection, the infiltrative nature of astrocytomas often precludes aggressive resection, and diagnosis is typically made by biopsy. After biopsy, radiation therapy constitutes the mainstay of treatment. Given the benefit of adding temozolomide chemotherapy to radiation therapy in treatment of supratentorial high-grade astrocytomas, this chemotherapy can be given with radiation for cord astrocytomas, although definitive clinical trial data supporting its use are not yet available.

Hemangioblastoma

Epidemiology

Hemangioblastomas are slow-growing vascular tumors that account for 3% to 13% of intramedullary spinal tumors. They typically occur in the fourth decade of life for sporadic tumors, but in the context of von Hippel-Lindau syndrome (VHL), tumors can occur earlier in life. VHL is a genetic condition in which there is a deficiency in degradation of an angiogenic factor (vascular endothelial growth factor [VEGF]), leading to relatively unopposed angiogenesis and formation of hemangioblastoma (as well as other vascular tumors, such as retinal angiomas and renal cell carcinoma). Although most hemangioblastomas are sporadic, the discovery of a hemangioblastoma in the cord should prompt the clinician to image the rest of the neural axis; if multiple tumors are found, then further investigation including abdominal imaging for renal carcinoma and possible genetic counseling regarding VHL is needed.

Diagnosis

On imaging, characteristic features include a cystic mass associated with an intensely enhancing nodule located eccentrically along the cyst wall. There can be significant T2 hyperintensity and sometimes a syrinx radiating rostral to the mass (Figure 58.2). Histologic features consist of numerous fine vascular channels.

Treatment

Surgical resection is the definitive treatment. For asymptomatic tumors, it is reasonable to observe with surveillance scans and intervene when the tumor enlarges or

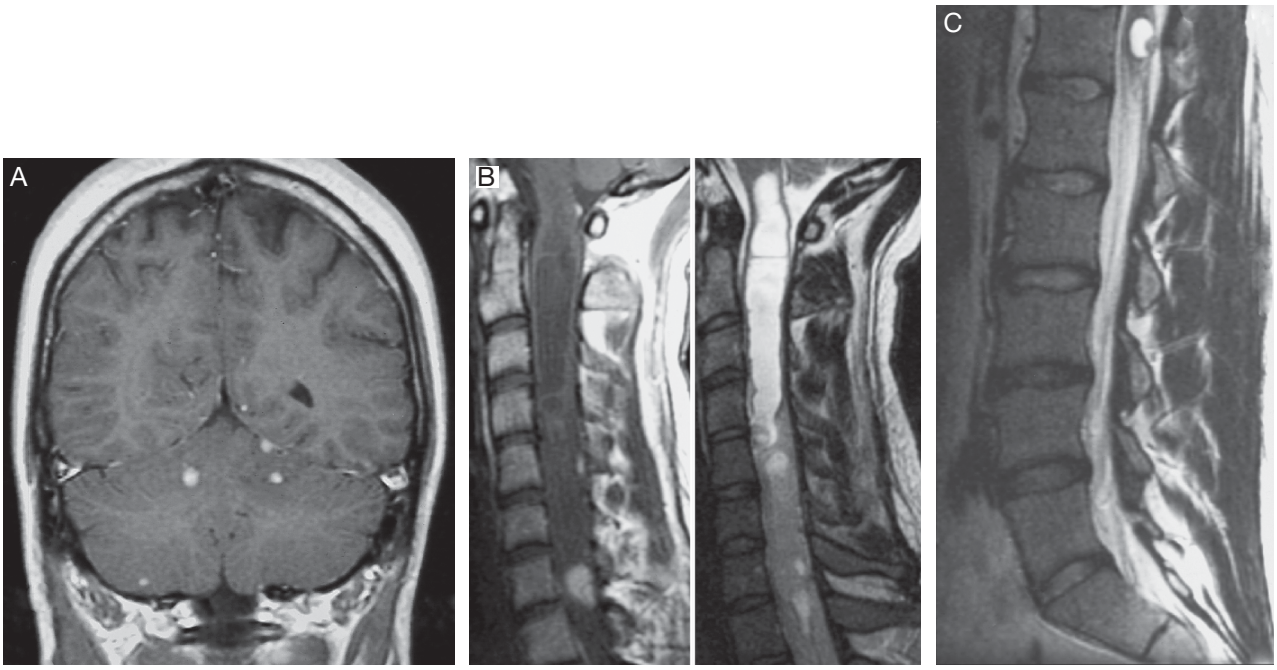

Figure 58.2 *Magnetic Resonance Images of Hemangioblastoma.*
A, Gadolinium-enhanced T1-weighted image showing multiple hemangioblastomas within cerebellar hemispheres bilaterally. B, Sagittal images (T2-weighted image on right and enhanced T1-weighted image on left) of the cervical spine of a patient with multiple hemangioblastomas showing a strongly enhancing tumor nodule at the level of vertebra C7 (left) and the associated large syrinx extending rostrally into the medulla (best seen on right). C, More typical appearance is that of a cystic lesion with a tumor nodule (strongly enhancing) (T2-weighted image).
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

starts to cause symptoms. Although radiotherapy has been tried, its role remains to be established in the treatment of hemangioblastomas. As yet, there is no clear role for chemotherapy, although a rational future direction involves targeting the angiogenic protein, VEGF, which is overexpressed in patients with VHL. Along these lines, clinical trials evaluating the VEGF inhibitor bevacizumab are ongoing. Whether targeting VEGF in sporadic hemangioblastoma is a viable option remains to be addressed.

Metastases

Metastasis of systemic tumors to the spinal cord parenchyma is rare, affecting 0.5% to 2% of all cancer patients. Most spine metastases affect the bone (eg, vertebral body, pedicle) to cause epidural cord compression. Cord parenchymal metastasis can occur from any primary systemic tumor, although the vast majority stem from tumors of the lung (50%), breast (10%), and melanoma (10%). Surgical resection is almost never a viable option because of the risk of worsening neurologic injury. If diagnosis of metastasis is suspect, then a biopsy can be considered. Radiation therapy is the preferred treatment modality. Chemotherapy use is limited to exquisitely chemosensitive tumors such as small cell carcinoma of lung or lymphoma. See also Chapter 60, "Metastatic Disease."

- In children, 90% of ependymomas are intracranial and 10% affect the spine; of the intracranial tumors, two-thirds are infratentorial. In adults, approximately 75% of ependymomas affect the spinal canal.
- Regardless of an ependymoma's location, the entire neural axis should be imaged, as these tumors can (albeit rarely) seed distant spine or brain structures, given their proximity to the cerebrospinal fluid compartment. Imaging is best done preoperatively so as to avoid enhancement of the meninges, which can occur in the postoperative setting.
- Hemangioblastomas typically occur in the fourth decade of life for sporadic tumors, but in the context of von Hippel-Lindau syndrome, tumors can occur earlier in life.

Intradural Extramedullary Tumors

Nerve Sheath Tumors

Peripheral nerve sheath tumors (PNSTs) can cause both a myelopathy (due to cord compression) and radiculopathy (due to compression of the spinal nerve root and extension into the neural foramen). Nonetheless, because of their slow growth rate, PNSTs are often asymptomatic.

Schwannomas

These tumors can arise sporadically or as a part of a genetic predisposition syndrome, NF2. Most schwannomas are incidentally discovered on spine imaging. These are well-circumscribed, homogeneously enhancing lesions. Small, asymptomatic lesions may be followed with surveillance imaging and treated if the lesion shows growth or starts to cause symptoms. The treatment of choice is surgical resection. See Chapter 59, "Peripheral Nerve Sheath Tumors," for additional details.

Neurofibromas

These tumors arise sporadically or as a part of neurofibromatosis 1. See Chapter 59, "Peripheral Nerve Sheath Tumors," for further details.

Meningiomas

Spinal meningiomas are more common in middle-aged women. The female to male ratio is higher for spinal meningiomas than for intracranial meningiomas.

From a clinical standpoint, the approach for spinal meningiomas is very similar to that for PNSTs. Like PNSTs, meningiomas are very slow-growing tumors and their symptomatology ranges from asymptomatic to symptoms of myelopathy, radiculopathy, or combined radiculomyelopathy, depending on size and location of tumor.

On imaging, they are typically homogeneously enhancing, well-circumscribed lesions (Figure 58.3). A radiographic feature (if present) that favors meningioma over PNST is the presence of enhancing dural tails, which is characteristic of meningiomas. Unlike PNSTs, meningiomas typically do not exit into the neural foramen. Most meningiomas are sporadic, but rarely they occur as a part of NF2, which should be considered in the context of multiple meningiomas. The great majority of meningiomas are benign (World Health Organization [WHO] grade I), but they can rarely transform to atypical (WHO grade II) or anaplastic/malignant (WHO grade III) forms.

Treatment of large and/or symptomatic tumors is surgical resection; radiation therapy is reserved for residual or inoperable tumors. The role of chemotherapy is limited.

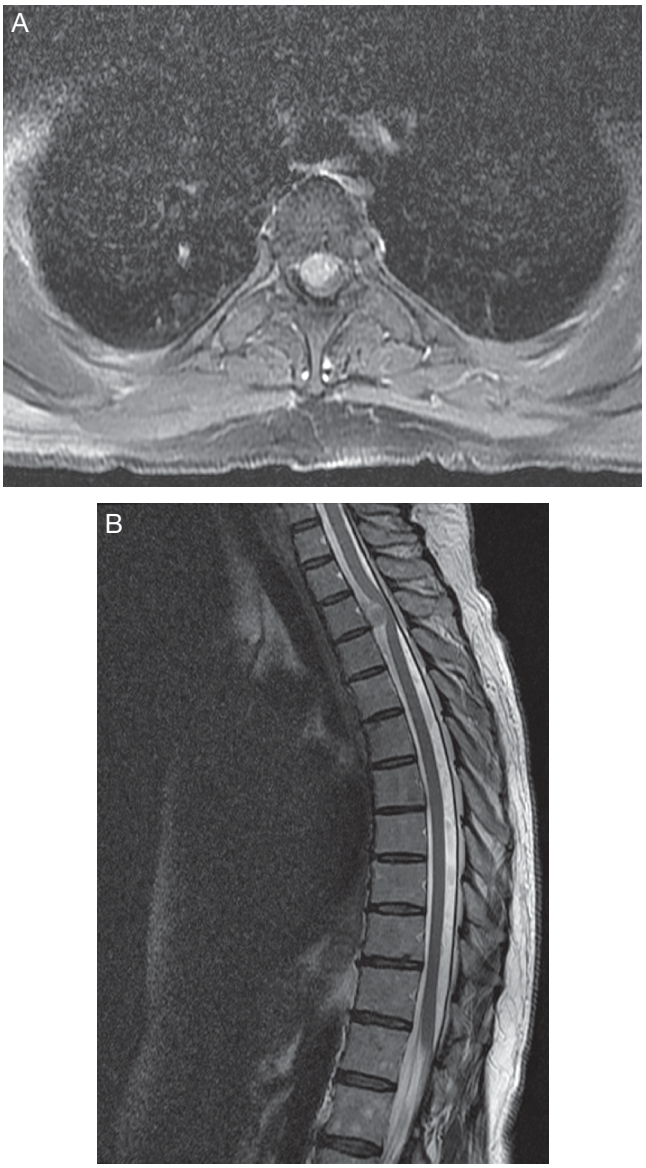

Figure 58.3 *Thoracic Spine Meningioma.*
Magnetic resonance imaging scan of the thoracic spine including T1 (axial) with gadolinium (A) and T2 sagittal (B) images reveals a 1×1.5-cm intradural extramedullary mass at T3 with associated cord compression.

Filum Ependymomas

Ependymomas that occur along the filum terminale and cauda equina comprise a distinct variant termed myxopapillary ependymomas (MPEs). The majority of MPEs are slow-growing tumors with a benign clinical course. MPEs can cause sensory and/or motor radiculopathic symptoms.

On imaging, they appear as heterogeneously enhancing, sausage-shaped masses arising from the filum terminale and involving the cauda equina. The *myxopapillary* prefix stems from the extensive papillary appearance admixed with mucin (*myxo-*) accumulation seen on microscopy.

Surgical resection is the most effective treatment. If gross total resection is not feasible, then radiotherapy is required for the residual tumor. While these are typically WHO grade I benign tumors, they can sometimes disseminate along the neural axis, leading to extensive coating of the leptomeninges with tumor. Imaging follow-up not only in the area of the cauda equina but periodic imaging of the entire neural axis is warranted in patients with residual tumor. The role of chemotherapy is limited.

- Because of their slow growth rate, peripheral nerve sheath tumors are often asymptomatic.
- The female to male ratio is higher for spinal meningiomas than for intracranial meningiomas.
- The majority of myxopapillary ependymomas are slow-growing tumors with a benign clinical course.

Extradural Tumors

Metastatic Disease

Overview

Extradural metastases occur at a very high frequency. At autopsy, vertebral metastases are seen in 45% of lung cancer patients, 75% of breast cancer patients, and as high as 90% of prostate cancer patients. The most critical point is early diagnosis and treatment, as this offers the best chance of averting neurologic morbidity.

Clinical Features

Back pain in a cancer patient, especially new or worsening pain, must be evaluated with a high index of suspicion of metastatic disease. Pain is often the earliest symptom of epidural metastasis, and in a great majority (>90%) of patients, it is the only symptom and offers a window of opportunity to diagnose and treat the patient so as to avert neurologic decline. Even in the absence of pain, percussion tenderness may be present on examination.

Diagnosis

Contrast-enhanced MRI is optimal for evaluation of suspected spine metastases. Plain radiographs are highly insensitive. In addition to MRI of the area suspected of being involved by tumor (eg, percussion tenderness or neurologic signs referable to that area), the entire spine should be imaged, as up to one-third of patients have multiple sites of epidural cord compression.

Management

For any patient with motor/sensory deficits, corticosteroids should be administered. A loading dose of 10 to 20 mg dexamethasone followed by 4 mg 3 or 4 times daily can be considered. Higher doses in the range of a 100-mg loading dose followed by 24 mg 4 times a day have been reported, but whether the higher doses offer a clear-cut clinical advantage is unclear and very high doses are associated with more adverse effects. See also Chapter 7, "Acute Spinal Cord Compression, Spinal Cord Trauma, and Peripheral Neural Injury."

Radiation therapy remains the mainstay of treatment. Once the area of epidural cord compression has been identified, radiation therapy should be started as soon as possible. Early diagnosis and treatment are critical, as ambulatory status at time of treatment highly correlates with ambulatory status after treatment. Patients who are ambulatory before radiation therapy have an 80% to 100% chance of being ambulatory after therapy. In contrast, of patients who have lost ambulatory status by the time treatment is started, only 2% to 6% are ambulatory after treatment.

A phase 3 study comparing surgery plus radiation vs radiation alone has shown improved outcome (ambulatory status after treatment) in carefully selected patients meeting the following criteria: single area of surgically accessible epidural tumor, life expectancy greater than 3 months, tumor not highly radiosensitive, and paraplegia not exceeding 48 hours. A surgical consultation should be considered for patients fulfilling these criteria, for patients who are receiving radiation but are clinically declining, or when there is a question of spinal instability due to metastatic disease.

Other Tumors

Other rare tumors such as chordomas, sarcomas, and lymphomas that affect the extradural compartment can radiographically resemble metastatic disease. In instances where a spinal tumor is identified on imaging but there is no personal history or systemic imaging (positron emission tomography or computed tomography) evidence of a systemic malignancy, then the spinal mass should be biopsied to obtain diagnosis.

- At autopsy, vertebral metastases are seen in 45% of lung cancer patients, 75% of breast cancer patients, and as high as 90% of prostate cancer patients.
- A loading dose of 10 to 20 mg dexamethasone followed by 4 mg 3 or 4 times daily can be considered for any cancer patient with motor/sensory deficits.
- Early diagnosis and treatment of epidural metastases are critical, as ambulatory status at time of treatment highly correlates with ambulatory status after treatment.

59 Peripheral Nerve Sheath Tumors

MARK E. JENTOFT, MD

Introduction

Nerve sheath tumors are those tumors involving the connective tissue surrounding a peripheral nerve. When they are found, a careful history and family history should be obtained to assess for association with neurofibromatosis 1 (NF1) or 2 (NF2) or other genetic disorders.

This chapter reviews the genetics, clinical features, diagnosis, and management of the common types of peripheral nerve sheath tumors. Features are also summarized in Table 59.1.

- When nerve sheath tumors are found, a careful history and family history should be obtained to assess for association with neurofibromatosis 1 or 2 or other genetic disorders.

Schwannoma

Overview and Genetics

Schwannomas are the most common type of peripheral nerve sheath tumor and are often solitary and sporadic unless associated with NF2 or schwannomatosis. Many sporadic schwannomas, though not syndrome related, do have a defect in the *NF2* gene on region 12 of the long arm of chromosome 22, which encodes for a protein called merlin. Schwannomas as a whole do not have a sex predisposition; however, studies report exceptions including a

Table 59.1 • A Comparison of Common Peripheral Nerve Sheath Tumors

Tumor	Genetics	Clinical Features	Pathologic Features
Schwannoma	Sporadic or NF2 (chromosome 22q12)	Intracranial: hearing loss, tinnitus, dizziness (cranial nerve VIII) Peripheral: palpable mass Spinal: pain, myelopathic symptoms	Spindle cell morphology Antoni A and B regions Verocay body
Neurofibroma	Sporadic or NF1 (chromosome 17)	Cutaneous palpable, nonpainful mass Can occur as extramedullary intradural tumor as well, with spinal symptoms	Spindle-shaped cells with elongated nuclei; collagen has "shredded carrot" appearance S-100–positive cells
Perineurioma	Can be associated with chromosome 22 abnormalities	Slowly progressive muscle weakness and atrophy in youth	"Pseudo-onion bulb" appearance
Malignant peripheral nerve sheath tumor	Sporadic or NF1 (chromosome 17)	Firm, rapidly growing mass of a peripheral nerve (pain and weakness of affected nerve)	Highly mitotic Cell crowding Nuclear enlargement Hyperchromasia

Abbreviations: EMA, epithelial membrane antigen; MPNST, malignant peripheral nerve sheath tumor; MRI, magnetic resonance imaging; NF1, neurofibromatosis 1; NF2, neurofibromatosis 2

female predominance for both intracranial schwannomas and cellular schwannomas. The tumors have a peak incidence between the fourth and sixth decades.

Clinical Presentation

Schwannomas often present as an asymptomatic palpable mass but may occasionally be painful. They can be subdivided by the location where they arise: peripheral, intracranial, intraspinal, and visceral. Peripheral schwannomas most often arise on the flexor surfaces of the extremities; however, they can also arise in the posterior mediastinum and retroperitoneum.

Intracranial schwannomas most commonly involve cranial nerve VIII and are termed acoustic or vestibular schwannomas (also known as acoustic neuromas). When present bilaterally, acoustic schwannomas are generally considered diagnostic for NF2 (see also Chapter 72, "Neurocutaneous Disorders"). Intracranial schwannomas generally arise at the transition point on the nerve between peripheral myelin (from Schwann cells) and central myelin (from oligodendroglial cells).

Intraspinal schwannomas may arise at any level and most commonly arise from sensory nerve roots. They may be intradural, extradural, or both. When both intradural and extradural, they often have a dumbbell appearance, as there is an expansile area on either side of the neural foramen. Visceral schwannomas are rare and most commonly occur in the stomach, though they have been described in other parts of the gastrointestinal tract as well as other organs.

Diagnosis

The diagnosis of an acoustic neuroma can be made with magnetic resonance imaging (MRI) with contrast (Figure 59.1). The acoustic neuroma is seen well on a contrast image as an intradural, extraaxial mass in the cerebellopontine angle. Some are intracanalicular only.

Peripheral schwannomas may be diagnosed by MRI of the affected area.

Pathologically, schwannomas are classified as conventional, cellular, melanotic, and epithelioid. They generally grow as discrete masses that are well encapsulated, originating within a nerve fascicle, expanding, and displacing the remaining fascicles of the involved nerve. The tumor is purely of Schwann cell differentiation and not composed of other nerve elements. Occasional axons may be entrapped within the tumor, but for the most part, schwannomas are relatively devoid of axons. Rarely, schwannomas may grow in a multinodular or plexiform pattern. These patterns occur most commonly in the head and neck and can be seen in both NF2 and schwannomatosis. Schwannomas are considered benign and only on very rare occasion undergo malignant transformation into a malignant peripheral nerve sheath tumor (MPNST).

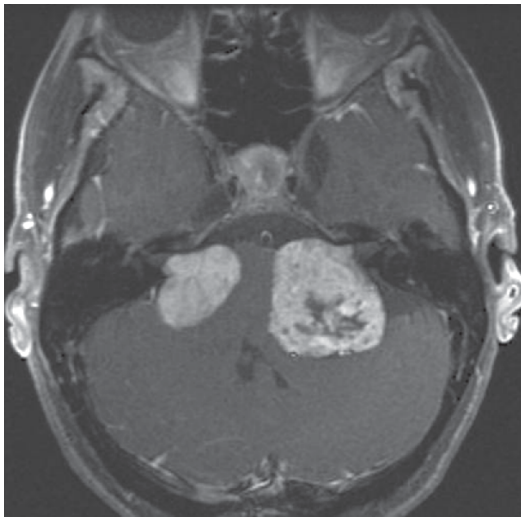

Figure 59.1 *Bilateral Acoustic Neuroma.*
Axial, T1 with contrast magnetic resonance imaging scan of the brain demonstrates bilateral enhancing, extraaxial tumors in the cerebellopontine angles consistent with neurofibromatosis 2.

Microscopically, the tumor cells have a spindle cell morphology and are surrounded by a fibrous capsule. Conventional schwannomas have alternating areas of hypercellularity (Antoni A areas) and hypocellularity (Antoni B areas) (Figure 59.2). The cell nuclei are often arranged in a palisaded pattern, which is termed a Verocay body. Schwannomas may have hyalinized blood vessels, cystic change, degenerative nuclear atypia, and collections of foamy histiocytes. Cellular schwannomas have a similar cellular morphology but contain only Antoni A areas and lack the hypocellular Antoni B regions. Melanotic schwannomas are very rare, contain melanin pigment, and most commonly involve the posterior spinal nerves. Reportedly up to one-fourth metastasize. A form of melanotic schwannoma called psammomatous melanotic schwannoma is a component of the Carney complex. Epithelioid schwannomas are also very rare and are characterized by their epithelioid morphology. They are considered benign and have similar staining characteristics as conventional schwannomas. Immunohistochemically, schwannomas stain positive for S-100 protein and will show a pericellular staining pattern for collagen IV, which highlights basement membrane. There is no staining of the tumor cells for epithelial membrane antigen (EMA) or neurofilament.

Management

Many schwannomas may be followed clinically, depending on the patient's symptoms, since many behave in a benign fashion and malignant transformation is rare. In the case of vestibular schwannoma, treatment options vary according

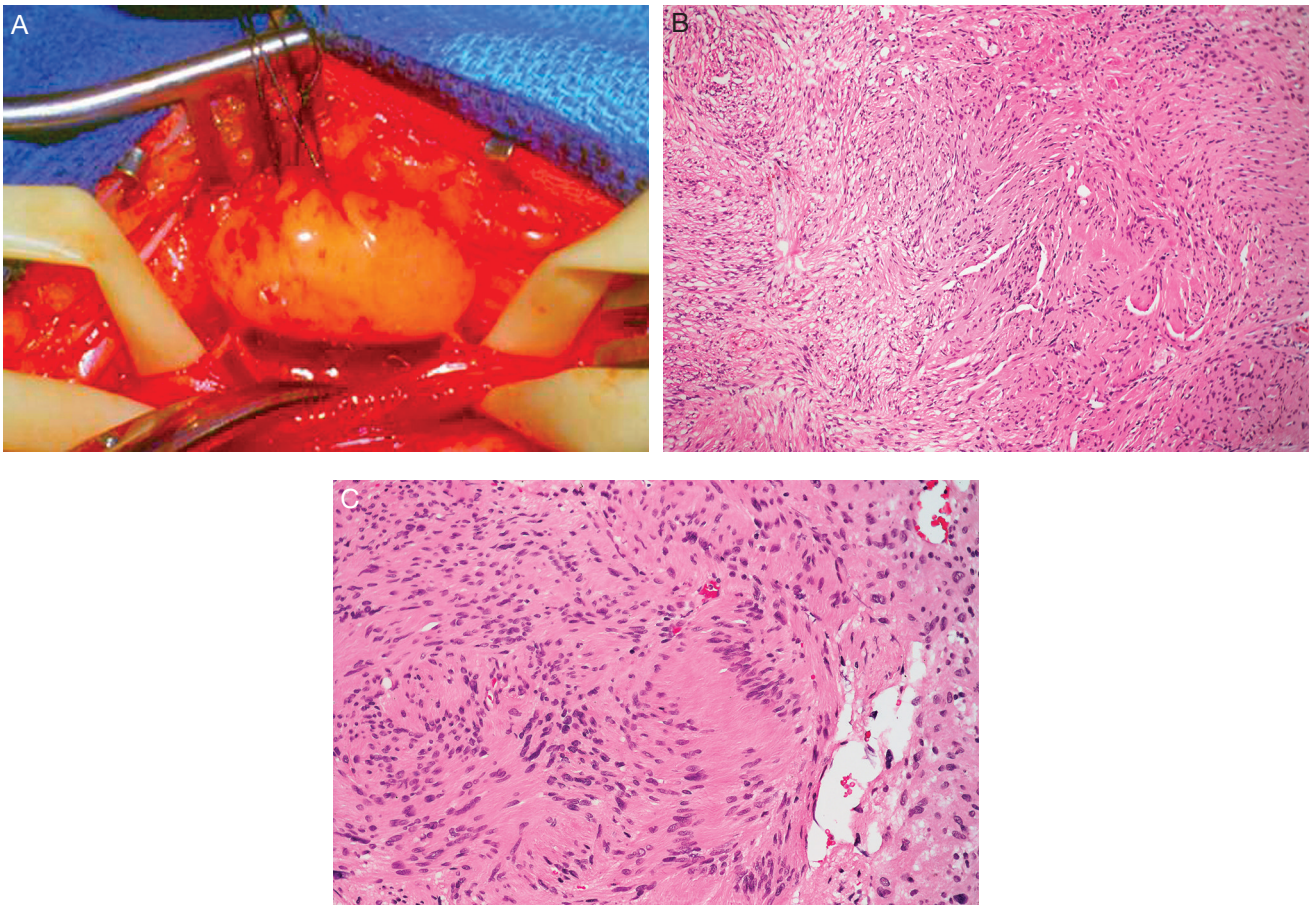

Figure 59.2 *Schwannoma.*
A, Schwannoma in situ appearing as well-encapsulated mass encasing nerve fascicle adjacent to preserved main nerve trunk. B, Histopathologic features include random Antoni A pattern (right) and Antoni B pattern (left) of cell arrangement. Antoni A pattern refers to palisading arrangement of spindle-shaped cells with elongated nuclei within tightly packed fascicles. Antoni B pattern is more loose, random arrangement of spindle-shaped cells within microcystic and myxoid background. C, Verocay bodies are columns of spindle-shaped cells with nuclear palisading, characteristically in Antoni A areas.
(A, Courtesy of Robert J. Spinner, MD, Mayo Clinic, Rochester, Minnesota. Used with permission. B and C, Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

to anticipated neurologic morbidity and hearing function. In the case of asymptomatic lesions with relatively well-preserved hearing, observation is typically recommended with serial contrast-enhanced imaging. If hearing has been significantly affected or if there are accompanying cranial neuropathies (cranial nerve VII of V), surgical resection or radiation therapy, or both, may follow.

- Intracranial schwannomas most commonly involve cranial nerve VIII and are termed acoustic or vestibular schwannomas (also known as acoustic neuromas).
- When present bilaterally, acoustic schwannomas are generally considered diagnostic for neurofibromatosis 2.
- The diagnosis of an acoustic neuroma can be made with magnetic resonance imaging with contrast.
- Schwannomas are considered benign and only on very rare occasion undergo malignant transformation into a malignant peripheral nerve sheath tumor.

Neurofibroma

Overview and Genetics

Neurofibromas are benign peripheral nerve sheath tumors that, unlike schwannomas, are composed of multiple cellular elements, which include Schwann cells, fibroblasts, and perineuriallike cells. Unlike schwannomas, which

have an expansile pattern of growth within nerves, neurofibromas have an infiltrative growth pattern within the parent nerve and thus may have numerous axons within them.

Neurofibromas can occur at any age and do not have a sex predilection. Most are sporadic and present as a superficial dermal or subcutaneous nodule. Neurofibromas also occur in the setting of NF1 and in this setting are often multiple. These patients have a defect in the *NF1* gene on chromosome 17, which encodes for a protein called neurofibromin (see also Chapter 72, "Neurocutaneous Disorders"). Neurofibromas may undergo malignant transformation into MPNSTs.

Clinical Presentation

Neurofibromas may have a localized, diffuse, or plexiform pattern of growth and be present within the skin (cutaneous), nerve (intraneural), or soft tissues. Cutaneous examples may be localized or diffuse, intraneural examples are localized or plexiform, and soft tissue examples tend to have a diffuse pattern of growth. Localized cutaneous neurofibromas are often painless and present as a palpable, freely movable mass. They are often solitary and sporadic unless present in the setting of NF1. Diffuse cutaneous neurofibromas are uncommon and often present with plaque-like thickening of the skin due to the permeative pattern of growth within the dermis and subcutaneous tissues. They are most commonly found in the head and neck region in children and young adults. Localized intraneural neurofibroma often presents with tingling or pain and is usually a superficially situated palpable mass as a result of fusiform enlargement of the involved nerve or nerve trunk. Plexiform neurofibromas are intraneural, involve multiple fascicles of the affected nerve, and grossly have a "bag of worms" appearance. Plexiform neurofibromas are virtually pathognomonic of NF1 when larger nerves are involved. They can also be associated with some diffuse growth (infiltration) into surrounding soft tissue. Massive soft tissue neurofibromas are characterized by a diffuse pattern of growth within the soft tissues, often causing localized enlargement of the affected area. In addition to the diffuse pattern of growth, massive soft tissue neurofibromas often contain a component with a plexiform growth pattern. These lesions are highly associated with NF1.

Diagnosis

The diagnosis of neurofibroma is generally made by clinical examination, MRI, and pathologic examination when necessary.

Microscopically, neurofibromas have a variable appearance but typically have a low cellularity and are made up of spindle-shaped cells that contain elongated wavy nuclei that have tapered ends (Figure 59.3). The spindle cells are within a background that typically is loosely arranged, often with a myxoid appearance with a varying amount of collagen deposition. This collagen often has a characteristic appearance that has been likened to shredded carrots. The tumor cells are S-100 positive. EMA staining is generally negative within the tumor, despite the presence of "perineuriallike cells"; however, it will

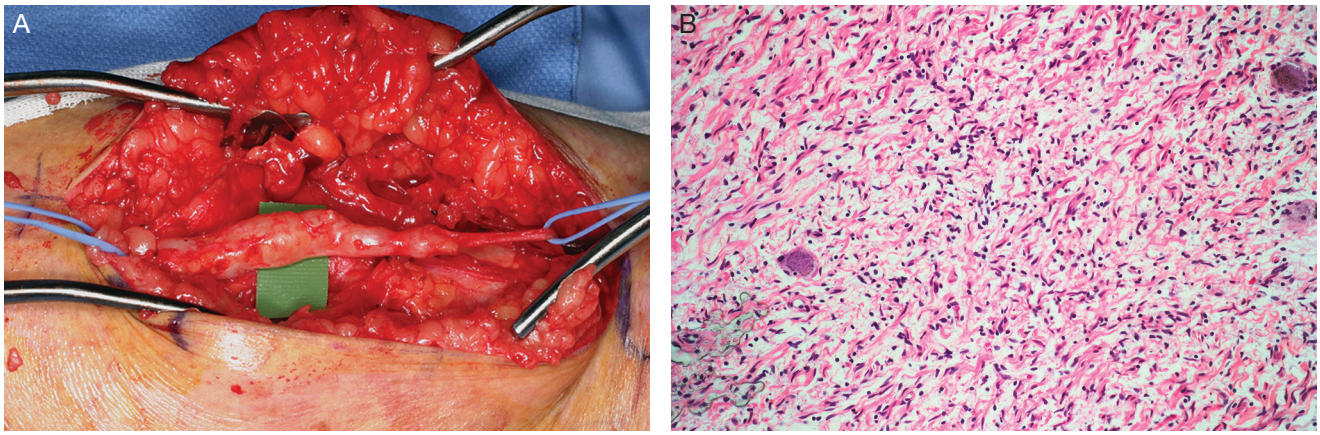

Figure 59.3 *Neurofibroma.*
A, Neurofibroma in situ. Note fusiform enlargement of affected nerve from infiltrative nature of tumor (sural nerve; left, proximal; right, distal). B, Histopathologic features include haphazard arrangement of spindle-shaped wavy cells in myxomatous and mucoid stroma or in between collagen fibers.
(A, Courtesy of Robert J. Spinner, MD, Mayo Clinic, Rochester, Minnesota. Used with permission. B, Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

highlight residual perineurium from an involved nerve fascicle.

Occasionally, neurofibromas are designated as atypical neurofibromas. These have some atypical histologic features but do not meet the criteria needed for a diagnosis of MPNST. These lesions should not be considered malignant.

Management

Treatment of neurofibromas may depend on symptoms and type of neurofibroma. The threshold for surgical excision of a solitary neurofibroma is low if the tumor is painful, has associated neurologic deficits, or demonstrates increased growth. Additionally, tumors such as plexiform neurofibromas that occur in the setting of NF1 have an increased risk of malignant transformation and warrant consideration for surgical excision, depending on the clinical situation.

- Neurofibromas occur in the setting of neurofibromatosis 1 and in this setting are often multiple.
- Neurofibromas may undergo malignant transformation into malignant peripheral nerve sheath tumors.

Perineurioma

Overview and Genetics

Perineuriomas are benign neoplasms that are entirely composed of perineurial cells and may be either intraneural or present in soft tissue. Interestingly, both patterns are associated with chromosome 22 abnormalities.

Clinical Presentation and Diagnosis

Perineuriomas often present in late adolescence and early adulthood and are not known to have a sex predisposition. Patients often present with slowly progressive (months to years) muscle weakness and may have associated muscle atrophy. The tumor causes fusiform expansion of the affected nerve due to a proliferation of perineurial cells.

The perineurial proliferation occurs around single axons within the affected nerve, giving rise to the microscopic appearance termed pseudo-onion bulbs. The perineurial cells wrap in layers around the axon similar to the layers of an onion. This has a somewhat similar microscopic appearance, albeit different pathologic features, to some hypertrophic neuropathies. The perineurial cells that make up the neoplasm stain positive for EMA. Neurofilament staining can be used to highlight the axons within the tumor and S-100 staining will highlight associated Schwann cells, but results with both of these methods will be negative within the tumor cells. Surgical resection of the tumor is curative; however, if there is residual function within the affected nerve, this may be taken into consideration prior to surgery.

Soft tissue perineuriomas are composed of perineurial cells but do not arise from identifiable nerves. They are more commonly found in females and typically occur in middle age. They present as a rounded, well-demarcated mass within the soft tissues. Although these lesions are well demarcated, they are not encapsulated. Microscopically, they are composed of cells with elongated nuclei with tapered ends. No pseudo-onion bulbs are present, but rather these tumors often have a fascicular or storiform pattern of growth. Like their intraneural counterparts, they stain positive for EMA and are cured by complete excision.

Malignant Peripheral Nerve Sheath Tumor

MPNST is a malignant neoplasm that arises from peripheral nerve or demonstrates nerve sheath differentiation. These tumors are rare and approximately half arise in the setting of NF1. More than half arise from a preexisting neurofibroma, most commonly a plexiform neurofibroma. MPNST arising from another type of tumor such as schwannoma or ganglioneuroma can occur, but is rare. MPNST more often occurs in women than men and has a peak incidence between the third and sixth decades of life, with the mean age being younger in patients with NF1 than in sporadic cases.

MPNSTs most commonly affect medium and large peripheral nerves and present as a firm, rapidly growing mass that results from the enlargement of the involved nerve; most tumors are larger than 5 cm. They also often cause associated pain and progressive neurologic deficit.

Most MPNSTs are high-grade neoplasms that have high mitotic activity and areas of necrosis; fewer are lower grade. Histologically, 3 features distinguish an MPNST from benign nerve sheath tumors: cell crowding, nuclear enlargement (greater than 3 times the size of a neurofibroma nucleus), and hyperchromasia.

MPNSTs have an aggressive behavior and require wide local excision and, at times, limb amputation. Radiation therapy with or without chemotherapy is also often used. Even with treatment, there is a high rate of recurrence, and poor prognostic signs include increased tumor size (>5 cm), NF1, and incomplete excision.

- Malignant peripheral nerve sheath tumors have an aggressive behavior and require wide local excision and, at times, limb amputation. Radiation therapy with or without chemotherapy is also often used.

60 Metastatic Disease

ALYX B. PORTER, MD

Introduction

Intracranial metastases are the most common brain tumors in adults and outnumber primary brain tumors by 10 to 1. Nearly 170,000 new cases of intracranial metastases are diagnosed per year in the United States, and these metastases have become the most common neurologic complication of cancer. Intracranial metastases are occurring with increased frequency as a result of improved therapies for systemic cancers that extend survival.

Most patients with brain metastases have lung cancer as the primary malignancy, followed in frequency by breast, melanoma, renal cell, and thyroid cancers. The prognosis when brain metastases are detected varies on the basis of the underlying cancer type. For example, a patient with brain metastases from inflammatory breast cancer may have a longer survival than a patient who has brain metastases with triple negative breast cancer, in which chemotherapeutic efficacy is limited.

This chapter reviews the approach and management of brain and spinal cord metastases. A summary of common primary tumors that metastasize to the brain is shown in Table 60.1.

- Intracranial metastases are the most common brain tumors in adults and outnumber primary brain tumors by 10 to 1.
- Most patients with brain metastases have lung cancer as the primary malignancy, followed in frequency by breast, melanoma, renal cell, and thyroid cancers.

Pathophysiology

Intracranial metastases are thought to spread through the arterial circulation and aggregate in capillaries that form at the gray matter–white matter junction. From that point, the cancer deposits interact with the endothelium and extravasate into the surrounding parenchyma. Each metastasis forms aberrant vasculature, causing blood-brain barrier permeability. The majority of brain metastases are found in the cerebral hemispheres and the cerebellum, followed in frequency by the brainstem. Pelvic and gastrointestinal tract tumors tend more commonly to metastasize to the posterior fossa than other tumor types.

Table 60.1 • The Most Common Types of Metastases in Descending Frequency of Primary Cancer

Brain Metastases	Hemorrhagic Metastases	Spine Metastases
Lung	Lung	Breast
Breast	Melanoma	Prostate
Melanoma	Renal cell	Lung
Renal cell	Thyroid	Renal cell
Thyroid	Choriocarcinoma	Myeloma
		Non-Hodgkin lymphoma

Clinical Presentation

Clinical presentation of brain metastases differs on the basis of tumor location and the extent of surrounding edema. Up to one-third of patients may be asymptomatic. Presenting symptoms may include a syndrome of increased intracranial pressure consisting of nocturnal headache, lethargy, nausea, vomiting, and altered mental status. Patients also may have focal symptoms, such as hemiparesis, visual field defects, seizures, or language disturbance.

Abbreviations: AED, antiepileptic drug; CNS, central nervous system; CT, computed tomography; KPS, Karnofsky performance status score; MRI, magnetic resonance imaging; RPA, recursive portioning analysis; RT, radiation therapy; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy

In some cases, the presenting symptoms and imaging may be most consistent with hemorrhagic stroke, requiring follow-up and contrast medium–enhanced imaging to exclude the possibility of an underlying mass lesion. In this instance, lung cancer, melanoma, renal cell cancer, thyroid cancer, and choriocarcinoma are the most common systemic cancers to present as a hemorrhage.

- The most common systemic cancers to present as a brain hemorrhage are lung cancer, melanoma, renal cell cancer, thyroid cancer, and choriocarcinoma.

Diagnosis

Contrast medium–enhanced imaging is the gold standard for detecting metastatic disease (Figure 60.1). On computed tomography (CT), the expectation is to see an isodense or hyperdense lesion in the gray matter–white matter junction, with surrounding vasogenic edema, mass effect, and, possibly, hemorrhage. After intravenous contrast dye is administered, the mass may be more clearly identified and could have a homogeneous appearance or a more heterogeneous appearance resembling a ring-enhancing lesion. Gadolinium-enhanced magnetic resonance imaging (MRI) is the gold standard of imaging when brain metastases are suspected. Approximately 75% of patients with intracranial metastases are found to have multiple lesions, and MRI is most sensitive in detecting these changes.

Treatment

Radiation Therapy

Unfortunately, besides the prophylactic cranial irradiation used in patients with non–small cell lung cancer, nothing can be done to prevent intracranial metastases. The treatment mainstay for intracranial metastases is based on radiation therapy (RT). The majority of patients with metastatic brain tumors eventually receive whole-brain radiation therapy (WBRT). Typically, WBRT is administered over 2 weeks and to a dose of 30 Gy. This treatment may be in addition to surgery or chemotherapy. Cognitive impairment after WBRT is the most commonly encountered adverse effect. The degree of impairment ranges from mild memory difficulties to dementia. Studies have looked at ways to reduce this complication, though little has been shown to decrease the frequency of its occurrence. Patients with cancer may have many reasons for impaired cognition, and when this report arises, thoughtful investigation should follow. Acetylcholinesterase inhibitors, *N*-methyl-D-aspartate receptor antagonists, and psychostimulants may be helpful.

Stereotactic radiosurgery (SRS) is another method for delivering radiation to metastatic brain tumors and requires a neurosurgeon for stereotactic head frame placement, in addition to MRI or CT. SRS allows precise delivery of a high dose of radiation to a defined target and is associated with less risk of treatment-related toxicity. SRS has a greater tumor-killing potential than WBRT and may be more effective against radioresistant tumors. SRS is preferred when 1 to 3 tumors have been found and measure less than 3 cm. Multiple lesions can be treated within a single session, and SRS can be useful in treating surgically inaccessible tumors. Occasionally, patients with brain metastases are treated with both WBRT and SRS. Some of the potential adverse effects of using both forms of radiation involve a higher risk of permanent brain damage, in addition to radiation necrosis.

Survival with RT is based on recursive portioning analysis (RPA). In patients younger than 65 years who have a good Karnofsky performance status (KPS) score (RPA class I), the median survival with WBRT is 7.1 months. RPA class II includes patients who are older than 65 years with a poor performance status (KPS score <70), and the median survival for this population is on the order of 2.3 months. RPA class III includes patients whose disease does not fit RPA class I or II, and the estimated median survival is 4.2 months.

Chemotherapy

In addition to treatment of the brain metastases with RT, patients may require treatment for systemic cancer. This treatment is often in the form of chemotherapy. Some chemotherapy drugs are helpful in treating brain metastases, though the options continue to be limited to small lipophilic agents because of the blood-brain barrier. Drugs such as temozolomide, nitrosoureas, irinotecan, topotecan, high-dose methotrexate, cytarabine, idarubicin, and etoposide have been shown to have central nervous system (CNS) penetrance.

For treatment of brain metastases in the clinical setting of non–small cell lung cancer, temozolomide and gefitinib may be useful. Lapatinib and trastuzumab have been shown effective in reducing CNS disease in the clinical setting of breast cancer. Cisplatin-based regimens have been effective in the treatment of germ cell tumors.

Neurologic Symptom Management

Management of neurologic symptoms caused by intracranial metastases may prove challenging. Of patients with intracranial metastases, 20% present with seizures. Prophylactic antiepileptic drug (AED) use in the clinical setting of brain metastases is discouraged, given its ineffective prevention of first seizures and untoward adverse effects. AEDs that induce the cytochrome P450 system should be avoided because of interference with corticosteroid treatment and chemotherapy. Newer agents should be considered, such as levetiracetam, topiramate, lacosamide,

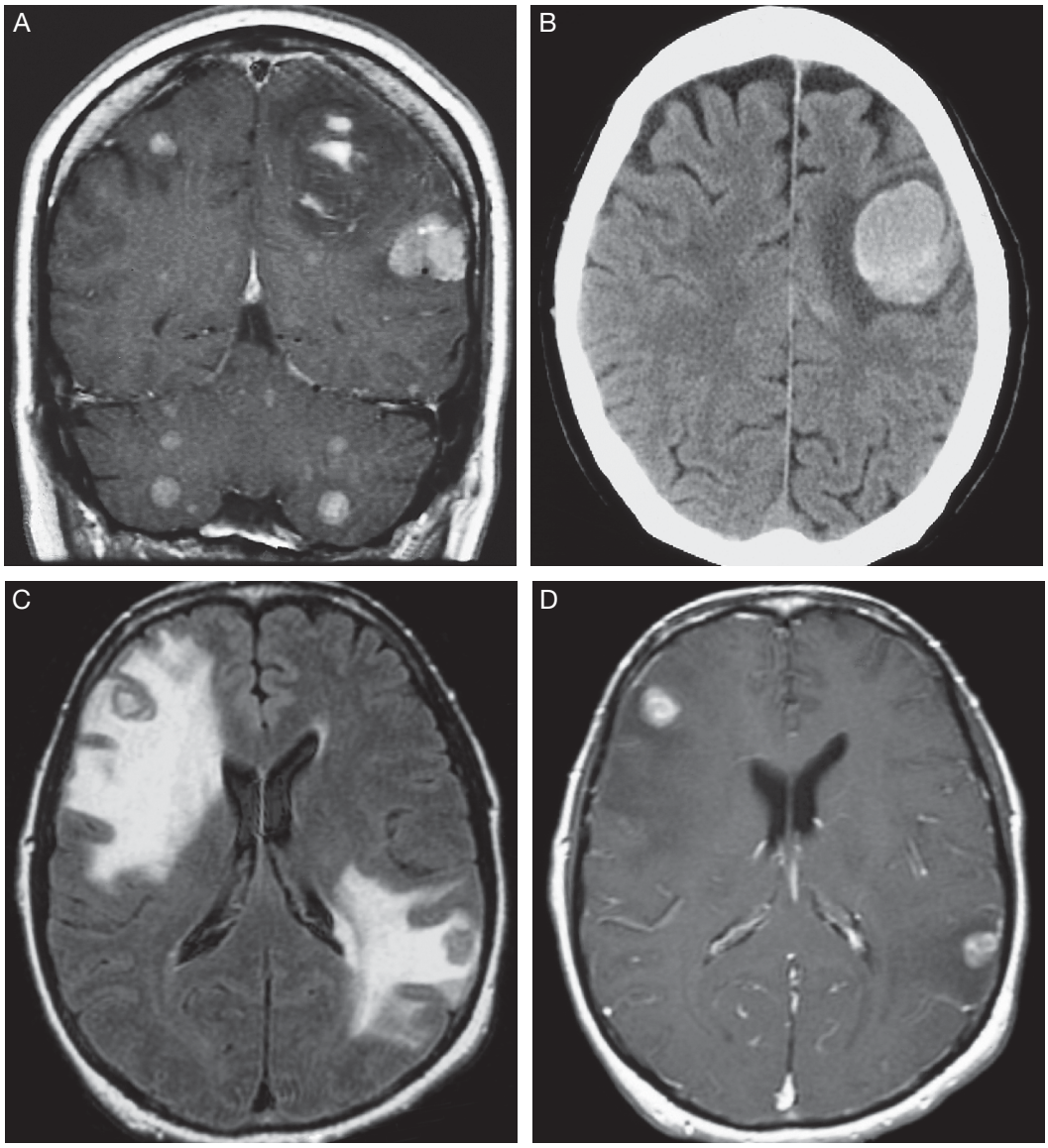

Figure 60.1 *Neuroimaging of Metastatic Cancer Shows Single or Multiple Enhancing Lesions at Junction of Gray and White Matter With Various Degrees of Surrounding Vasogenic Edema, Hemorrhage, or Necrosis.*
A, Gadolinium-enhanced coronal T1-weighted image of metastatic melanoma shows numerous enhancing masses throughout brain. B, unenhanced CT of a different patient with metastatic melanoma shows subacute hemorrhage into the metastatic focus at parasagittal posterior left frontal cortex. C, Axial FLAIR and, D, enhanced axial T1-weighted images show 2 enhancing foci of metastasis at junction of gray and white matter, with surrounding vasogenic edema. The primary tumor was metastatic lung adenocarcinoma.
(Adapted from Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627–78. Used with permission of Mayo Foundation for Medical Education and Research.)

and lamotrigine, given the improved adverse effect profiles and reduced drug interactions.

Patients with intracranial metastases may come to medical attention with focal neurologic symptoms, altered consciousness, or signs of cerebral edema, or a combination. Corticosteroids are recommended, with dosing from 4 to 16 mg daily in divided doses. Common adverse effects associated with corticosteroid use include mood disturbance, hyperglycemia, immunosuppression, weight gain, gastrointestinal tract bleeding, and osteopenia. For malignant cerebral edema, surgery may be required, in addition to osmotic diuretics and hyperventilation.

Surgery

Neurosurgery is preferred for patients of younger age who have good performance status, absent or limited systemic disease, and solitary metastasis. Surgical resection of tumor has been found to improve survival nearly 2- to 3-fold. The recommended approach is that radiation follow surgical resection because surgery has no effect on the development of additional brain metastases or leptomeningeal disease.

Leptomeningeal Metastases

The risk of leptomeningeal metastases increases with longer survival. The most common solid tumors causing leptomeningeal disease are breast cancer, lung cancer, and melanoma. Hematologic cancers can result in leptomeningeal disease in up to 24% of patients.

As with intraparenchymal metastases, treatment of leptomeningeal metastases is limited by the blood-brain barrier. Intrathecal chemotherapies that have shown benefit include methotrexate, cytarabine, and thiotepa. One-third of patients with leptomeningeal metastases die solely from their CNS disease, with stable systemic disease.

- The majority of patients with metastatic brain tumors eventually receive whole-brain radiation therapy (WBRT).
- Stereotactic radiosurgery (SRS) has a higher tumor-killing potential than WBRT, and it may be more effective against radioresistant tumors. SRS is preferred when the patient has 1 to 3 tumors that measure less than 3 cm.
- In patients younger than 65 years who have a good Karnofsky performance status score (recursive portioning analysis class I), the median survival with WBRT is 7.1 months.
- Antiepileptic drugs that induce the cytochrome P450 system should be avoided because of interference with corticosteroid treatment and chemotherapy.
- The most common solid tumors causing leptomeningeal disease are breast cancer, lung cancer, and melanoma.

Spinal Cord Metastases

Epidemiologic Factors

Metastases to the spinal column can present as intradural, intramedullary, intradural extramedullary, or extradural disease. Most patients with metastatic disease to the spine have vertebral or epidural disease. Breast, prostate, and lung cancers are the most common solid tumors to metastasize to the spine, followed by renal cell carcinoma, myeloma, and non-Hodgkin lymphoma.

Pathophysiologic Characteristics

Spine metastases are thought to arise from hematogenous spread or direct extension, or both. The Batson plexus—a venous, low-pressure system extending from epidural veins to the thoracoabdominal wall and veins of the head and neck—is the vascular system by which cancer deposits may spread to the spine. Another mechanism is the concept of arterial emboli, in which metastases embolize to the rich vasculature of the bony spine.

Clinical Presentation

Thoracic back pain is the most common report in spinal cord metastasis, followed by symmetrical lower extremity weakness and sensory changes. The sensory changes may vary and range from radicular pain and sensory loss to a sensory spinal level. Typically, bowel and bladder involvement parallels weakness, and isolated dysfunction is rare. Patients also may present with a cauda equina compression.

Management

Symptom management is aimed at pain control, which includes use of opioids, corticosteroids, and neuropathic pain medications. Corticosteroids not only improve pain, they also reduce peritumoral edema and neurologic deficit. When weakness is appreciated, corticosteroid therapy should be implemented immediately to reverse the neurologic deficit.

Chemotherapy options depend on the chemosensitivity or chemoresistance of the primary tumor. For example, germ cell tumors and non-Hodgkin lymphoma are highly chemosensitive. Radiation is currently the standard of care for treatment of metastatic disease to the spine. Prognosis depends on radiosensitivity of the primary tumor. Breast cancer, small cell lung cancer, prostate cancer, lymphoma, and myeloma are radiosensitive. By comparison, melanoma and renal cell carcinoma tend to be radioresistant. External beam RT is given in 10 fractions to a total of 30 Gy. SRS body treatment may be given to a dose of 8 to 18 Gy over 1 to 3 sessions. Adverse effects associated with radiation to the spine include radiation myelopathy, which can be acute (weeks to months after treatment) to chronic (years later). Surgery is limited for patients whose health deteriorates or whose disease does not respond to RT.

Prognosis is poor after patients have metastatic disease to the spine, with a median survival of 6 months. Patients who are ambulatory at diagnosis have a slightly improved survival (8–10 months) compared with those who are not ambulatory (2–4 months). Breast and prostate cancers tend to be associated with slightly longer survival (9–10 months) than lung cancer (3 months).

Intradural intramedullary metastases are rare and occur in only about 0.9% to 2.1% of patients with cancer. Approximately 50% of patients with intramedullary metastases have lung primary cancer.

Presenting symptoms of such metastases are pain, weakness, and Brown-Séquard syndrome. Opioids and neuropathic pain medication are often used. The role of surgery is limited in this patient population, and RT in addition to corticosteroid therapy is the mainstay of treatment. Prognosis is universally poor, with 75% of patients having a 1-month progression to paraplegia.

- Breast, prostate, and lung cancers are the most common solid tumors to metastasize to the spine, followed by renal cell carcinoma, myeloma, and non-Hodgkin lymphoma.
- Breast cancer, small cell lung cancer, prostate cancer, lymphoma, and myeloma are radiosensitive.

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61 Neurologic Complications of Radiation and Chemotherapy

GRETCHEN E. SCHLOSSER COVELL, MD; ALYX B. PORTER, MD

Introduction

Separate from neurosurgery, radiation and chemotherapy have been used in the treatment of malignant and benign tumors of the brain and spinal cord. Though effective, these treatments can be associated with serious neurologic adverse effects. This chapter reviews the adverse effects of these treatments.

Radiation

Overview

External beam radiation therapy (RT) is a common mode of radiation and is most effective for high-grade glioma. Intensity-modulated RT and stereotactic radiosurgery (SRS) are usually reserved for pituitary tumors, skull-base masses, and primary parenchymal tumors. Whole-brain radiation is often the option chosen to treat metastases to the brain, but it also can be considered for treatment of primary central nervous system (CNS) lymphoma, germinoma, or medulloblastoma.

As may be expected, the higher the dose or duration of radiation, the higher is the risk of radiation adverse effects on the nervous system. In addition, very young patients and elderly patients are at higher risk for adverse effects. These effects can be acute, subacute, or delayed from the time of treatment (Table 61.1).

Brain irradiation may cause acute adverse effects, such as headache, fever, nausea, and vomiting. These effects are usually temporary and respond to symptom-specific therapies. Subacute complications often begin within weeks to months after the initial treatment and may persist. These symptoms may include fatigue, cognitive decline, endocrine dysfunction, and focal neurologic deficits. Delayed symptoms occur months to even years after the initial RT, and they can be disabling and often are irreversible. For example, radiation can lead to central radiation necrosis, leukoencephalopathy, atherosclerosis, stroke, and even radiation-induced secondary cancers.

Table 61.1 • Complications of Radiation Therapy for Central Nervous System Tumors

Acute
Acute encephalopathy
Radiation myelopathy
Subacute
Radiation necrosis
Radiation myelopathy
Chronic
Radiation necrosis
Radiation myelopathy
Radiation-induced dementia, cognitive impairment, and leukoencephalopathy
Strokelike migraine attacks after radiation therapy (SMART) syndrome
Accelerated atherosclerosis
Peripheral nerve injury (cranial or peripheral nerve)
Endocrine dysfunction
Radiation-induced tumor (eg, meningioma)

Radiation Necrosis

Irradiation may lead to radiation necrosis in up to 20% of patients treated for intracranial or extracranial tumors.

Abbreviations: CNS, central nervous system; MRI, magnetic resonance imaging; RT, radiation therapy; SMART, strokelike migraine attacks after radiation therapy; SRS, stereotactic radiosurgery

This adverse effect may occur at doses greater than 55 Gy, given in fractions of 1.8 to 2.0 Gy, as well as in cases of interstitial brachytherapy or SRS, which delivers higher doses of radiation to the tumor volume. Additional risk factors include large lesion volume at irradiation, age greater than 60 years, such vascular risk factors as stroke and diabetes mellitus, and concomitant chemotherapy.

Radiation necrosis usually occurs 1 or 2 years after irradiation, but it has been reported to occur anywhere from 3 months to 30 years after treatment. The difficulty with this complication is that radiation necrosis can mimic recurrent tumor radiographically. Methods to distinguish radiation necrosis from recurrent tumor include advanced imaging modalities, such as perfusion magnetic resonance imaging (MRI), positron emission tomography, and single-photon emission computed tomography. However, in many cases, tissue biopsy is required to distinguish between the 2 entities. Radiation necrosis may respond to dexamethasone. Other investigational methods include the use of bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor receptors, and hyperbaric oxygen.

- Radiation necrosis usually occurs 1 or 2 years after irradiation, but it has been reported to occur anywhere from 3 months to 30 years after treatment.
- Methods to distinguish radiation necrosis from recurrent tumor include advanced imaging modalities, such as perfusion magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography. In many cases, however, tissue biopsy is required to distinguish between the 2 entities.

Acute Encephalopathy

Encephalopathy immediately after RT may manifest as drowsiness, headache, and nausea. The presumed cause is a breakdown of the blood-brain barrier, causing a transient increase in brain edema and intracranial pressure. Acute encephalopathy after RT usually responds well to corticosteroid therapy. Corticosteroid treatment may be started before the initiation of RT, to prevent acute encephalopathy in cases of large tumors with sizeable preexisting edema.

Transient cognitive impairment can occur within weeks after RT. In these cases, verbal memory is most often affected but usually has a good prognosis for recovery because it typically will not progress to the delayed complication of radiation-induced dementia. Somnolence syndrome is another subacute encephalopathy that affects children in particular and is defined as extreme lethargy, nausea, anorexia, and irritability. This complication usually occurs weeks after irradiation and can follow a monophasic course and show good recovery within weeks. In studies done during the active period of adverse symptoms, electroencephalography shows diffuse slowing that resolves as symptoms improve.

Radiation-Induced Dementia, Cognitive Impairment, and Leukoencephalopathy

Radiation-induced dementia is a delayed complication that may affect more than 10% of patients within an average of 2 years after RT. The clinical spectrum of radiation-induced dementia ranges from mild clinical impairment to severe dementia. Risk factors include radiation dose, radiation duration, age greater than 40 years, and concomitant chemotherapy. With cognitive impairment after irradiation, long-term changes on MRI include white-matter hyperintensities and global cortical atrophy. Among the pathologic characteristics, leukoencephalopathy shows gliosis, edema, and demyelination. Unfortunately, the exact mechanism of this neurotoxic damage caused by radiation is not known. Impaired neurogenesis of the hippocampus specifically is thought to possibly contribute to the cognitive dysfunction, as well as axon loss due to the combination of inflammation, upregulated cytokines, and oxidative damage.

Leukoencephalopathy is due to microscopic disease of the white matter and can lead to inattention and memory impairment, apathy, gait instability, and incontinence. This complication usually occurs after whole-brain RT and can be associated with confluent T2 or fluid-attenuated inversion recovery signal abnormalities in the periventricular regions on MRI. The transition to cognitive dysfunction depends on premorbid cognitive function and radiation dose, with an increased likelihood in patients receiving a total radiation dose greater than 6,000 cGy in 30 fractions, daily fractions greater than 2.0 Gy, and concomitant chemotherapy.

- Risk factors for radiation-induced dementia, cognitive impairment, and leukoencephalopathy include radiation dose, duration, age greater than 40 years, and concomitant chemotherapy.

Radiation-Induced Vasculopathy

Blood vessels are susceptible to radiation damage because of hypoxia leading to ischemic tissue necrosis, inflammation, hyalinization, and thrombosis in the microvasculature. The damage can cause accelerated atherosclerosis, stenosis, occlusive disease, microangiopathy, and vascular malformations. Accelerated atherosclerosis is seen most

frequently in the carotid artery, particularly in patients receiving RT for head and neck cancers.

A rare and possibly underrecognized vascular complication due to radiation toxicity is SMART (strokelike migraine attacks after RT) syndrome, characterized by migraine headaches, focal neurologic deficits that mimic stroke, and, occasionally, seizures. Studies have shown that symptoms start at 2 to 10 years after RT, and MRI during these attacks shows contrast medium enhancement and transient cortical thickening. Therefore, radiation-induced vasculopathy can mimic ischemic disease or leptomeningeal enhancement. The pathophysiologic factors are not well known, but they may be similar to those of the vasculopathy seen in posterior reversible encephalopathy syndrome. Posterior reversible encephalopathy syndrome involves fluctuating vasoconstriction and vasodilation that ultimately causes breakdown of the blood-brain barrier, with predilection for the parieto-occipital regions. Similarly, the parieto-occiptial regions are most vulnerable to the changes seen in SMART syndrome.

- Accelerated atherosclerosis is seen most frequently in the carotid artery, particularly in patients receiving radiation therapy for head and neck cancers.
- Strokelike migraine attacks after radiation therapy (SMART) syndrome is characterized by migraine headaches, focal neurologic deficits that mimic stroke, and, occasionally, seizures.

Myelopathy

In patients receiving 4,000 cGy to the spinal cord for primary or secondary spinal cord cancers, radiation-induced myelopathy may manifest as an acute, subacute, or chronically progressive syndrome. Spinal cord infarction is a rare but possible complication resulting from arterial damage based on the mechanisms listed earlier. Transient myelopathies may occur 3 to 6 months following radiation and can include symptoms such as Lhermitte sign, paraparesis, and paresthesias. Contrast medium–enhanced MRI of the spine may show mild cord edema and deformity with subtle contrast medium enhancement. In patients with delayed symptoms (occurring years following RT), the course is a chronic, progressive spinal cord syndrome that may include paralysis; urinary dysfunction or bowel dysfunction, or both; and sensory discrepancies. The MRI may show spinal cord atrophy and possibly some of the signs seen with acute transient myelopathies. Corticosteroids may be most helpful in the management of acute and subacute spinal cord syndromes. Chronic progressive myelopathies often fail to respond to treatment.

Peripheral Nervous System Complications

Although a rare complication from irradiation, some cranial nerves are highly susceptible to radiation effects—in particular, optic, hypoglossal, spinal accessory, vagus, trigeminal, and abducens nerves. These cranial neuropathies after irradiation often occur insidiously over 5 to 8 years, with slow progression of such symptoms as visual loss, gaze palsy, trapezius muscle weakness and atrophy, dysphagia, dysarthria, decreased palate elevation, tongue or uvular deviation, or absence of gag reflex. The optic nerves and chiasm are most at risk for damage when radiation is directed toward retinal, pituitary, or anterior skull-base tumors. A skull-base tumor may affect the lower cranial nerves and the hypoglossal nerve in particular.

The hypoglossal nerve has a tortuous course from the nuclei of the medulla oblongata to the tongue, which can be well visualized on MRI. This nerve's proximity to the skull base, parapharyngeal region, oropharynx, and cervical lymphatics along its course places it at high risk for irradiation injury. Mechanisms of injury include direct injury to the nerve and secondary damage from surrounding tissue fibrosis or vasculopathy. Neuropathies of lower cranial nerves may develop years after irradiation, as seen in documented cases of nasopharyngeal neoplasms. A reported feature on electromyography is myokymia, most often seen in affected trapezius, sternocleidomastoid, masseter, and tongue muscles. Myokymic discharges are spontaneous and occur only for a few seconds at a time and at a constant rate. Other potential electromyography features may include high-amplitude motor unit potentials with long duration, reduced interference, fibrillation potentials, positive sharp waves, or complex repetitive discharges.

The brachial and lumbosacral plexuses also are vulnerable to radiation injury. Symptoms of brachial and lumbosacral plexopathy include pain, allodynia, and weakness or numbness, or both. On the basis of the location of the tumor being treated, patients with breast and lung cancers are at greatest risk for radiation-induced brachial plexopathies. The presence of myokymia on electromyography and negative contrast medium–enhanced imaging support the diagnosis of radiation injury rather than a plexopathy resultant of infiltrating tumor. In cases of pelvic, testicular, or para-aortic neoplasms, the lumbosacral plexus may be adversely involved.

- The optic nerves and chiasm are most at risk for damage when radiation is directed toward retinal, pituitary, or anterior skull-base tumors.
- The brachial and lumbosacral plexuses are vulnerable to radiation injury.

Endocrine Dysfunction

Irradiation continues to be a leading cause of iatrogenic hypopituitarism affecting the hypothalamic-pituitary axis and can occur up to 10 years after the completion of RT. Radiation doses that exceed 30 to 50 Gy are associated with hormone insufficiency. Regular testing of pituitary

function can allow for early diagnosis and treatment with hormone replacement as needed. Irradiation often affects growth hormone, with thyrotropin and adrenocorticotropic hormone the next likely hormones to be affected. Growth hormone irregularity is recognized clinically in children receiving irradiation but should be considered in adults undergoing RT also. Thyroid dysfunction is a frequent cause of fatigue in adults who have received radiation, and the fatigue should be investigated.

- Thyroid dysfunction is a frequent cause of fatigue in adults who have received radiation, and the fatigue should be investigated.

Radiation-Induced Tumors

Secondary cancers in the nervous system may occur after irradiation, even with an exposure of less than 10 Gy. These tumors may develop years after the initial radiation treatment at the site of the primary tumor or at its margin. The types of tumors reported to occur following cranial irradiation include meningioma (most commonly), glioma, sarcomas, and malignant peripheral nerve sheath tumors. The unique histology of these tumors differentiates them from the primary tumor, and radiation-induced cancers can be more difficult to treat because they may be resistant to RT.

- The types of tumors reported to occur following cranial irradiation include meningioma (most commonly), glioma, sarcomas, and malignant peripheral nerve sheath tumors.

Chemotherapy

Overview

Several variables determine susceptibility for neurotoxicity after chemotherapy, including patient age, chemotherapy dose accumulation and duration, drug metabolism and clearance, and concomitant RT. Each class of chemotherapeutics comes with its own risk of neurologic complications and is described herein. Table 61.2 summarizes the most common chemotherapy-related adverse neurologic effects.

Alkylating Agents

Alkylating agents directly damage DNA and therefore prevent cancer cell reproduction. These agents work in all phases of the cell cycle, which allows them to be effective in solid tumors and many types of hematologic malignancy. Alkylating agents include mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide, melphalan, carmustine, streptozocin, lomustine, busulfan, dacarbazine, thiotepa, altretamine, and temozolomide. The platinum drugs include cisplatin, carboplatin, and oxaliplatin and are often grouped with alkylating agents because they destroy cells through a similar mechanism of action.

Of the alkylating agents, the nitrosoureas (eg, carmustine) and platinum drugs (eg, cisplatin) are most likely to cause toxicity to the CNS, as manifested by acute encephalopathy, stroke, or leukoencephalopathy. These adverse events are heightened when the drugs are given through an intra-arterial route. However, ifosfamide is likely to cause acute diffuse encephalopathy when given at high intravenous doses. The symptoms of acute diffuse encephalopathy usually resolve after a few days but may recur after repeat doses. Other alkylating agents (eg, busulfan, cyclophosphamide, procarbazine, temozolomide) are less likely to adversely impact the CNS at moderate doses.

Antimetabolites

The antimetabolites are a class of drugs that disrupt nucleic acid stability and cell growth by substituting the normal building blocks of RNA and DNA. These drugs cause damage only through the synthesis phase and are used to treat leukemias, breast cancer, and gastrointestinal neoplasms, among other cancer types. The class is broad, including 5-fluorouracil,

Table 61.2 • Neurologic Complications From Commonly Used Chemotherapy Agents

Agent	Indication	Neurotoxicity
5-Fluorouracil	Breast and gastrointestinal tract cancers	Acute cerebellar syndrome, leukoencephalopathy
Cisplatin, carboplatin, and oxaliplatin	Multiple solid tumor cancers	Peripheral neuropathy, ototoxicity, vestibulopathy, encephalopathy
Cytarabine	Leukemia, lymphoma, intrathecal therapy for leptomeningeal metastases	Acute encephalopathy, peripheral neuropathy, acute cerebellar syndrome, aseptic meningitis, myelopathy
Methotrexate	Lymphoma, intrathecal therapy for leptomeningeal metastases	Acute encephalitis, aseptic meningitis, leukoencephalopathy, myelopathy
Taxanes	Breast and ovarian cancers	Peripheral neuropathy
Vinca alkaloids	Hematologic cancers, breast cancer, lung cancer, sarcoma	Peripheral neuropathy, autonomic neuropathy

6-mercaptopurine, methotrexate, capecitabine, cladribine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, hydroxyurea, pemetrexed, pentostatin, and thioguanine.

Of the antimetabolites, methotrexate, 5-fluorouracil, and capecitabine can cause neurotoxicity by inducing multifocal leukoencephalopathy, polyneuropathy, aseptic meningitis, myelopathy, lumbosacral radiculopathy, posterior reversible encephalopathy syndrome, and cerebellar syndrome. Up to 10% of patients have aseptic meningitis after receiving intrathecal or intraventricular chemotherapy with antimetabolites, such as methotrexate and cytarabine. The symptoms of aseptic meningitis include headache, nausea, nuchal rigidity, and fever acutely within the time of drug administration. Often, these symptoms are self-limited and can be improved or prevented with a short course of dexamethasone given for a few days after the chemotherapy injection.

Topoisomerase Inhibitors

Topoisomerase inhibitors interfere with enzymes that aid in separating the DNA strands during replication. These agents target certain leukemias and lung, ovarian, gastrointestinal, and other cancers. Examples of topoisomerase I inhibitors include topotecan and irinotecan (CPT-11). Topoisomerase II inhibitors include etoposide (VP-16) and teniposide. VP-16 specifically has been documented to rarely cause acute encephalopathy and polyneuropathy.

Mitotic Inhibitors

Mitotic inhibitors halt mitosis or inhibit enzymes from making proteins needed for cell reproduction. These drugs affect the M phase of the cell cycle but can damage cells in all phases of reproduction. Examples include paclitaxel, docetaxel, ixabepilone, estramustine, and vinca alkaloids such as vincristine and vinblastine. These agents are effective in treating breast cancer, lung cancer, myelomas, lymphomas, and leukemia.

Mitotic inhibitors are notorious for peripheral nerve damage, which is a dose-limiting factor in the use of these chemotherapy drugs. Vinca alkaloids cause a sensorimotor axonal peripheral neuropathy by disrupting the microtubule formation, which is critical for transport. The taxanes, paclitaxel and docetaxel can cause an acute pain syndrome through an unknown mechanism and an axonal peripheral neuropathy through microtubule disruption.

- Mitotic inhibitors are notorious for peripheral nerve damage, which is a dose-limiting factor in the use of these chemotherapy drugs.

Miscellaneous Chemotherapy Drugs

Some chemotherapy drugs act in unique ways and therefore do not fit well into the other categories. These include the enzyme L-asparaginase and the monoclonal antibody against vascular endothelial growth factor, bevacizumab.

L-asparaginase inhibits the hepatic synthesis of critical coagulation factors and therefore rarely causes sinus thrombosis and intracerebral hemorrhage in patients. Bevacizumab may cause deep vein thrombosis, myocardial infarction, pulmonary embolism, colon perforation, and ischemic stroke, or intracerebral hemorrhage, or a combination, in 1% to 5% of patients undergoing treatment.

- Bevacizumab may cause deep vein thrombosis, myocardial infarction, pulmonary embolism, colon perforation, and ischemic stroke, or intracerebral hemorrhage, or a combination, in 1% to 5% of patients undergoing treatment.

Leukoencephalopathy

The most common chemotherapeutic agents that might cause encephalopathy are methotrexate, vincristine, ifosfamide, cyclosporine, fludarabine, cytarabine, 5-fluorouracil, cisplatin, and the interferons. Acute encephalopathy is manifested by normal MRI, slowing on electroencephalography, and transient fluctuation in mental status, which is usually reversible. In contrast, chronic leukoencephalopathy may show MRI with white-matter disease and atrophy. Methotrexate, given intrathecally or at high doses, is the main offender in chemotherapy-induced leukoencephalopathy. This complication is often seen in children receiving treatment of meningeal leukemia or adults getting methotrexate for primary CNS lymphoma. The severity of white matter changes and long-term cognitive deficits vary, and some patients recover while others have a progressive course that can cause severe dementia, seizures, gait instability, and even coma. Pathologic evaluation shows foci of necrosis with surrounding demyelination, oligodendrocyte loss, axonal damage, and, rarely, vascular damage or microangiopathy.

- Methotrexate, given intrathecally or in high doses, is the main offender in chemotherapy-induced leukoencephalopathy.

Peripheral Neuropathy

Involvement of the peripheral nervous system usually manifests as distal length-dependent, peripheral neuropathy and is a complication of chemotherapy agents, including cisplatin, vincristine, taxanes, suramin, and thalidomide. The main mechanism of damage is disruption of the microtubule formation, which disturbs axonal transport. Paresthesias and hypoesthesia in a stocking-glove distribution continue to be the most commonly reported symptoms, although extremely painful peripheral neuropathy, autonomic dysfunction, and devastating proprioceptive loss are also reported. These symptoms can be hyperacute after chemotherapy, or delayed by weeks to months from the treatment dose. Treatment may include duloxetine, gabapentin, amitriptyline, pregabalin, and opioids.

62 Paraneoplastic and Other Autoimmune Neurologic Disorders

ANDREW MCKEON, MB, BCH, MD

Introduction

Broadly speaking, a paraneoplastic disorder occurs because of the remote effects of malignancy, rather than because of direct tumor invasion. Paraneoplastic neurologic disorders come about because of vigorous immune responses directed against antigens expressed in tumors. The vigor of the immune response usually ensures that neoplasm is confined to the primary organ and regional lymph nodes. The neurologic presentation is often the first clue to the existence, or recurrence, of cancer.

Autoimmune neurologic disorders may also arise in nonparaneoplastic contexts. A common example of this is acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) (see Chapter 8, "Neuromuscular Disease in the Neuroscience Intensive Care Unit"). In many cases the autoimmune neurologic disorder remains idiopathic (not proven paraneoplastic or parainfectious), but the diagnosis is made because of typical clinical, radiologic, serologic, or cerebrospinal fluid (CSF) findings.

A General Approach to Suspected Paraneoplastic Disease

Symptomatology

Symptoms are usually acute or subacute in onset and rapidly progress. In any individual patient the neurologic presentation may be a classic unifocal disorder (eg, pure limbic encephalitis in a patient with voltage-gated potassium channel complex antibody) or multifocal disorder (eg, chorea and myelopathy in a patient with collapsin response mediator protein 5 immunoglobulin G [CRMP-5 IgG]). The antibodies, common neurologic findings, and oncologic associations are described in the tables. Antibodies with neuronal nuclear or cytoplasmic antigens are listed in Table 62.1; all of these, with the exception of 65-kDa isoform of glutamic acid decarboxylase (GAD65) antibody, are usually detected in a paraneoplastic context. Antibodies with neural plasma membrane targets are described in Table 62.2; cancer is encountered with this group of antibodies to varying degrees.

Differential Diagnosis and Diagnostic Testing

Other causes of subacute-onset neurologic disorders need to be considered in the differential diagnosis (infectious, neoplastic, toxic, metabolic, other inflammatory [eg, multiple sclerosis, vasculitis, sarcoidosis], rapidly progressive neurodegenerative). In addition to IgG antibody marker testing in serum, other testing that aids confirmation of an autoimmune diagnosis includes imaging, neurophysiological, and CSF evaluations. One or more of the following are suggestive of (though not entirely specific for) an autoimmune neurologic diagnosis: an elevated protein level, white blood cell count, IgG index, and IgG synthesis rate and oligoclonal bands. The search for cancer may be aided by detection of a specific antibody. For example, Purkinje cell cytoplasmic antibody (PCA) 1 (anti-Yo) will refine the

Abbreviations: AChR, acetylcholine receptor; ANNA, antineuronal nuclear antibody; CRMP-5 IgG, collapsin response mediator protein 5 immunoglobulin G; CSF, cerebrospinal fluid; GAD65, 65-kDa isoform of glutamic acid decarboxylase; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; PCA, Purkinje cell cytoplasmic antibody

Table 62.1 • Neuronal Nuclear and Cytoplasmic Antibodies

Antibody	Oncologic Association	Neurologic Presentation
PCA-1 (anti-Yo)	Ovarian or other müllerian (gynecologic tract) adenocarcinoma, breast adenocarcinoma	Cerebellar ataxia, brainstem encephalitis, myelopathy, radiculopathies, peripheral neuropathies
PCA-2	Small cell carcinoma	Limbic encephalitis, ataxia, brainstem encephalitis, Lambert-Eaton syndrome, peripheral and autonomic neuropathies
PCA-Tr	Hodgkin lymphoma	Cerebellar ataxia
ANNA-1 (anti-Hu)	Small cell carcinoma	Limbic encephalitis, brainstem encephalitis, autonomic neuropathies, sensory neuronopathy, other peripheral neuropathies
	Neuroblastoma (in children)	Opsoclonus-myoclonus syndrome (in children)
ANNA-2 (anti-Ri)	Small cell carcinoma, breast adenocarcinoma	Dementia, limbic encephalitis, brainstem encephalitis, myelopathy, peripheral neuropathy
ANNA-3	Aerodigestive tract carcinomas (eg, lung, esophagus)	Brainstem encephalitis, limbic encephalitis, myelopathy, peripheral neuropathy
AGNA	Small cell carcinoma	Neuropathy, Lambert-Eaton syndrome, limbic encephalitis
CRMP-5 IgG (anti-CV2)	Small cell carcinoma, thymoma	Subacute-onset dementia, personality change, aphasia, depression, chorea, ataxia, myelopathy, radiculopathy, neuropathy, Lambert-Eaton syndrome
Amphiphysin IgG	Small cell carcinoma, breast adenocarcinoma	Limbic encephalitis, aphasia, other subacute-onset dementias Stiff person phenomena, myelopathy, neuropathy
Ma1, Ma2 Ab	Testicular (Ma2); breast, colon, testicular (Ma1 and Ma2 together)	Limbic encephalitis, hypothalamic disorder, brainstem encephalitis
GAD65 Ab	Rare reports of thymoma; renal cell, breast, or colon adenocarcinoma (usually other accompanying antibodies)	Stiff man syndrome, ataxia, seizures, limbic encephalitis, brainstem encephalitis, ophthalmoplegia, parkinsonism, myelopathy

Abbreviations: Ab, antibody; AGNA, antiglial nuclear antibody; ANNA, antineuronal nuclear antibody; CRMP-5, collapsin response mediator protein 5; GAD65, 65-kDa isoform of glutamic acid decarboxylase; IgG, immunoglobulin G; PCA, Purkinje cell cytoplasmic antibody; Tr, Trotter (named after John Trotter, who first described this antibody in 1976).

Adapted from McKeon A, Pittock SJ. Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol. 2011 Oct;122(4):381–400. Epub 2011 Sep 22. Used with permission.

cancer search to breast and gynecologic system. CSF testing for paraneoplastic antibodies may complement serologic testing when results of the latter have been negative.

Management

The primary therapeutic modality for a paraneoplastic neurologic disorder is treatment of the cancer in the standard way (one or more of surgery, chemotherapy, and radiation therapy). One or more immunotherapeutic modalities (corticosteroids, intravenous immunoglobulin, plasma exchange, cyclophosphamide) may provide additional neurologic improvements when cancer remission has been achieved, though responses are variable. In general, patients with neurologic disorders and antibody targeting neural plasma membrane proteins (Table 62.2) are the most immunotherapy-responsive, commonly showing early improvements with corticosteroids, intravenous immunoglobulin, and plasma exchange. For this group, "steroid-sparing" immunotherapies are often required to maintain remission (eg, azathioprine, mycophenolate mofetil, rituximab).

- Antibodies with neuronal nuclear or cytoplasmic antigens, with the exception of GAD65 antibody, are usually detected in a paraneoplastic context.
- In general, patients with neurologic disorders and antibody targeting neural plasma membrane proteins are the most immunotherapy-responsive, commonly showing early improvements with corticosteroids, intravenous immunoglobulin, and plasma exchange.

Specific Disorders

Descriptions of paraneoplastic and other autoimmune neurologic disorders may be organized in a rostrocaudal anatomical order.

Ophthalmic Disorders

Retinopathy may have a paraneoplastic cause. Symptoms include painless visual loss with night blindness, light-induced glare, photosensitivity, and peripheral ring-like scotomas. Funduscopic examination findings are

Table 62.2 • Antibodies Targeting Ion Channels and Other Plasma Membrane Proteins

Antibody	Oncologic Association	Neurologic Presentation
VGKC complex Ab (some antibodies have specificity for LGI1 or CASPR2)	Various (20% of patients): small cell lung carcinoma; thymoma; adenocarcinoma of breast, prostate	Limbic encephalitis, amnestic syndrome, executive dysfunction, personality change, disinhibition, hypothalamic disorder, brainstem encephalitis, ataxia, extrapyramidal disorders, myoclonus, peripheral and autonomic neuropathy
NMDA receptor Ab	Ovarian teratoma (50% of patients)	Anxiety, psychosis, seizures, amnestic syndrome, dyskinesias
AMPA receptor Ab	Thymic tumors, lung carcinomas, breast carcinoma	Limbic encephalitis, nystagmus, seizures
GABA-B receptor Ab	Small cell lung carcinoma, other neuroendocrine neoplasia	Limbic encephalitis, orolingual dyskinesias
P/Q- and N-type calcium channel Ab	Small cell carcinoma, breast or gynecologic adenocarcinoma	Encephalopathies, myelopathies, neuropathies, Lambert-Eaton syndrome
NMO-IgG	Rare reports of thymoma and other solid tumors	Relapsing optic neuritis, transverse myelitis, encephalopathies
Neuronal ganglionic AChR Ab	Adenocarcinoma, thymoma, small cell carcinoma (30% of patients)	Dysautonomia
Muscle AChR Ab	Thymoma, thymic carcinoma, lung carcinoma	Myasthenia gravis, occasional other paraneoplastic contexts
Glycine receptor Ab	Thymoma, lymphoma (10% of patients)	Stiff man syndrome and variants
GluR5 Ab	Hodgkin lymphoma	Limbic encephalitis

Abbreviations: Ab, antibody; AChR, acetylcholine receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; CASPR, contactin-associated protein; GABA, γ-aminobutyric acid; GluR, glutamate receptor; IgG, immunoglobulin G; LGI1, leucine-rich, glioma inactivated 1; NMDA, *N*-methyl-D-aspartate; NMO, neuromyelitis optica; VGKC, voltage-gated potassium channel.

From McKeon A, Pittock SJ. Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol. 2011 Oct;122(4):381–400. Used with permission.

normal. The electroretinogram shows abnormal responses. Autoantibodies described include CRMP-5 IgG and recoverin antibody (both associated with small cell lung carcinoma). Optic neuritis and uveitis may rarely occur on a paraneoplastic basis. Severe and often bilateral optic neuritis is a classic manifestation of neuromyelitis optica (NMO).

Limbic Encephalitis

Patients typically present with a combination of memory problems, personality change, focal seizures, and altered mood. Disorders with emphasis of one of these components (eg, seizures) over the others are sometimes encountered.

Magnetic resonance imaging (MRI) usually reveals T2 signal abnormality in unilateral or bilateral hippocampal regions. Herpesvirus infection needs to be considered and excluded. Serologic and oncologic associations are protean (Table 62.1 and Table 62.2).

Opsoclonus-Myoclonus Syndrome

This disorder is more classically encountered in childhood but is sometimes found in adults. Patients complain of vision disturbance and tremulousness. In addition, children often present with disturbed sleep and screaming spells. Lightninglike irregular movements of the eyes (opsoclonus) and limbs (myoclonus) give the characteristic clinical appearance. In children, neuroblastoma (often associated with antineuronal nuclear antibody [ANNA] 1 [anti-Hu], Table 62.1) needs to be carefully sought with body computed tomography or MRI imaging and homovallinic acid measurements in urine. In adults, a paraneoplastic cause is encountered in about 15% of cases (diverse cancer types); parainfectious causes (eg, human immunodeficiency virus infection) have also been reported.

Outcome in children is variable, even with resolution of the movement disorder; long-term cognitive sequelae have been reported in some children. Adult patients with an idiopathic or parainfectious cause usually have an excellent clinical outcome with short courses of immunotherapy.

Cerebellar Degeneration

Cerebellar ataxia is likely the most common central nervous system paraneoplastic neurologic disorder. Prior to the onset of ataxia, affected patients often complain of diplopia, vertigo, nausea, and vomiting. Symptoms and signs

(nystagmus, ataxic dysarthria, gait and limb incoordination) often progress rapidly. Classic antibody-cancer associations include PCA-1 (anti-Yo) with ovarian or breast carcinoma and P/Q-type calcium channel antibody with lung carcinoma.

Chorea

Paraneoplastic chorea most often arises in a subacute, severe, and generalized fashion and may be accompanied by other neurologic manifestations such as peripheral neuropathy and cognitive impairment. Weight loss of more than 10 lb usually occurs. A classic oncologic combination is small cell lung carcinoma and CRMP-5 IgG. Nonparaneoplastic autoimmune choreas are also recognized; these include chorea associated with lupus and antiphospholipid syndrome, and Sydenham chorea (a parainfectious disorder that occurs after ß-hemolytic streptococcus infection).

Brainstem Encephalitis

Disorders of eye movement and balance, parkinsonism, and multiple cranial neuropathies are typical clinical presentations. Classic antibody associations include Ma1 and Ma2 antibodies, in which sleep disorders (including narcolepsy with cataplexy) have been reported. Patients with Ma2 antibody alone (also known as anti-Ta) are usually young men with testicular carcinoma, who generally have a good neurologic prognosis. Patients with both Ma1 and Ma2 antibodies (also known as anti-Ma) have an even sex distribution, may have a variety of neoplasm types, and often have a poor neurologic prognosis. Patients with ANNA-2 (anti-Ri) autoimmunity and brainstem encephalitis may manifest jaw dystonia and paroxysmal laryngeal spasm.

Myelopathy

Paraneoplastic myelopathy is often mistaken for primary progressive multiple sclerosis, because the onset age is similar (sixth and seventh decades), the presentation is spinal cord predominant, T2 signal abnormalities are seen on MRI, and oligoclonal bands may be detected in CSF. The clinical course is insidious in half of patients and rapid in half, and is accompanied by longitudinally extensive T2 signal abnormalities (often tract-restricted) on MRI in two-thirds (Figure 62.1). CRMP-5 IgG and amphiphysin antibodies are commonly encountered, and cancer associations are diverse. Outcomes are generally poor, with more than half of patients becoming wheelchair dependent. The severe autoimmune transverse myelitis of NMO (typically an idiopathic autoimmune disorder) can also easily be distinguished from multiple sclerosis with MRI. NMO lesions are longitudinally extensive (at least 3 vertebral segments) and involve the central or whole cord. Multiple sclerosis lesions, by contrast, are typically restricted to short cord segments and have peripheral locations.

Stiff Man (Stiff Person) Syndrome Spectrum Disorders

Patients classically present with stiffness and spasms of the lumbar and proximal lower extremity regions. Exaggerated startle responses and loss of protective reflexes while falling (described by Moersch and Woltman at Mayo Clinic as "falling as if a wooden man") are also characteristic. More-limited disorders (stiff limb, stiff trunk) and a more severe and widespread entity (progressive encephalomyelitis with rigidity and myoclonus) have also been described and sometimes have a paraneoplastic cause. The classic and variant disorders are unified by their electrophysiology (exaggerated brainstem and spinal reflexes), serologic findings (GAD65 antibody, glycine receptor antibody, or both), coexisting autoimmune disorders (one or both of type 1 diabetes mellitus and thyroid disease coexist in half of affected patients), and responses to immunotherapy. A stiff man–like phenotype with involvement of one or both lower extremities can also be observed in women with amphiphysin autoimmunity and breast cancer.

Peripheral Neuropathies

The peripheral somatic nervous system is the single most common part of the neuraxis affected by paraneoplastic neurologic disorders. Peripheral neuropathy may occur in isolation or as a component of a multifocal neurologic disorder. Sensory neuronopathy is a classic disorder often detected in patients with small cell lung carcinoma associated with ANNA-1. Sensorimotor neuropathies, small fiber neuropathies, and mixed somatic and autonomic neuropathies are also well recognized in a paraneoplastic context. Nonparaneoplastic autoimmune and inflammatory neuropathies are beyond the scope of this discussion but are discussed in chapter 40, "Peripheral Nerve Disorders".

Autonomic Neuropathies

Patients may present with one or more of the following: mydriasis, dry mouth, gastrointestinal dysmotility disorders (early satiety, nausea, small bowel pseudoobstruction, constipation), orthostatic hypotension, heat intolerance (due to inability to sweat), and bladder symptoms. Severe disorders are usually called pandysautonomia. More-limited disorders (such as autoimmune gastrointestinal dysmotility) have been appreciated in recent years.

The context for autoimmune dysautonomia can be either paraneoplastic (eg, ANNA-1–related) or idiopathic (eg, α_3-ganglionic acetylcholine receptor [AChR] antibody–related).

Neuromuscular Junction Disorders

The characteristic symptoms and signs of myasthenia gravis (weakness and abnormal fatigability of muscle) commonly involve extraocular muscles, often followed by bulbar

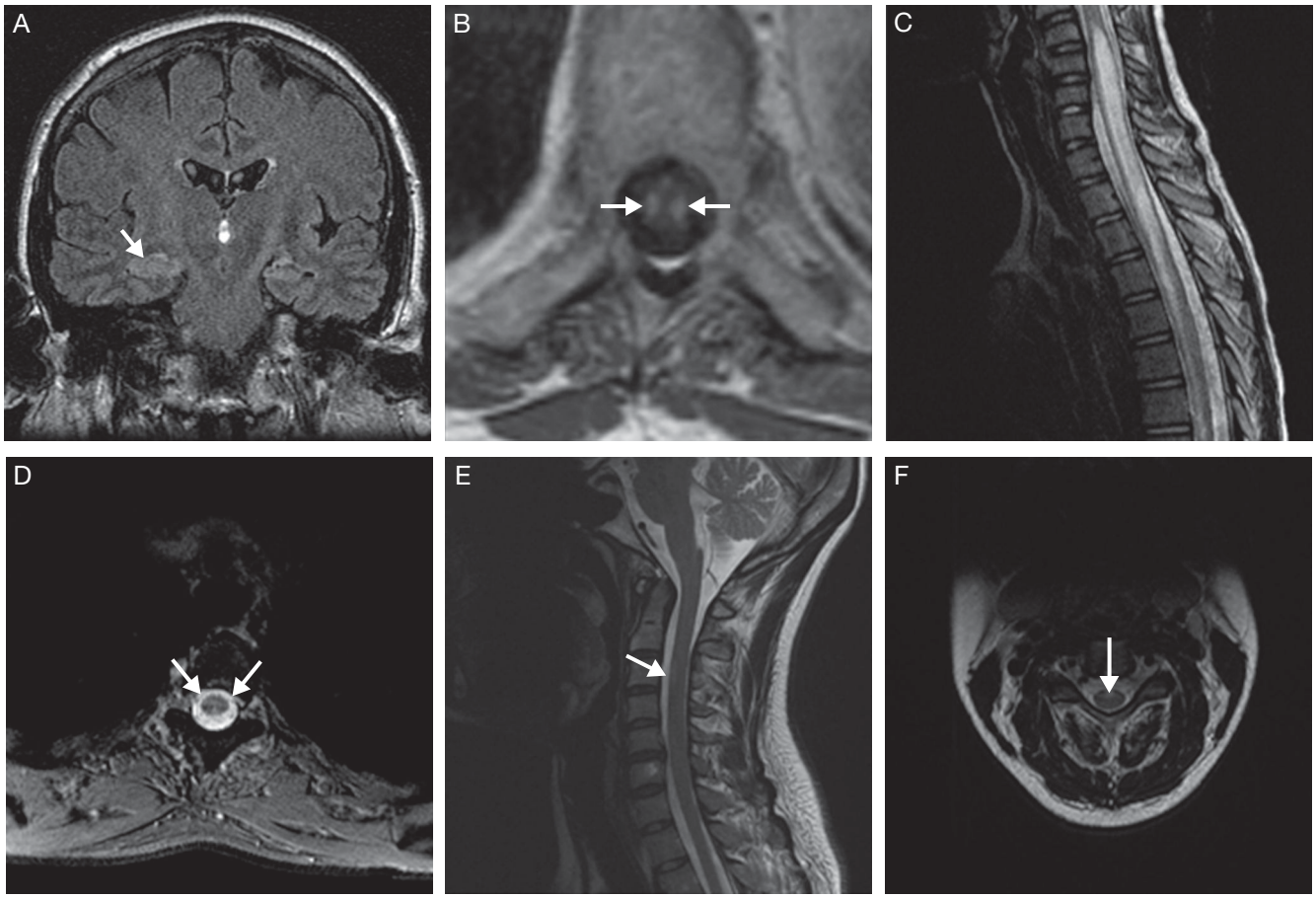

Figure 62.1 *Imaging Findings in Paraneoplastic Disease.*
A, Coronal T2 MRI of brain shows bilateral hippocampal hyperintensity in a patient with limbic encephalitis.
B, Axial T1 post-contrast MRI of thoracic spine shows increased signal in lateral corticospinal tracts in a patient with paraneoplastic myelopathy. C, Sagittal T2 MRI of spine shows a longitudinally extensive lesion in a patient with neuromyelitis optica (NMO). D, Axial image shows whole-cord T2 signal change in a patient with NMO. In contrast to paraneoplastic myelopathy and NMO, a patient with multiple sclerosis has a small peripheral T2 signal abnormality demonstrated on sagittal (E) and axial (F) T2 images of cervical spine.
(B, Adapted from Flanagan EP, McKeon A, Lennon VA, Kearns J, Weinshenker BG, Krecke KN, et al. Paraneoplastic isolated myelopathy: clinical course and neuroimaging clues. Neurology. 2011 Jun 14;76[24]):2089–95. Used with permission. C, Adapted from McKeon A, Lennon VA, Lotze T, Tenenbaum S, Ness JM, Rensel M, et al. CNS aquaporin-4 autoimmunity in children. Neurology. 2008 Jul 8;71[2]:93–100. Epub 2008 May 28. Used with permission.)

muscle and limb muscle involvement. Muscle nicotinic AChR binding and/or modulating antibodies are detected in 90% of patients. Antibody targeting muscle-specific kinase is detected in 38% of patients with myasthenia gravis who are AChR antibody negative. Chest computed tomography or MRI may reveal evidence of a paraneoplastic cause (thymoma or thymic carcinoma). See Chapter 41, "Neuromuscular Junction Disorders," for more details.

Patients with Lambert-Eaton syndrome most commonly present with subacute progressive fatigue and weakness, which worsens with exertion and improves with rest. A history of transient clinical facilitation of strength following brief exercise is rare. Antibody targeting nerve terminal (presynaptic) calcium channels of the P/Q and N types is found in more than 90% of patients. See Chapter 41, "Neuromuscular Junction Disorders," for more details.

Myopathies

Both dermatomyositis and polymyositis are known to sometimes occur in a paraneoplastic context. The relative risk of malignancy is likely somewhat higher among patients with dermatomyositis than among those with polymyositis. Adenocarcinomas of the cervix, lung, ovaries, pancreas, bladder, and stomach account for 70% of the cancers associated with inflammatory myopathies.

Antibody targeting the 54-kDa isoform of signal recognition particle is detected in patients with an autoimmune (uncommonly paraneoplastic) rapidly progressive necrotizing myopathy; reported cancers include colon carcinoma and Hodgkin lymphoma.

- Patients with limbic encephalitis typically present with a combination of memory problems, personality change, focal seizures, and altered mood.
- In children, neuroblastoma (often associated with ANNA-1 [anti-Hu]) needs to be carefully sought with body computed tomography or MRI imaging and homovallinic acid measurements in urine.
- Cerebellar ataxia is likely the most common central nervous system paraneoplastic neurologic disorder.
- Classic antibody-cancer associations include PCA-1 (anti-Yo) with ovarian or breast carcinoma and P/Q-type calcium channel antibody with lung carcinoma.
- Paraneoplastic myelopathy is often mistaken for primary progressive multiple sclerosis, because the onset age is similar (sixth and seventh decades), the presentation is spinal cord predominant, T2 signal abnormalities are seen on MRI, and oligoclonal bands may be detected in CSF.

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Questions and Answers

Questions

Multiple Choice (choose the best answer)

X.1. Which posterior fossa tumor, typically occurring in childhood, can be cured with a gross total resection?
a. Central neurocytoma
b. Glioblastoma multiforme
c. Medulloblastoma
d. Brainstem glioma
e. Pilocytic astrocytoma

X.2. What is the gold standard treatment of grade IV astrocytoma (glioblastoma multiforme)?
a. Radiotherapy
b. Chemotherapy
c. Resection
d. Radiotherapy and chemotherapy
e. Palliative care only

X.3. What initial dose of corticosteroids should you give to treat a patient with an acute epidural cord compression resulting from metastatic disease?
a. Prednisone 5 mg orally
b. Dexamethasone 10 mg intravenously (IV)
c. Methylprednisolone 500 mg IV
d. Hydrocortisone 20 mg orally
e. None—giving corticosteroids to this patient would be too risky

X.4. A 37-year-old woman with breast cancer comes to the emergency department with new-onset focal motor seizures. Magnetic resonance imaging (MRI) with a contrast agent shows a solitary 2-cm right frontal heterogeneously enhancing mass lesion with surrounding vasogenic edema. In addition to starting therapy with a non–enzyme-inducing antiepileptic drug and dexamethasone, what should you recommend?
a. A medical oncology consultation for chemotherapy
b. A neurosurgical consultation for resection
c. A radiation oncology consultation for whole brain radiotherapy
d. An infectious disease consultation for antibiotics
e. Observation

X.5. A 75-year-old man with stage IV non–small cell carcinoma was treated with prophylactic cranial radiotherapy to prevent brain metastases. His family brings him to your office with complaints about his cognition and failure to thrive. What should you recommend?
a. Ordering an electroencephalogram
b. Delaying contrast MRI of the brain because he did not present with focal features
c. Ordering bloodwork (including a complete blood cell count, electrolyte levels, and thyrotropin level), to look for systemic and metabolic causes
d. Initiating therapy with oral citalopram
e. Initiating therapy with high-dose parenteral corticosteroids

X.6. A 65-year-old woman has been treated for breast cancer and comes to your office with a painful peripheral neuropathy. Which chemotherapeutic agent likely caused her symptoms?
a. Cisplatin
b. Methotrexate
c. Bevacizumab
d. Temozolomide
e. Tamoxifen

X.7. A 37-year-old man with a history of IV drug abuse comes to the emergency department with altered mental status. Imaging shows multifocal, diffuse, homogeneously enhancing mass lesions, which are of concern for primary central nervous system lymphoma. What should you recommend?
a. Testing for human immunodeficiency virus
b. Serologic testing for Epstein-Barr virus
c. Radiation oncology consultation for whole brain radiotherapy
d. Dexamethasone 10 mg IV
e. Choices *a* and *b*

X.8. A 28-year-old woman comes to your office panicking because she presented to her family physician with dysmenorrhea and nipple discharge and was told that she has a brain tumor. What is the most likely abnormality found on her MRI?
a. Pituitary adenoma
b. Glioma
c. Primary central nervous system lymphoma
d. Acoustic neuroma
e. Ependymoma

X.9. A 45-year-old man has chronic dysequilibrium and decreased hearing on the left. MRI shows a dumbbell-shaped homogenously enhancing mass extending into the left internal auditory canal. What should you recommend?
a. Neurosurgical resection of the lesion and sacrifice of cranial nerve VIII
b. Whole brain radiotherapy
c. Observation with follow-up imaging in 6 months if his symptoms do not change
d. Chemotherapy
e. High-dose parenteral corticosteroids

X.10. A 30-year-old woman has MRI of the brain with and without a contrast agent for evaluation of classic migraine. MRI shows a subcentimeter dural-based, parafalcine, homogeneously enhancing mass without any parenchymal T2 or fluid-attenuated inversion recovery (FLAIR) signal change. What is the most likely cause of this mass?
a. Hemangiopericytoma
b. Lymphoma
c. Metastasis
d. Meningioma
e. Ganglioglioma

X.11. A 65-year-old woman with a history of breast cancer presents with chronic progressive ataxia, diplopia, and vertigo. What should you recommend?
a. MRI of the brain with and without a contrast agent
b. Paraneoplastic panel
c. Vestibular rehabilitation
d. Otolaryngology consultation for peripheral vertigo
e. Choices *a* and *b*

X.12. A 75-year-old man with a 60-pack-year smoking history presents with dysautonomia and progressive fatigable weakness that improves with rest. What antibody is most commonly associated with this syndrome?
a. Neuromyelitis optica immunoglobulin G (NMO-IgG)
b. Purkinje cell cytoplasmic antibody type 1 (PCA-1)
c. Glutamic acid decarboxylase 65 (GAD65) antibodies
d. P/Q- and N-type calcium channel antibodies
e. CRMP5 antibody

X.13. A 30-year-old man has bilateral acoustic neuromas that were found on MRI. Expression of which protein has been disrupted?
a. Neurofibromin
b. p53
c. Merlin
d. Amyloid
e. Tau

X.14. On MRI of the thoracic spine, an intramedullary contrast-enhancing nodule with an accompanying cyst spans 3 segments. What underlying genetic disorder must be excluded?
a. Neurofibromatosis 1
b. Neurofibromatosis 2
c. von Hippel-Lindau disease
d. Cowden syndrome
e. Multiple endocrine neoplasia type 1

X.15. A 28-year-old man presents with chronic progressive cauda equina syndrome. MRI shows a heterogenously enhancing sausage-shaped mass. What is the recommended definitive treatment?
a. Chemotherapy
b. Surgical resection
c. Radiotherapy
d. High-dose parenteral corticosteroids
e. Observation

Answers

X.1. Answer e.
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X.2. Answer d.
Schiff D, Arrillaga-Romany IC, Chamberlain MC, Clarke JL, Cohen BH, Dalmau JO, et al. Neuro-oncology. Continuum: Lifelong Learn Neurol. 2012 Apr;18(2):263–501.

X.3. Answer b.
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X.4. Answer b.
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X.5. Answer c.
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X.6. Answer a.
Schiff D, Kesari S, Wen PY, editors. Cancer neurology in clinical practice: neurologic complications of cancer and its treatment. 2nd ed. Totowa (NJ): Humana Press; c2008. 636 p.

X.7. Answer e.
Schiff D, Arrillaga-Romany IC, Chamberlain MC, Clarke JL, Cohen BH, Dalmau JO, et al. Neuro-oncology. Continuum: Lifelong Learn Neurol. 2012 Apr;18(2):263–501.

X.8. Answer a.
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X.9. Answer c.
Schiff D, Arrillaga-Romany IC, Chamberlain MC, Clarke JL, Cohen BH, Dalmau JO, et al. Neuro-oncology. Continuum: Lifelong Learn Neurol. 2012 Apr;18(2):263–501.

X.10. Answer d.
Schiff D, Arrillaga-Romany IC, Chamberlain MC, Clarke JL, Cohen BH, Dalmau JO, et al. Neuro-oncology. Continuum: Lifelong Learn Neurol. 2012 Apr;18(2):263–501.

X.11. Answer e.
Schiff D, Arrillaga-Romany IC, Chamberlain MC, Clarke JL, Cohen BH, Dalmau JO, et al. Neuro-oncology. Continuum: Lifelong Learn Neurol. 2012 Apr;18(2):263–501.

X.12. Answer d.
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X.13. Answer c.
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X.14. Answer c.
Schiff D, Arrillaga-Romany IC, Chamberlain MC, Clarke JL, Cohen BH, Dalmau JO, et al. Neuro-oncology. Continuum: Lifelong Learn Neurol. 2012 Apr;18(2):263–501.

X.15. Answer b.
Schiff D, Arrillaga-Romany IC, Chamberlain MC, Clarke JL, Cohen BH, Dalmau JO, et al. Neuro-oncology. Continuum: Lifelong Learn Neurol. 2012 Apr;18(2):263–501.

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Section
XI

Neurologic Infectious Disease

Allen J. Aksamit Jr, MD, *editor*

63 Syndromic Approach to Neuroinfectious Diseases

JENNIFER A. TRACY, MD

Introduction

A general approach to clinical syndromes associated with infection of the nervous system can be useful when infection is in the differential diagnosis. This chapter provides a general overview of clinical syndromes of neurologic infectious disease. Subsequent chapters review bacterial, viral, fungal, and protozoan infections and prion disorders.

Meningitis

Definition and Overview

Meningitis is inflammation of the leptomeninges caused by either infectious or noninfectious processes. The infectious agents that can cause meningitis include bacteria, mycobacteria, viruses, and fungi. During assessment of the likely causative organism, consideration should be given to patient demographics, such as age, region of residence, recent travel, vaccination status, and associated medical comorbidities (including recent infection, surgical procedures, immunosuppression, diabetes mellitus, and alcohol abuse). Particular features of meningitis, including time course, symptom severity, associated rash, area of meninges involved, and findings on neuroimaging and lumbar puncture, are also very useful in patient assessment.

Etiology

The most common bacterial pathogens in neonates with meningitis are group B streptococci, *Escherichia coli*, and *Listeria monocytogenes*. In children 2 months or older, the most common bacterial pathogens are *Streptococcus pneumoniae* and *Neisseria meningitidis*, and in the unvaccinated, *Haemophilus influenzae*. In adolescents and young adults, *N meningitidis* is most common. In adults with meningitis, *S pneumoniae* is the most common bacterial pathogen; other possible pathogens include *N meningitidis, Staphylococcus, L monocytogenes*, and gram-negative bacilli. In immunocompromised patients or elderly patients, *L monocytogenes* should be given stronger consideration. Other important bacteria that should be considered according to individual patient risk factors include *Borrelia burgdorferi* (causative agent of Lyme disease), *Treponema pallidum* (causative agent of syphilis), and *Mycobacterium tuberculosis* (causative agent of tuberculosis); these 3 bacteria have a greater tendency to cause subacute meningitis than the other bacterial agents described. Vaccination status should be assessed in determining individual risk for many of these agents.

Viral meningitis tends to occur seasonally, with a greater incidence in summer. Enteroviruses are the most common identified cause, but many other viruses can produce similar syndromes. Herpes simplex virus (HSV) type 2 (HSV-2) is the next most common identifiable viral cause. Human immunodeficiency virus (HIV) infection should also be considered.

Potential yeast or fungal causes include *Cryptococcus neoformans, Histoplasma capsulatum, Aspergillus fumigatus, Coccidioides immitis, Blastomyces dermatitidis*, and *Candida albicans*. Fungal meningitis is much more likely to occur in immunocompromised patients (eg, patients

Abbreviations: CJD, Creutzfeldt-Jakob disease; CMV, cytomegalovirus; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HSV-2, herpes simplex virus type 2; HTLV, human T-lymphotropic virus; MRI, magnetic resonance imaging; VZV, varicella zoster virus

with AIDS, transplant patients receiving immunosuppressive therapy, and patients receiving chemotherapy).

In aseptic meningitis, clinical and laboratory (eg, cerebrospinal fluid [CSF]) tests show evidence of meningitis, but routine studies are negative for bacteria. The most common cause is enterovirus; other possibilities are listed in Box 63.1.

Clinical Features

An acute or subacute, severe course is more indicative of a bacterial cause; viral meningitis is generally acute or subacute but less severe, and patients may be less likely to seek medical attention. Fungal or mycobacterial meningitis tends to evolve subacutely over 1 to 4 weeks.

The principle symptoms of meningitis are fever, headache, stiff neck, photophobia, and nausea or vomiting. Two of the 4 symptoms of fever, headache, stiff neck, and mental status changes are present in 90% of patients with meningitis, whereas all 4 are present in only 20%. In acute bacterial meningitis, mental status changes are common and sometimes quite severe. In a minority of cases, focal neurologic findings (eg, cranial nerve palsy) can coexist, particularly in situations with high intracranial pressure or involvement of the basilar meninges (where cranial nerves exiting the brainstem can be affected) and in cases of meningoencephalitis, in which the brain parenchyma is affected in addition to the meninges.

Box 63.1 • Differential Diagnosis of Aseptic Meningitis

- Infection from viral agent
  - Enteroviruses
  - Herpes simplex virus type 1 or 2
  - Epstein-Barr virus
  - Varicella zoster virus
  - Human immunodeficiency virus
  - Arboviruses
  - Lymphocytic choriomeningitis virus
  - Colorado tick fever (arenavirus)
- Systemic diseases
  - Sarcoidosis
  - Leukemia
  - Lymphoma
  - Behçet syndrome
  - Lupus cerebritis
  - Parainfectious syndromes
  - Carcinomatosis
- Infection from bacterial agent
  - Partially treated bacterial meningitis
  - *Listeria monocytogenes*
  - *Mycobacterium tuberculosis*
  - Spirochetes: *Treponema pallidum, Borrelia burgdorferi*
- Infection from fungal agent
  - Coccidioides immitis
  - *Cryptococcus neoformans*
  - *Histoplasma capsulatum*
  - *Blastomyces dermatitidis*
- Drugs
  - NSAIDs
  - Azathioprine
  - Trimethoprim-sulfamethoxazole
  - Isoniazid
  - Intravenous immunoglobulin
  - Muromonab-CD3

Abbreviation: NSAID, nonsteriodal anti-inflammatory drug.

Physical Examination

Important findings on physical examination of a patient with meningitis include fever and signs of increased intracranial pressure manifesting as meningismus: nuchal rigidity, Kernig sign (with hip flexion of 90°, the knee cannot be fully extended), Brudzinski sign (with passive neck flexion, patient flexes hip and knee). Very young children with fontanelles that are not closed have fontanelle bulging; these patients may lack objective signs of increased intracranial pressure and may have less specific signs and symptoms of infection. A petechial or purpuric rash may be an important clue to meningococcal meningitis, and a bull's-eye rash can suggest Lyme meningitis.

Differential Diagnosis and Diagnostic Approach

The differential diagnosis for an infectious meningitis includes sarcoidosis, meningitis associated with an autoimmune disease (eg, Behçet syndrome), chemical meningitis (agents include commonly prescribed and over-the-counter medications), and carcinomatous meningitis or meningeal lymphomatosis (Box 63.1). A meningitic clinical syndrome may result from vascular disease, intracranial bleeding, or venous sinus thrombosis. Patients with other sources of increased intracranial pressure, such as neoplasm or other space-occupying lesion, may show clinical features of meningitis but often with associated localizing neurologic symptoms or signs.

Neuroimaging should be performed, and magnetic resonance imaging (MRI) of the brain with gadolinium may show leptomeningeal enhancement and provide information about the area of the meninges involved. CSF evaluation should be performed, with assessment of opening pressure, cell count and type, glucose and protein levels, and appropriate studies for the suspected infectious source. Cytology is important for cases of suspected carcinomatous or lymphomatous infiltration of the meninges.

Table 63.1 • Cerebrospinal Fluid Characteristics of Different Types of Meningitis

Meningitis Type	Pressure	Glucose Level	Protein Level	Cells	Cell Type
Bacterial	Elevated	Decreased	Increased	Increased; usually >1,000/μL	Polymorphonuclear
Viral	Normal or elevated	Normal	Normal or increased	Increased; usually <1,000/μL	Mononuclear; may be predominantly polymorphonuclear in first 48 h
Fungal	Normal or elevated	Normal or decreased	Increased	Increased; usually <1,000/μL	Mononuclear in most cases
Tuberculous	Elevated	Decreased	Increased	Increased	Mononuclear
Lyme	Normal or elevated	Normal or decreased	Increased	Increased	Mononuclear
Syphilitic	Normal or elevated	Normal or decreased	Increased	Increased	Mononuclear

Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.

Typical CSF findings for bacterial, viral, fungal, and mycobacterial meningitis are outlined in Table 63.1. Peripheral blood tests usually show an increased white blood cell count and should include evaluation for infectious agents in the peripheral blood. Blood cultures should be used in the evaluation of bacterial meningitis because 80% of patients can have bacteremia at the time of bacterial meningitis.

Potential Complications

Potential complications of bacterial meningitis include associated sepsis with cardiovascular instability, hearing loss, cerebritis, hydrocephalus, and direct infection or spasm of the vasculature. Waterhouse-Friderichsen syndrome, which includes hemorrhage into the adrenal glands, can result from severe meningococcemia and should be considered in severely hypotensive patients.

- Particular features of meningitis, including time course, symptom severity, associated rash, area of meninges involved, and findings on neuroimaging and lumbar puncture, are very useful in patient assessment.
- The most common bacterial pathogens in neonates with meningitis are group B streptococci, *E coli*, and *L monocytogenes*.
- In adults with meningitis, *S pneumoniae* is the most common bacterial pathogen; other possible pathogens include *N meningitidis, Staphylococcus, L monocytogenes*, and gram-negative bacilli. In immunocompromised patients or elderly patients, *L monocytogenes* should be given stronger consideration.
- Two of the 4 symptoms of fever, headache, stiff neck, and mental status changes are present in 90% of patients with meningitis, whereas all 4 are present in only 20%.
- Important findings on physical examination of a patient with meningitis include fever and signs of increased intracranial pressure manifesting as meningismus: nuchal rigidity, Kernig sign (with hip flexion of 90°, the knee cannot be fully extended), Brudzinski sign (with passive neck flexion, patient flexes hip and knee).
- Typical CSF findings for bacterial, viral, fungal, and mycobacterial meningitis are outlined in Table 63.1.

Encephalitis

Definition and Overview

Encephalitides often involve the meninges and the brain parenchyma. Therefore, patients with encephalitis and patients with meningitis often have many of the same clinical features, including clinical symptoms and signs of increased intracranial pressure, general infectious signs such as fever, and disorientation or other disturbances of mental status.

The origin of most encephalitides is viral. After entering the body, viruses spread by either a hematogenous route or a transneuronal route by axonal transport and involve brain parenchyma. Common findings are early changes in the level of consciousness, focal neurologic findings, behavioral disturbances, and seizure activity.

Etiology

HSV type 1 and West Nile virus are the most commonly identified viral causes of encephalitis, although many other agents can be causative (eg, varicella zoster virus [VZV], Epstein-Barr virus, human herpesvirus 6, HSV-2, eastern and western equine encephalitis viruses, LaCrosse virus,

St Louis encephalitis virus, and Japanese encephalitis virus). Rabies virus should be considered in the appropriate clinical context. Lyme disease and other bacterial, mycobacterial, and fungal causes are also possible. Whipple disease (caused by *Tropheryma whipplei*) is exceedingly rare, but typical neurologic manifestations include dementia, ataxia, myoclonus, and ophthalmoplegia, and the disease should be considered if a patient has a chronic encephalopathic process with gastrointestinal tract dysfunction.

Differential Diagnosis and Diagnostic Approach

The differential diagnosis for infectious encephalitis includes autoimmune-mediated or paraneoplastic encephalitis. Peripheral blood testing for evidence of associated connective tissue disease may be important. Paraneoplastic antibody testing can be performed on peripheral blood and CSF. In patients for whom a paraneoplastic cause is strongly considered, more extensive malignancy screening should be instituted. Depending on the clinical scenario and neuroimaging appearance, demyelinating disease, such as acute disseminated encephalomyelitis and other postinfectious encephalitis syndromes, should be considered. It is also important to recognize that encephalopathy can occur as part of a severe systemic infection rather than as a primary encephalitis.

- Encephalitides often involve the meninges and the brain parenchyma. Therefore, patients with encephalitis and patients with meningitis often have many of the same clinical features, including clinical symptoms and signs of increased intracranial pressure, general infectious signs such as fever, and disorientation or other disturbances of mental status.

Fever With Focal Deficit (Abscess or Focal Encephalitis)

Definition and Overview

An *abscess* is a focal area of inflammation, most commonly due to infection. An abscess can form either by hematogenous spread of infection (in which case the abscess will often form at the gray-white junction) or by direct extension of another infection (eg, sinusitis, otitis, dental infection, infective endocarditis, or meningitis). Abscesses can be single or multiple; multiple abscesses suggest hematogenous spread from another source.

Etiology

The usual pathogenic causes of abscesses are *Streptococcus* or *Staphylococcus* species, but many organisms (eg, gram-negative bacteria and anaerobes) can cause abscesses, depending on the initial source of infection, immunocompromised status, and recent surgery (including interventions such as routine dental procedures). Multiple organisms are common. Fungal causes include *Aspergillus, Cryptococcus, Candida, Histoplasma*, and *Blastomyces* (many of which are discussed in the Meningitis section above). *Nocardia* and *Toxoplasma* can cause brain abscesses, usually in immunosuppressed patients. In addition, mucormycosis can cause severe vascular invasive disease. These causes should be given particular consideration for immunosuppressed and diabetic patients.

Clinical Features

Patients with cerebral abscesses present with fever, headache, and focal neurologic findings that depend on the location of the abscess. Patients may have seizures, associated ventriculitis or meningitis, and complications of increased intracranial pressure.

Differential Diagnosis and Diagnostic Approach

The differential diagnosis includes neoplastic disease, either primary or metastatic. Sarcoidosis or other focal immune-mediated processes can produce a similar clinical picture. Demyelinating disease, such as tumefactive multiple sclerosis, should be considered in patients with brain abscess. Any focal space-occupying lesion can produce a similar clinical syndrome, but neuroimaging helps with proper differentiation.

Peripheral blood studies (eg, white blood cell count and blood cultures) should be performed. Cultures are often negative, though, because the bacteremia associated with seeding the brain has passed when neurologic focal symptoms are apparent.

Neuroimaging is crucial diagnostically. MRI generally shows 1 or more focal T2-hyperintense lesions, often with surrounding edema. In later stages, there may be capsule formation with "ring enhancement" around the lesion. For most patients with brain abscess, spinal tap is contraindicated and of low yield. In general, surgical drainage of an abscess and use of antibiotics are required for successful treatment. This also allows culturing to identify a causative organism.

Treatment

Epidural bacterial abscesses, either cranial or spinal, and subdural empyemas are also potentially life-threatening infections that cause high morbidity. These generally arise from the local spread of infection and require surgical drainage and antibiotic treatment. Symptoms and physical signs are similar to those of general infection, but focal findings are dependent on the abscess location.

- An abscess can form either by hematogenous spread of infection (in which case the abscess will often form at the gray-white junction) or by direct extension of another infection (eg, sinusitis, otitis, dental infection, infective endocarditis, or meningitis).
- The usual pathogenic causes of abscesses are *Streptococcus* or *Staphylococcus* species, but many organisms (eg, gram-negative bacteria and anaerobes) can cause abscesses.

Infectious Myelopathy

Definition and Overview

Myelitis is an inflammation or infection of the spinal cord. Infectious myelitis often occurs as part of a wider syndrome of encephalomyelitis but can occur in isolation.

Etiology

Myelopathy can result from epidural or subdural abscesses directly compressing the spinal cord or from a direct infection. Pott disease, caused by *M tuberculosis* infection of the vertebral body structure of the spine, can result in collapse of the vertebra or epidural extension and resultant cord compression. Direct infection of the spinal cord parenchyma is rare but can be caused by bacteria, viruses, fungi, parasites, and tuberculosis. Abscesses can occur within the cord itself.

Viral infections with VZV, human T-lymphotropic virus (HTLV) type 1, HSV-2, and cytomegalovirus (CMV) can cause infectious myelopathy or polyradiculopathy, particularly in immunosuppressed patients. Lyme disease can cause myelitis. Although polio is now exceedingly rare, other enteroviruses (eg, coxsackievirus and echovirus) can produce myelitis. West Nile virus, rabies virus, St Louis encephalitis virus, and Japanese encephalitis virus infection can damage anterior horn cells, producing a similar clinical phenotype often with a meningitic or encephalitic component. Tick-borne encephalitis and Japanese encephalitis could be considered depending on the risk factors.

Syphilis, as meningovascular syphilis or tabes dorsalis, can damage the spinal cord. HIV-associated vacuolar myelopathy should be considered; both HTLV infection and HIV infection produce subacute to chronic myelopathies.

Clinical Features

Myelopathy symptoms and signs include weakness below the level of the lesion, which, depending on the location in the spinal cord, can be unilateral or bilateral and can involve lower motor neuron pathways (causing flaccid weakness) and upper motor neuron pathways (causing spastic weakness). Sensory loss can occur below the level of the lesion; since large-fiber sensation (touch, pressure, proprioception, and vibration) largely travels up the spinal cord ipsilaterally, and small-fiber sensation (pain and temperature) largely travels contralaterally, this information can be helpful for localizing the lesion. Lesions in the thoracic and upper lumbar cord can also affect the autonomic system and lead to autonomic failure and autonomic instability; if cephalad enough, these lesions can cause Horner syndrome. Bowel, bladder, and sexual dysfunction can also occur. (See Chapter 38, "Myelopathies.")

Differential Diagnosis and Diagnostic Approach

The differential diagnosis includes other immune-mediated and paraneoplastic processes. (See Chapter 38, "Myelopathies.") Sarcoidosis and connective tissue diseases can be associated with myelopathies. Transverse myelitis can occur in isolation or as part of multiple sclerosis, neuromyelitis optica, or acute disseminated encephalomyelitis. Vascular causes such as spinal cord infarction or hemorrhage produce a rapid onset of symptoms and signs. Vasculitis can occur within the spinal cord. Structural causes must be prominent on the differential diagnosis and include neoplasms and vascular malformations. Most neurodegenerative causes of a myelopathy phenotype, such as hereditary spastic paraparesis, spinocerebellar ataxia, and amyotrophic lateral sclerosis (when there is only motor involvement), progress more slowly than typical infectious myelopathies but may be considered in selected cases.

When infectious myelopathy is suspected, CSF evaluation is important, as is MRI of the affected area of spinal cord. There may be areas of increased T2-signal intensity, sometimes with focal cord enlargement or gadolinium enhancement (or both). These help to establish the diagnosis and rule out possible mimics. Depending on the clinical syndrome, MRI evaluation of the brain can be useful to assess for encephalomyelitis or for evidence of more widespread demyelinating disease.

- Myelopathy can result from epidural or subdural abscesses directly compressing the spinal cord or from a direct infection.
- When infectious myelopathy is suspected, CSF evaluation is important, as is MRI of the affected area of spinal cord.

Infectious Radiculopathies and Acute Flaccid Paralysis

Definition and Overview

Infections may predominantly affect the roots of the spinal nerves or cranial nerves (or both), resulting in radicular symptoms and signs. In some cases, patients present with flaccid paralysis.

Etiology

Unless there is direct extension of a bacterial or fungal infection, infectious radiculopathies are usually viral in origin, with HSV-2, CMV, or VZV as potential causes. Infectious viral radiculopathies are more common in immunosuppressed patients. Lyme disease can also produce a similar clinical picture.

Clinical Features and Physical Examination

Patients with radiculopathies present with weakness in a particular myotome or with numbness, paresthesias, or pain in a particular dermatomal distribution (or with combinations of these features). In patients with polyradiculopathy, areas of motor and sensory involvement may be more widespread. Patients with cervical radiculopathies present with upper extremity symptoms and signs, and patients with lumbosacral radiculopathies present with lower extremity symptoms and signs. If the cauda equina is involved, the patient can also have bowel and bladder dysfunction and decreased perineal sensation. Patients with thoracic radiculopathies typically present with hemicircumferential symptoms and signs (or circumferential if bilateral), and weakness can manifest as outpouching of an area of the abdominal wall. A careful neurologic examination is important to recognize radiculopathy and isolate the involved nerve roots. Features such as fever, rigors, weight loss, and an associated rash can be clues toward an infectious cause.

Differential Diagnosis and Diagnostic Approach

The differential diagnosis of infectious radiculopathy is wide. Structural causes, such as direct nerve root compression from a disk, spondylosis, or spinal stenosis, are important to consider. Inflammatory causes can lead to radiculopathy; diabetic amyotrophy is a well-known cause of focal pain, weakness, and sensory impairment. Diabetic patients are also more likely to have painful thoracic radiculopathies. Arachnoiditis can cause radicular symptoms. Another consideration is malignant infiltration of spinal fluid, leading to deposits of malignant cells on nerve roots.

MRI of the clinically involved area should be performed. If infection is possible, lumbar puncture should be performed, with routine CSF studies and testing for suspected organisms. The peripheral blood should be evaluated for an elevated white blood cell count, markers of inflammation (eg, erythrocyte sedimentation rate), and suspected organisms. Nerve conduction studies and electromyography can be helpful to confirm the clinical diagnosis of radiculopathy and to exclude more widespread involvement, such as a polyradiculoneuropathy. In cases of pure radiculopathies, sensory nerve action potentials should be normal, which can be helpful for localization.

- Unless there is direct extension of a bacterial or fungal infection, infectious radiculopathies are usually viral in origin, with HSV-2, CMV, or VZV as potential causes.

Infection in an Immunocompromised Host

Infection in an immunocompromised host may include direct opportunistic infection as a result of immunosuppression. Causes of immunocompromise may include systemic HIV infection, malignancy, immunosuppressive therapy for malignancy or transplant, and diabetes mellitus.

An immunocompromised patient can be at increased risk for neurologic infection overall but has a significantly increased susceptibility to invasive fungal and mycobacterial infections. Cryptococcal meningitis is more common in immunosuppressed patients, as is toxoplasmosis (caused by a protozoon), which can result in either encephalitis or focal lesions. Patients with progressive multifocal leukoencephalopathy, caused by the JC virus, may present with focal neurologic findings, such as hemiparesis or visual disturbances, depending on the location of the lesions. CMV infection and other viral infections can become reactivated in immunosuppressed patients and cause syndromes as discussed in other sections.

- An immunocompromised patient can be at increased risk for neurologic infection overall but has a significantly increased susceptibility to invasive fungal and mycobacterial infections.

Rapidly Progressive Dementia Due to Infection

Although some of the infectious syndromes previously described, such as the encephalitides, can result in profound cognitive decline that can occur rapidly, another important category of diseases to consider is prion disease. Prions are a type of protein that, when misfolded, can lead to amplification of further misfolded proteins and result in cellular neuronal death. Prion diseases can be sporadic, inherited, or iatrogenic. These include sporadic Creutzfeldt-Jakob disease (CJD), familial CJD, variant CJD, Gerstmann-Straüssler-Scheinker disease, fatal familial insomnia, and kuru. (See Chapter 69, “Prion Disorders: Creutzfeldt-Jakob Disease and Related Disorders.”)

The differential diagnosis includes, in addition to other infectious causes, autoimmune and paraneoplastic diseases, which can be partially evaluated by assessment of thyroid peroxidase antibodies, markers of connective

tissue disease, and paraneoplastic antibodies (in peripheral blood and CSF). MRI of the brain is important and may show highly suggestive features of the prion diseases on diffusion-weighted imaging. Electroencephalography may show periodic discharges, but it may also show other abnormalities, or it can be normal. Particularly with more slowly progressing forms of disease, other neurodegenerative disorders should be in the differential diagnosis, including spinocerebellar ataxias and various degenerative dementias.

64 DNA and RNA Viral Infections of the Nervous System

MICHEL TOLEDANO, MD; ALLEN J. AKSAMIT JR, MD

Introduction

Viruses may cause acute, subacute, or, rarely, chronic infection of the nervous system. The most common acute syndromes of nervous system infections are meningitis and encephalitis, but viruses can also affect the spinal cord and the peripheral nervous system.

Viruses can be classified in many ways. One classification scheme assesses the type of nucleic acid (DNA or RNA), its strandedness (double or single), its sense, and its method of replication (Box 64.1).

This chapter reviews common pathologic DNA and RNA viral syndromes and management. Retroviral infections are covered in Chapter 65, "Retroviral Infections of the Nervous System."

Clinical Syndromes

Viral Meningitis

Viral infection of the meninges is one of the causes of lymphocytic meningitis. The classic clinical presentation of viral meningitis includes fever, headache, photophobia, nuchal rigidity, myalgias, and nausea and vomiting without alteration in the level of consciousness. Cerebrospinal fluid (CSF) findings are characterized by a lymphocytic or mononuclear pleocytosis, mildly elevated protein, and usually a normal glucose concentration. Enteroviruses are the most common cause of viral meningitis (Box 64.2).

Box 64.1 • Classification of Viruses Commonly Encountered in Clinical Practice

- DNA viruses
  - Herpes viruses: HSV-1, HSV-2, EBV, CMV, HHV-6
  - JC virus
- RNA Viruses
  - Rhabdoviruses: rabies virus
  - Arboviruses: eastern and western equine encephalitis viruses, tick-borne encephalitis viruses, dengue virus, Japanese encephalitis virus, St Louis encephalitis virus, West Nile virus, yellow fever virus, LaCrosse virus, Colorado tick fever virus, Rift Valley fever virus, African horse sickness virus, and others
  - Paramyxoviruses: measles virus, mumps virus
  - Influenza virus
  - Enteroviruses: poliovirus, coxsackievirus, echovirus, enterorvirus 71, rhinovirus
- Retroviruses
  - Human immunodeficiency virus (HIV)
  - Human T-lymphotropic virus type 1 (HTLV-1)

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2.

Viral Encephalitis

Viral encephalitis is a viral infection of the brain parenchyma. Pathologically it often occurs concurrently with

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; VZV, varicella zoster virus

Box 64.2 • Etiology of Viral Meningitis

California encephalitis virus
Colorado tick fever virus
Enteroviruses
Epstein-Barr virus
Herpes simplex virus types 1 and 2
Human immunodeficiency virus
Influenza virus types A and B
Lymphocytic choriomeningitis virus
Mumps virus
West Nile virus

meningitis and can be referred to as meningoencephalitis. Clinically, it is characterized by acute onset of fever, headache, alteration in the level of consciousness, and behavioral disturbances. Additionally, patients with viral encephalitis can present with focal neurologic deficits and seizure activity. Herpes simplex virus (HSV) type 1 (HSV-1) is the most common nonepidemic viral cause (Box 64.3). In general, encephalitis is characterized histologically by perivascular lymphocytic infiltration of the brain parenchyma and meninges with edema and sometimes frank necrosis. Microglial nodules are a pathologic hallmark of viral encephalitis. Some forms of viral encephalitis are associated with intracellular inclusions, which are helpful for identifying specific causes.

Box 64.3 • Etiology of Viral Encephalitis

Arboviruses
- California encephalitis virus
- Colorado tick fever virus
- Eastern equine encephalitis virus
- Japanese encephalitis virus
- St Louis encephalitis virus
- Venezuelan equine encephalitis virus
- Western equine encephalitis virus

Enteroviruses
- Coxsackievirus
- Echovirus
- Enteroviruses 70 and 71

Herpesviruses
- Cytomegalovirus
- Epstein-Barr virus
- Herpes simplex virus types 1 and 2
- Human herpesvirus type 6
- Varicella zoster virus

Measles virus

• Microglial nodules are a pathologic hallmark of viral encephalitis.

Herpesviridae

Herpesviridae (the herpesviruses) is a family of DNA viruses that includes HSV-1 and HSV type 2 (HSV-2), cytomegalovirus (CMV), varicella zoster virus (VZV), human herpesvirus type 6 (HHV-6), and Epstein-Barr virus (EBV). Clinical features of herpesvirus infections are summarized in Table 64.1 and described in further detail below.

Herpes Simplex Virus Type 1

Epidemiology

HSV-1 is a DNA virus in the herpesvirus family. It is the most common cause of sporadic fatal encephalitis in children 6 months or older and in adults. It can also cause an acute facial paralysis (Bell palsy).

Clinical Syndrome

Acute Encephalitis

HSV-1 encephalitis has a predilection for the medial and anterior temporal lobes, orbitofrontal cortex, insular cortex, and other limbic structures. The clinical picture is characterized by focal neurologic deficits, including hemiparesis and aphasia, focal seizure activity, headache, fever, altered level of consciousness, and behavioral changes.

Diagnosis

Magnetic resonance imaging (MRI) is the preferred imaging modality for detecting the early lesions of HSV-1 infection. T2-weighted hyperintensities are seen in the medial and inferior temporal lobes, insula, and orbitofrontal areas (Figure 64.1). These structures are often affected bilaterally and asymmetrically.

On CSF analysis, protein is elevated, and a lymphocytic pleocytosis is usually present. Red blood cells or xanthochromia (or both) may be present as a consequence of hemorrhagic necrosis, but this is not a reliably specific finding. Polymerase chain reaction (PCR) for HSV-1 DNA in the CSF is highly sensitive and specific but may be negative in the first 24 to 48 hours. It may remain positive for at least 2 weeks in up to 25% of cases.

Electroencephalography can help with diagnosis of HSV-1 encephalitis by showing periodic lateral epileptiform discharges, which are suggestive although not diagnostic.

Brain biopsy is not required for diagnosis, but it can be performed to distinguish HSV-1 encephalitis from other forms of limbic encephalitis when PCR testing is negative

Table 64.1 • Herpesviruses: Clinical Syndromes, Diagnosis, and Management

Virus	Clinical Syndrome	Diagnosis	Treatment
HSV-1	Acute encephalitis	MRI: T2-weighted hyperintensities in temporal and orbitofrontal regions CSF PCR for HSV-1	Acyclovir
HSV-2	Neonatal encephalitis Recurrent lymphocytic meningitis	CSF PCR for HSV-2	
VZV	Herpes zoster Ramsay Hunt syndrome Segmental paresis Encephalitis Myelitis Reye syndrome	Clinical diagnosis CSF PCR for VZV in selected situations	Acyclovir, valacyclovir, or famciclovir
CMV	Congenital infection Encephalitis Chorioretinitis Lumbosacral polyradiculopathy	CSF PCR for CMV	Ganciclovir with or without foscarnet
HHV-6	Encephalitis (limbic) (usually in transplant patients)	HHV-6 PCR	Ganciclovir and foscarnet
EBV	Meningoencephalomylelitis (rare) HIV-associated primary CNS lymphoma	For primary CNS lymphoma: MRI shows focal enhancing mass and CSF PCR is positive for EBV DNA	For CNS lymphoma in AIDS, palliative chemoradiotherapy and antiretrovirals

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; VZV, varicella zoster virus.

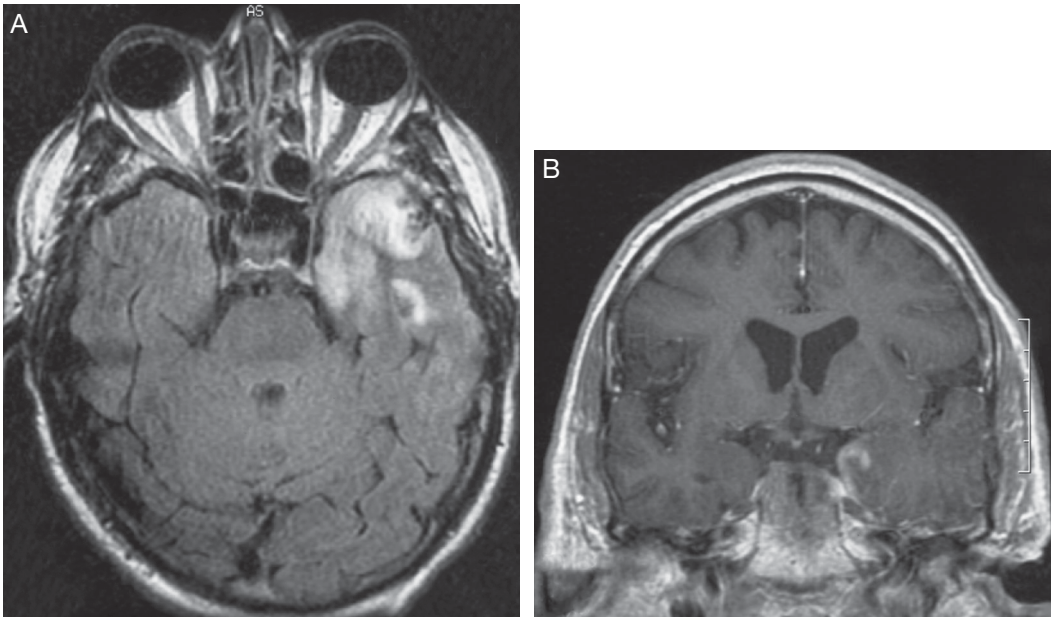

Figure 64.1 *Herpes Simplex Virus (HSV) Encephalitis.*
Magnetic resonance imaging from a 69-year-old man with HSV encephalitis shows a multifocal signal abnormality involving the anterior left temporal lobe and consisting of foci of blood surrounded by edema with patchy gadolinium enhancement. A, Axial fluid-attenuated inversion recovery sequence; B, Coronal postcontrast T1-weighted sequence.
(Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

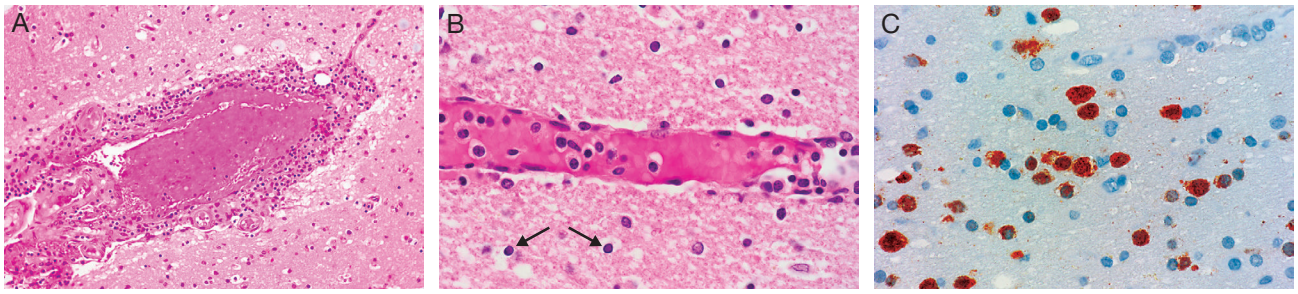

Figure 64.2 *Histologic Features of Herpes Encephalitis. A, Perivascular mononuclear infiltrates. B, Homogenous-appearing viral inclusions (arrows). C, Viral inclusions are more apparent with immunohistochemical staining of herpes simplex virus antigens.*

(Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

and HSV-1 encephalitis is highly suspected. Pathology shows perivascular mononuclear infiltrates and microglial activation with microglial nodules. Hemorrhagic necrosis may be present. Specific intranuclear eosinophilic viral inclusions are characteristic histopathologic features of herpes encephalitis (Figure 64.2).

Treatment

Intravenous acyclovir 10 mg/kg 3 times daily for 14 to 21 days is the standard of care and should be initiated empirically as soon as HSV-1 encephalitis is suspected.

- HSV-1 encephalitis has a predilection for the medial and anterior temporal lobes, orbitofrontal cortex, insular cortex, and other limbic structures.
- PCR for HSV-1 DNA in the CSF is highly sensitive and specific but may be negative in the first 24–48 hours. It may remain positive for at least 2 weeks in up to 25% of cases.
- Electroencephalography can help with diagnosis of HSV-1 encephalitis by showing periodic lateral epileptiform discharges, which are suggestive although not diagnostic.

Herpes Simplex Virus Type 2

Epidemiology

HSV-2 is a herpesvirus that causes genital herpes. HSV-2 is the main pathogen in neonatal HSV infections and the etiologic agent of recurrent lymphocytic meningitis (Mollaret meningitis).

Clinical Syndromes

Neonatal HSV Encephalitis

A neonate acquires HSV-2 by passing through the birth canal of a latently or overtly infected mother. HSV-2 produces a generalized neonatal encephalitis.

Recurrent Lymphocytic Meningitis

Recurrent lymphocytic meningitis is characterized by recurrent attacks of fever, headache, and meningeal irritation lasting between 2 and 5 days. PCR for HSV-2 is highly sensitive and specific. MRI findings may be normal or show leptomeningeal enhancement.

Varicella Zoster Virus

Epidemiology

Primary infection with VZV, a member of the herpesvirus family, results in chickenpox usually without neurologic sequelae. The most common neurologic manifestation is herpes zoster (shingles).

Clinical Syndromes

Herpes Zoster

Herpes zoster results from local reactivation of latent virus in dorsal root ganglia after trauma or when cell-mediated immunity is decreased from age or immunosuppression. Clinically, it is characterized by radicular pain and paresthesias in spinal or cranial dermatomes, followed by a pruritic vesicular rash that develops within 3 to 4 days and crusts by 10 days (Figure 64.3). The most common sites of involvement are (in descending order) the thoracic spine, the cervical spine, and the lumbar spine. About 20% of cases have a cranial nerve distribution.

Although symptoms usually resolve within 2 weeks, some patients have pain, dysesthesia, and allodynia in the previously affected region 1 to 6 months after initial resolution. This condition, known as postherpetic neuralgia, is by far the most common complication of herpes zoster and usually occurs in patients older than 50 who had sensory symptoms before the onset of rash.

To decrease the duration and severity of acute neuritis, antiviral therapy with acyclovir, valacyclovir, or famciclovir can be considered for patients presenting with uncomplicated

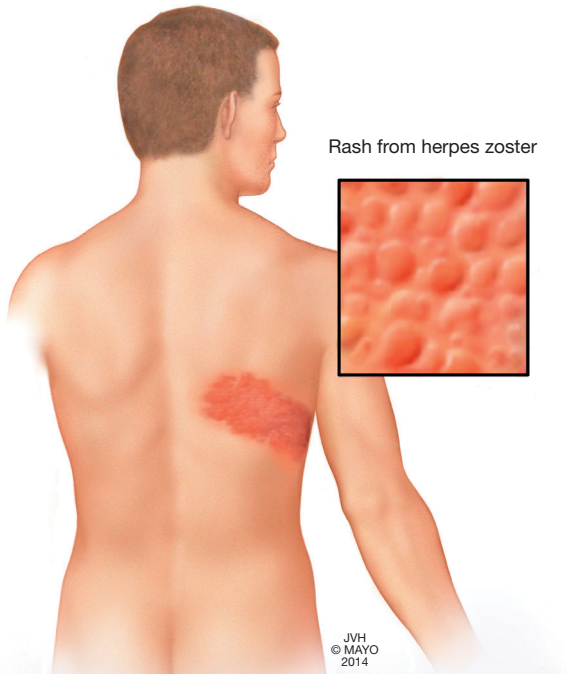

Figure 64.3 *Drawing of Herpes Zoster Rash. Herpes zoster rash is typically a vesicular rash (inset) located in a single dermatome. (Used with permission of Mayo Foundation for Medical Education and Research.)*

zoster within 72 hours of symptom onset. Initiation of glucocorticoid therapy can be considered, although its effectiveness is contested. Postherpetic neuralgia is treated symptomatically with neuromodulating agents, tricyclic antidepressants, or topical lidocaine. In 2006, a vaccine for the prevention of herpes zoster was approved for patients older than 60. In 2011, the vaccine was also approved for patients 50 to 59 years old. The vaccine reduces the incidence of herpes zoster by about 51% and the incidence of postherpetic neuralgia by 67%.

Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus results from viral reactivation in the ophthalmic division of the trigeminal nerve. This can be associated with conjunctivitis, keratitis, uveitis, or iritis and can result in vision loss. It can also be associated with a granulomatous arteritis and small-vessel microangiitis, resulting in multifocal or hemorrhagic cerebral infarctions. Intravenous antivirals may preserve vision in patients with herpes zoster ophthalmicus.

Ramsay Hunt Syndrome

Ramsay Hunt syndrome is caused by viral reactivation in the geniculate ganglion of the facial nerve, resulting in facial paresis and a herpetic rash in the external auditory canal. Antiviral therapy may improve the outcome of facial paralysis in these patients.

Segmental Paresis

Between 5% and 30% of patients with VZV infection have a motor weakness that affects myotomal muscles and roughly corresponds to the dermatomal distribution of the skin lesions (although they are not confined to these). The weakness usually develops within 2 to 3 weeks after the onset of the skin eruption.

Encephalitis

In a small proportion of children (<1%) encephalitis and acute cerebellar ataxia develop within 1 week after the onset of chickenpox. VZV encephalitis in immunosuppressed patients can also occur days to months after herpes zoster or, rarely, without any history of herpetic rash. Treatment is with acyclovir.

Myelitis

Transverse myelitis occasionally complicates herpes zoster. Myelitis is a more frequent complication in immunocompromised patients and involves direct spread of VZV from the dorsal root ganglia centrally into the spinal cord.

Reye Syndrome

Reye syndrome is an acute, noninflammatory encephalopathy resulting from cerebral edema and elevated ammonia levels in pediatric patients with hepatic dysfunction due to microvesicular fatty infiltration of the liver. Classically, it is induced by aspirin use during VZV or influenza B virus infections. Treatment is supportive.

- Herpes zoster results from local reactivation of latent virus in dorsal root ganglia after trauma or when cell-mediated immunity is decreased from age or immunosuppression.
- To decrease the duration and severity of acute neuritis, antiviral therapy with acyclovir, valacyclovir, or famciclovir can be considered for patients presenting with uncomplicated zoster within 72 hours of symptom onset.
- Reye syndrome is an acute, noninflammatory encephalopathy resulting from cerebral edema and elevated ammonia levels in pediatric patients with hepatic dysfunction due to microvesicular fatty infiltration of the liver.

Cytomegalovirus

Epidemiology

CMV is the largest of the herpesviruses. Primary infection is usually benign, and up to 80% of adults in the United States are seropositive by the age of 40. Infection is symptomatic predominantly in immunocompromised hosts and infected newborns.

Clinical Syndrome

Clinical syndromes associated with CMV infection include congenital infection, encephalitis, chorioretinitis (can occur in patients with human immunodeficiency virus [HIV]-AIDS), and lumbosacral polyradiculopathy.

Encephalitis and Ventriculoencephalitis

Patients with CMV encephalitis present clinically with forgetfulness, memory impairments, apathy, and confusion that develop over weeks. They may also have ventriculoencephalitis and present clinically with confusion, cranial nerve palsies, nystagmus, and hydrocephalus that develop over days.

Diagnosis

Diagnosis is by identifying CMV in the CSF with the use of PCR. The CSF shows a mononuclear pleocytosis. In ventriculoencephalitis, a linear homogenous signal can be seen around the ventricles on T2-weighted MRI.

CMV affects ependymal cells and microglia. Histologically, CMV encephalitis is characterized by microglial nodules and Cowdry type A intranuclear inclusions (Figure 64.4).

Treatment

The mainstay of treatment is ganciclovir with or without foscarnet.

- Clinical syndromes associated with CMV infection include congenital infection, encephalitis, chorioretinitis (can occur in patients with HIV-AIDS), and lumbosacral polyradiculopathy.

Human Herpesvirus Type 6

Epidemiology

HHV-6 is ubiquitous, and 95% of the population is seropositive by adulthood. Primary infection during infancy or childhood results in roseola infantum (also called sixth disease or exanthema subitum).

Clinical Syndromes

HHV-6 has been reported to be the etiologic agent of encephalitis (usually limbic encephalitis) in bone marrow and solid organ transplant recipients. HHV-6 has also been associated with focal encephalitis in HIV patients and even in some immunocompetent patients, but its etiologic role in these patients is unclear.

Diagnosis and Treatment

HHV-6 DNA can be detected with PCR. Treatment with ganciclovir and foscarnet may be effective for the treatment of HHV-6 central nervous system (CNS) infections.

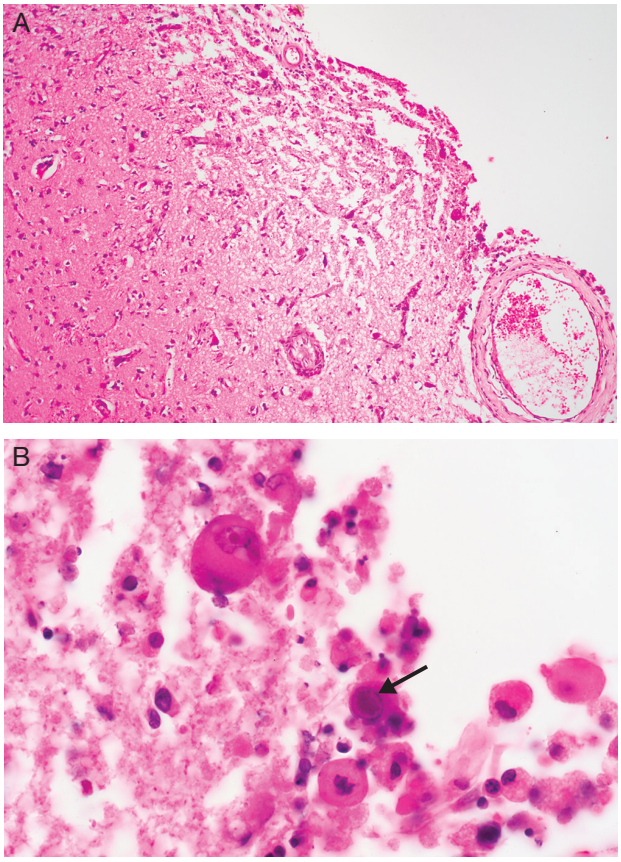

Figure 64.4 *Cytomegalovirus Ventriculitis.*
A, Necrosis and rarefaction of the ventricular surface. B, The ventricular surface is filled with large cells with nuclei containing the typical Cowdry type A intranuclear inclusion bodies (arrow) with the surrounding pale halo that is characteristic of cytomegalovirus infection.
(Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

Epstein-Barr Virus

Epidemiology

EBV is a human B-lymphotropic virus. Nearly 100% of the adult population is seropositive by adulthood. Primary infection can result in infectious mononucleosis, which is characterized by cervical lymphadenopathy, pharyngitis, splenomegaly, and mononuclear lymphocytosis.

Clinical Syndromes

Neurologic Complications of Acute Infection

Neurologic complications of acute infection are rare (<1% of patients) but include meningoencephalitis, transverse myelitis, polyradiculoneuropathy, optic neuritis, and

cranial nerve neuropathies, including facial palsy. Treatment is supportive.

HIV-Associated Primary CNS Lymphoma

After acute infection, EBV remains latent in epithelial cells and B lymphocytes. EBV is detected in a majority of primary CNS lymphomas in AIDS patients and is found to a much lesser extent in lymphomas from immunocompetent patients.

Diagnosis and Treatment

The diagnosis of primary CNS lymphoma in HIV patients is based on computed tomographic or MRI evidence of a focal enhancing mass (usually solitary) and a PCR positive for EBV DNA in the CSF. If PCR is negative and suspicion remains high, brain biopsy may be necessary.

Treatment of primary CNS lymphoma in AIDS patients is palliative with chemoradiotherapy and antiretrovirals.

- EBV is detected in a majority of primary CNS lymphomas in AIDS patients and is found to a much lesser extent in lymphomas from immunocompetent patients.

JC Virus and Progressive Multifocal Leukoencephalopathy

Epidemiology

JC virus is a ubiquitous DNA virus, and antibodies to the virus are present in 85% of the general population by age 9. Primary infection is asymptomatic, but the virus is thought to be the etiologic agent of progressive multifocal leukoencephalopathy (PML). PML occurs almost exclusively in patients who have HIV infection, a lymphoproliferative or myeloproliferative disease, a granulomatous or inflammatory disorder, or solid organ malignancies; patients receiving antirejection immunosuppressive drugs after organ transplant; and patients treated with natalizumab for multiple sclerosis. PML is thought to result from reactivation of latent virus and secondary infection of oligodendrocytes and astrocytes.

Clinical Manifestations

The disease is characterized clinically by subacutely progressive cognitive deficits (memory impairment, psychomotor retardation, inattentiveness), focal deficits (hemiparesis, ataxia, dysarthria), and seizures.

Diagnosis

On MRI, PML appears as single or multiple T2 hyperintense lesions in the juxtacortical white matter or near the deep gray matter, most commonly in the parietooccipital regions. Typically, there is little or no enhancement and examination of the CSF is normal, but PCR can detect JC virus DNA with a reported sensitivity around 80% and a specificity of more than 90%. If PCR is negative but suspicion is high according to clinical and radiographic characteristics, brain biopsy should be pursued.

Foci of PML are frequently located near blood vessels, and confluent demyelination is seen. Histologically, PML is characterized by reactive astrocytes that have a bizarre appearance and enlarged "ballooned" oligodendrocytes with large, dark-pink, "ground-glass" nuclei containing virions (Figure 64.5). On electron microscopy, virus particles appear in 2 forms: filamentous (like spaghetti) and spherical (like meatballs).

Treatment and Prognosis

PML is usually progressive and fatal. The average length of survival is 1 to 3 months after diagnosis. Outcome is slightly different for patients with HIV and natalizulimab-associated infection. With highly active antiretroviral therapy, the 1-year survival rate has increased from 10% to more than 50%. Survival of patients with natalizumab-associated PML appears to be more than 70% with discontinuation of the drug. Cytarabine has been used in patients with PML and hematologic malignancy. For others, discontinuation or reduction of immunosuppression should be pursued.

- Progressive multifocal leukoencephalopathy (PML) occurs almost exclusively in patients who have HIV infection, a lymphoproliferative or myeloproliferative disease, a granulomatous or inflammatory disorder, or solid organ malignancies; patients receiving antirejection immunosuppressive drugs after organ transplant; and patients treated with natalizumab for multiple sclerosis.
- PCR can detect JC virus DNA with a reported sensitivity around 80% and a specificity of more than 90%.

Rabies Virus

Epidemiology

Rabies virus is an RNA virus. Rabies is almost always due to the bite of an infected animal, although some patients do not have known exposure. Bats are the most common animals responsible for the transmission of human rabies in the United States. Viral inoculation is thought to occur at the site of the bite. Retrograde and transsynaptic transport carries the virus up the peripheral nerves to the CNS, causing encephalomyelitis.

The incubation period is 1 to 2 months after exposure, although it may be shorter if the peripheral nerves are directly inoculated or if the site of inoculation is in the head or face.

Clinical Syndromes

Some patients have a nonspecific flulike illness shortly before they develop paresthesias, dysesthesias, or numbness

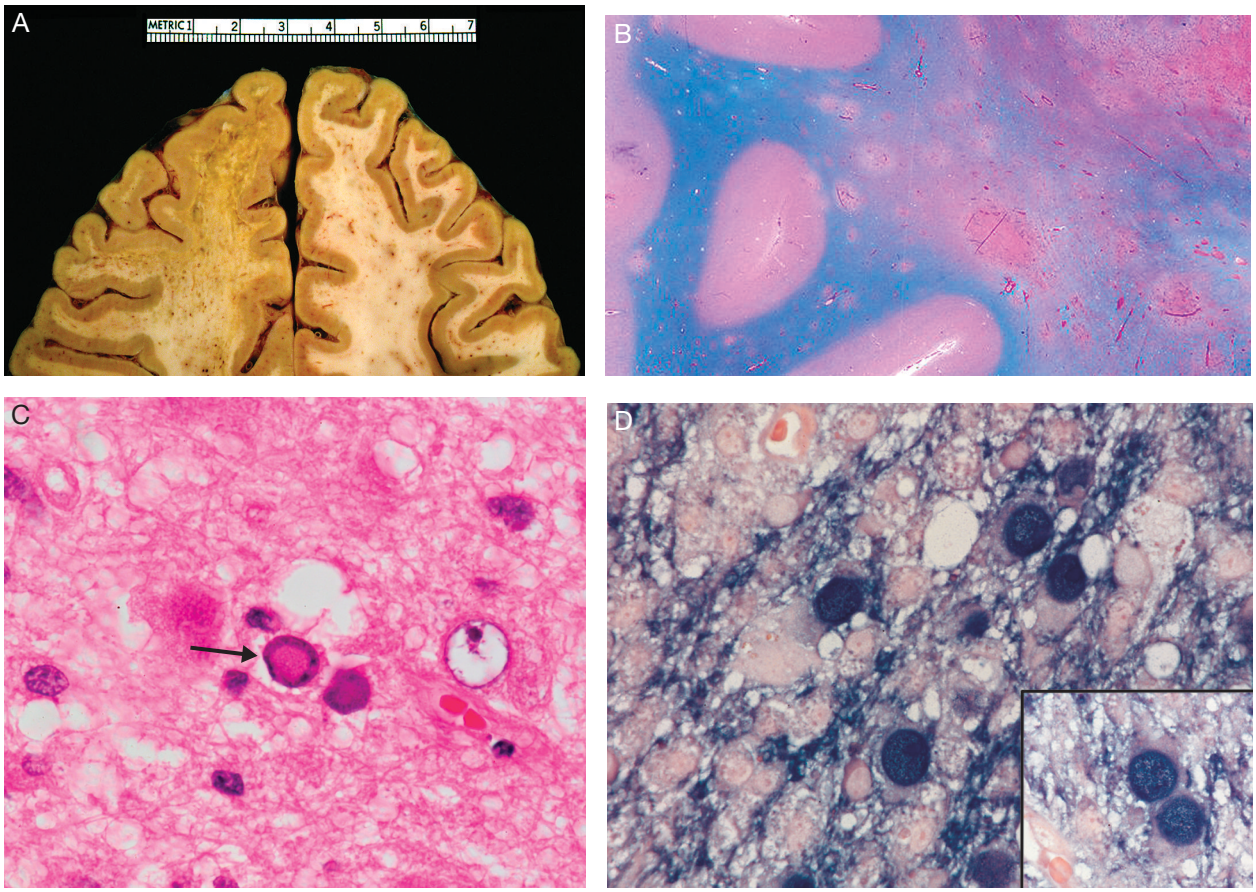

Figure 64.5 *Progressive Multifocal Leukoencephalopathy.*
A, Macroscopic examination of a postmortem specimen from a 35-year-old patient with AIDS shows extensive granular cavitation of the juxtacortical white matter in the right frontal lobe. B, The granular appearance of the white matter is due to the confluence of multiple foci of demyelination. C, Oligodendrocytes with intranuclear inclusions (arrow) filled with virions are characteristic of this condition. D, Immunohistochemical staining for JVC virus antigens is better for showing the inclusions. (Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

at the site of the bite. The local symptoms can then spread along the limb or to the ispilateral side of the face and progress to either site.

Encephalitic Form

Patients with rabies present with fluctuations in mentation, behavior, and consciousness; persistent fever; hypersalivation combined with extreme dysphagia due to pharyngeal spasms (hydrophobia); psychosis; autonomic dysfunction; and, eventually, seizures and coma before death.

Paralytic Form

A paralytic form, which occurs in less than 20% of patients, is characterized by ascending weakness and areflexia due to an axonal polyradiculoneuropathy leading to respiratory failure and death.

Diagnosis

CSF is usually normal, although mild lymphocytic pleocytosis is not uncommon. MRI may show nonspecific T2 hyperintensities with or without enhancement. Before death, the diagnosis can be made by virus-specific immunofluorescent staining of skin biopsy specimens, isolation of virus from the saliva, or detection of anti-rabies antibodies in serum or CSF. PCR for viral RNA is also available and can be performed on skin or CSF samples.

Histologically, rabies is characterized by Negri bodies, which are viral inclusions in the cytoplasm of Purkinje cells, and hippocampal pyramidal cells that resemble bullet-shaped particles on electron microscopy (Figure 64.6).

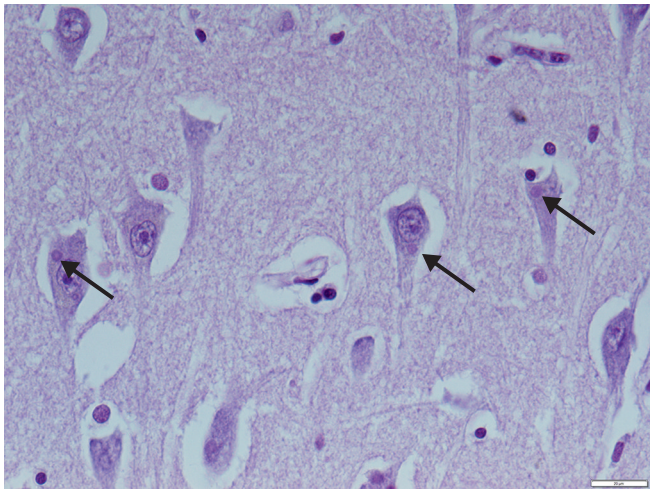

Figure 64.6 *Rabies. Hippocampal pyramidal cells are shown with characteristic viral inclusions, Negri bodies (arrows).*

Treatment

Postexposure prophylaxis is the only available treatment. Immediate cleansing of the wound should be followed by prompt administration of rabies immune globulin and rabies vaccine. Postexposure prophylaxis is not effective after the onset of neurologic symptoms.

- Patients with rabies present with fluctuations in mentation, behavior, and consciousness; persistent fever; hypersalivation combined with extreme dysphagia secondary to pharyngeal spasms (hydrophobia); psychosis; autonomic dysfunction; and, eventually, seizures and coma before death.

Poliovirus

Epidemiology

Poliovirus, an RNA virus, is a member of the family Picornaviridiae and is the etiologic agent of poliomyelitis. Natural polio infection occurs through ingestion of the virus, which infects the oropharyngeal and intestinal mucosa. Dissemination of the virus to the CNS is poorly understood. It may occur by hematogenous spread or by retrograde axonal transport from muscle to spinal cord and brain.

Clinical Syndrome

About 95% of infected patients are asymptomatic, but 5% have a nonspecific viral syndrome characterized by myalgia, headache, sore throat, fever, nausea, and vomiting. In a fraction of these patients, paralytic polio develops, which is characterized by focal myalgia, fasciculations, and weakness leading to flaccid paralysis. Poliovirus affects the lower extremities more than the upper extremities, which are affected more than the bulbar muscles. The likelihood of paralytic polio developing increases with age.

Diagnosis, Treatment, and Prognosis

Stool cultures for poliovirus are diagnostic for acute poliomyelitis. There is no treatment for poliomyelitis. Prophylaxis with an inactivated killed vaccine is routine in the United States, and the last case of naturally occurring poliomyelitis was in 1979. The oral vaccine, which contains a live-attenuated virus, is still used in some developing countries but is associated with postvaccination polio in about 0.04 per 100,000 vaccinations.

Half the patients with paralytic polio recover fully, 25% recover with mild disability, and the remaining 25% are left with severe disability. Between 5% and 10% die of neuromuscular respiratory failure. Postpolio syndrome, a recurrence of flaccid paralysis in a previously affected musculature 10 to 15 years after infection, occurs in 20% to 30% of patients.

- Poliovirus affects the lower extremities more than the upper extremities, which are affected more than the bulbar muscles.
- Stool cultures for poliovirus are diagnostic for acute poliomyelitis.

Arboviruses

Epidemiology

Arboviruses are carried by arthropods (ticks and mosquitoes) and cause seasonal epidemic encephalitis, mostly during the summer and early fall.

LaCrosse virus is the most important arboviral cause of pediatric encephalitis in the United States, whereas Japanese encephalitis virus is probably the most common cause of arthropod-borne encephalitis in the world. The most important tick-borne causes of viral encephalitis are Powassan virus and Colorado tick fever virus.

Clinical Features

Clinically, most arbovirus infections are characterized by meningoencephalitis, but severity varies (Table 64.2). West Nile viral infections may also produce asymmetric lower motor neuron paralysis related to anterior horn cell damage.

Diagnosis and Treatment

The characteristic CSF abnormalities found in the CSF of patients with arboviral meningoencephalitis include an initial polymorphonuclear leukocytic pleocytosis with a shift to a lymphocytic or mononuclear pleocytosis, normal to slightly elevated protein, and a normal glucose

Table 64.2 • Clinical Syndromes of Arboviruses

Arbovirus	Geographic Region	Vector	Reservoir	Clinical Presentation	Prognosis
West Nile virus	Entire US, southern Canada	Mosquitoes (*Culex*)	Birds	Febrile flulike illness followed by nausea, abdominal pain, and diarrhea and symptoms of encephalitis Patients can have a coarse tremor, myoclonus and parkinsonian features Direct infection of anterior horn cells results in acute asymmetric poliomyelitis-like flaccid paralysis	Mortality is about 10% for patients with encephalitis Complete recovery is unlikely for patients with poliomyelitis-like illness
California encephalitis virus, LaCrosse virus	Midwestern US	Mosquitoes (*Aedes triseriatus*)	Birds	Aseptic meningitis or mild encephalitis predominantly affecting children <12 y old Seizures affect >50% of children; focal neurologic signs affect >20% of children	Usually self-limited and uncomplicated Mortality rate <1%, but neurologic sequelae in about 15% of patients
St Louis encephalitis virus	Western, southeastern, and midwestern US	Mosquitoes (primarily *Culex*)	Birds	Severity of illness increases with age Encephalitis with psychotic features can develop in the elderly Slow progression of encephalitis, generalized fatigue, and tremors	Mortality rate, 20%
Western equine encephalitis virus	Western North America	Mosquitoes (primarily *Culex*)	Birds	Mostly asymptomatic, although can cause meningoencephalitis in children <1 y old or adults >50 y old	If encephalitis develops, mortality rate is 10%
Eastern equine encephalitis virus	Eastern seaboard and Gulf coast of US	Mosquitoes (primarily *Aedes, Coquillettidia,* and *Culex*)	Birds	Abrupt onset of high fever and convulsions with rapid progression to coma Neurologic sequelae are common	Mortality, about 60%
Japanese encephalitis virus	China, Southeast Asia, India, and Sri Lanka	Mosquitoes (*Culex tritaenio-rhynichus*)	Birds, pigs	Most common cause of arthropod-borne human encephalitis worldwide High fever with malaise, headache, nausea, and vomiting lasting 1–6 d Can progress to a severe fulminant encephalitis with seizures eventually leading to coma and death Patients can have extrapyramidal symptoms, including tremor, axial rigidity, and choreoathetosis Involvement of anterior horn cells can result in flaccid paralysis	Mortality, 30%; approximately 50% of survivors have sequelae

Abbreviation: US, United States.

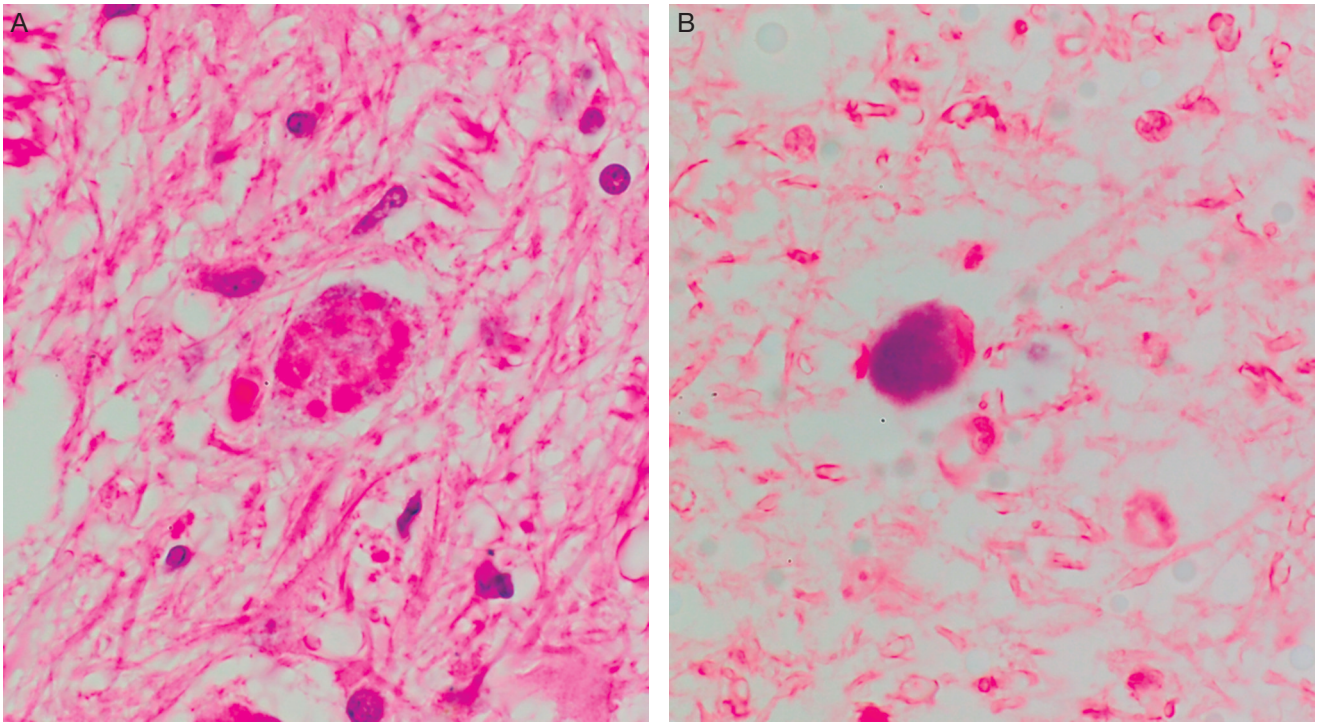

Figure 64.7 *Measles Virus.*
A, A multinucleated cell with intranuclear inclusions of measles virus in subacute sclerosing panencephalitis. B, Immunohistochemistry staining for the viral antigens is better for showing the viral inclusions.
(Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

concentration. Diagnosis is established by demonstrating immunoglobulin M antibodies in the serum or CSF. PCR for CSF is available for West Nile virus.

Treatment is supportive, but prophylactic vaccination for Japanese encephalitis is available.

- Arboviruses are carried by arthropods (ticks and mosquitoes) and cause seasonal epidemic encephalitis, mostly during the summer and early fall.
- Clinically, most arbovirus infections are characterized by meningoencephalitis, but severity varies.
- Diagnosis of arboviral meningoencephalitis is established by demonstrating immunoglobulin M antibodies in the serum or CSF. PCR for CSF is available for West Nile virus.

Measles Virus

Overview and Epidemiology

The measles virus is an RNA virus generally spread through infected respiratory secretions. The incidence of measles has significantly decreased with immunization. The CNS may be involved in the acute infection—rarely in delayed infection—resulting in either inclusion body encephalitis or subacute sclerosing panencephalitis.

Clinical Features

Acute infection results in fever, maculopapular rash, and cough. When the CNS is involved, patients may present with aseptic meningitis, encephalitis, or transverse myelitis.

Two rare delayed complications of measles virus infection include measles inclusion body encephalitis and subacute sclerosing panencephalitis. Patients with measles inclusion body encephalitis present with rapidly progressive dementia 1 to 6 months after the acute illness. Patients with subacute sclerosing panencephalitis present 2 to 12 years after the measles infection with gradual behavioral disturbance, seizures, dementia, spasticity, and movement disorders (myoclonus, chorea, and ataxia). Eventually patients with subacute sclerosing panencephalitis progress to coma and die. In this condition electroencephalography shows generalized, repetitive polyphasic sharp and slow waves, often in conjunction with myoclonic jerks. Pathology shows parenchymal and leptomeningeal perivascular lymphocytic infiltrates in the cortex and white matter with intranuclear inclusions (Figure 64.7).

65 Retroviral Infections of the Nervous System

MICHEL TOLEDANO, MD; ALLEN J. AKSAMIT JR, MD

Introduction

Retroviruses are a family of viruses that replicate by reverse transcription. This family includes human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV). This chapter reviews neurologic manifestations of these retroviruses.

Human Immunodeficiency Virus

Epidemiology

A retrovirus in the lentivirus family, HIV has 2 forms, HIV-1 and HIV-2. HIV-1 is associated with the global AIDS pandemic, whereas HIV-2 causes an AIDS-like illness primarily in West Africa, although pockets of infection exist globally.

HIV preferentially infects $CD4^+$ cells, typically affecting monocytes, T lymphocytes, and microglia. The viral envelope glycoprotein gp120 binds to CD4 and to the CCR5 (macrophages) and CXCR4 (T cells) receptors, allowing the virus to enter the cell. Primary infection affects macrophages first, and patients homozygous for a deletion in CCR5 are relatively resistant to infection. Infected macrophages fuse with CD4 T cells, and the virus spreads to organs such as the brain, spleen, and lymph nodes. Replication in host cells leads to cell death and severe immunodeficiency.

The main routes of transmission are by blood and genital secretions, typically by sexual contact or intravenous drug use. Screening of blood products and organ donors is now routine. Mother-to-infant transmission can occur in utero, during birth, or through breast milk.

Primary Infection

Primary infection may be associated with a flulike illness, which can include fever, malaise, myalgias, a maculopapular rash, and rarely aseptic meningitis. During the clinical latent period that follows, the patient is asymptomatic but viral reproduction continues and the CD4 count decreases. This latent period lasts 10 years on average. Invariably, patients have symptoms suggestive of reduced cell-mediated immunity. As the CD4 counts continue to decrease, opportunistic infections and AIDS develop (Table 65.1). With the exception of aseptic meningitis, most neurologic complications occur during the later stages. Without treatment, neurologic symptoms develop in more than 50% of HIV patients during the course of

Table 65.1 • Opportunistic Infections Encountered in HIV Infection According to CD4 Cell Count

CNS Disease	CD4 Cell Count/μL
Syphilitic meningitis	>500
Tuberculous meningitis	200–500
Toxoplasmosis	<200
Cryptococcal meningitis	<200
CMV encephalitis, polyradiculopathy	<50
PML	<50

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; HIV, human immunodeficiency virus; PML, progressive multifocal leukoencephalopathy.

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy

their illness. Highly active antiretroviral therapy (HAART) has decreased the incidence of neurologic complications.

Other Clinical Manifestations and Associated Syndromes

Aseptic Meningitis

Aseptic meningitis is a monophasic illness that usually occurs within the first 6 weeks of seroconversion. Patients may have HIV antibodies in their blood, but they may test positive for p24 antigen only in the early course of infection. Typically, this is a self-limited disease.

HIV-Associated Dementia

HIV-associated dementia usually occurs late in an HIV infection, when the CD4 cell count is less than 200/μL, and is thought to be related to the HIV infection itself. The incidence has decreased considerably since the introduction of HAART and is currently between 7% and 15%. The prevalence, however, may be increasing as patients with HIV live longer. Clinically, HIV-associated dementia is characterized by slowly progressive behavioral changes and subcortical dementia (poor attention, bradyphrenia, memory loss, and bradykinesia).

Magnetic resonance imaging (MRI) demonstrates diffuse T2-signal abnormalities in the periventricular white matter and generalized atrophy (Figure 65.1).

Histologically, there is periventricular and perivascular inflammation with multinucleated giant cells and reactive gliosis.

HIV-Associated Vacuolar Myelopathy

HIV-associated vacuolar myelopathy usually occurs late in the disease, which differentiates it from the far less common HIV transverse myelitis associated with acute infection. HIV-associated vacuolar myelopathy is characterized by the subacute progression of spastic paraparesis, bladder dysfunction and sensory loss (primarily proprioception). The disease is caused by degeneration of the posterior and lateral columns of the spine.

Histologic findings include spongiform change with vacuolization of myelin sheaths, lipid-laden macrophages and microglia, and multinucleated giant cells.

HIV-Associated Neuromuscular Disease

Neuromuscular conditions associated with HIV infection or its treatment are listed in Table 65.2.

Treatment

The mainstay of HIV therapy includes HAART, which generally refers to a cocktail of several antiretroviral medications (6 separate classes of medications). HAART decreases the viral load and has dramatically increased life expectancies and decreased opportunistic infections. General adverse effects of some of the medications include hepatotoxicity, lactic acidosis, rash, and dyslipidemia. Potential neurologic adverse effects of the medications are listed in Table 65.3).

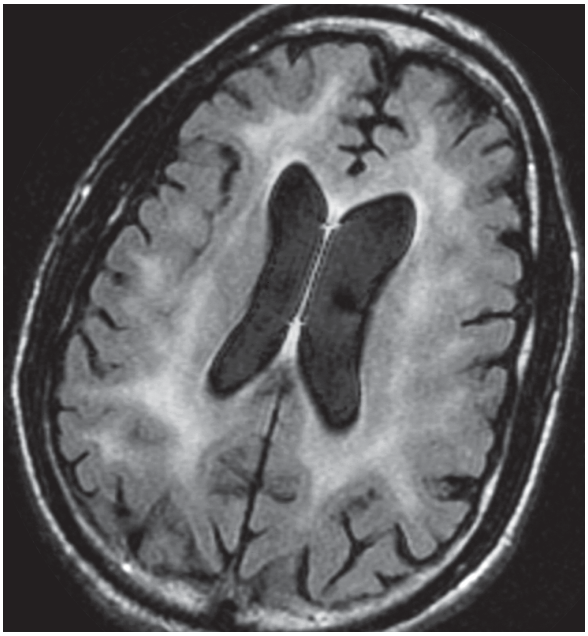

Figure 65.1 *Human Immunodeficiency Virus–Associated Dementia.*
Magnetic resonance imaging shows the characteristic feature: diffuse, confluent, ill-defined periventricular white matter hyperintense lesions on axial fluid-attenuated inversion recovery sequences.
(Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

- HIV preferentially infects $CD4^+$ cells, typically affecting monocytes, T lymphocytes, and microglia.
- Clinically, HIV-associated dementia is characterized by slowly progressive behavioral changes and subcortical dementia (poor attention, bradyphrenia, memory loss, and bradykinesia).
- HIV-associated vacuolar myelopathy usually occurs late in the disease, which differentiates it from the far less common HIV transverse myelitis associated with acute infection.
- The mainstay of HIV therapy includes HAART.

Opportunistic Infections Common With HIV Infection

Toxoplasmosis

Toxoplasmosis usually occurs in patients with CD4 cell counts less than 100/μL. The infection is caused

Table 65.2 • Neuromuscular Disease Associated With Human Immunodeficiency Virus (HIV) Infection

Condition	Description
Distal sensory polyneuropathy	Painful, symmetric, predominantly sensory (small fiber more than large fiber) axonal neuropathy that develops late in the disease It is clinically apparent in up to 30% of patients with AIDS
Antiretroviral-associated neuropathy	Associated with nucleoside analogues such as didanosine, zalcitabine, and stavudine Clinically and electrophysiologically, it resembles primary HIV neuropathy and can be distinguished only by empirical removal of the offending agent
Cranial mononeuropathies and mononeuritis multiplex	Mononeuropathies are an uncommon clinical manifestation of neurologic disease in HIV-positive patients and can involve either cranial or peripheral nerves Facial nerve palsy is the most common cranial neuropathy HIV-infected patients with mononeuropathy multiplex and CD4 cell counts <200/μL should be evaluated for cytomegalovirus infection Hepatitis B surface antigen and hepatitis C antibody should also be considered
Demyelinating polyradiculoneuropathy	The 2 major forms of acquired inflammatory demyelinating polyradiculoneuropathy are acute demyelinating polyradiculoneuropathy and chronic inflammatory demyelinating polyradiculoneuropathy Both have occurred in patients with underlying HIV infection Treatment is with intravenous immunoglobulin or plasma exchange
Lumbosacral polyradiculopathy	Rapidly progressing lumbosacral polyradiculopathy (cauda equina syndrome) occurs mainly in HIV-infected patients with CD4 cell counts of <50/μL The most common cause is cytomegalovirus Sacral radiculomyelitis can occur with primary HSV-2 infection at any stage of HIV disease
HIV-associated myopathy	Characterized by progressive muscle weakness (proximal muscles more than distal muscles), myalgias, and mild elevation of creatine kinase Pathophysiology is unclear
Antiretroviral-associated neuromuscular weakness	Zidovudine and stavudine can cause progressive muscular weakness and myalgias Mechanism is thought to be due to mitochondrial toxicity
Motor neuron disease	An amyotrophic lateral sclerosis–like illness can occur late in the course of HIV infection Improves with antiretroviral therapy

by reactivation of latent *Toxoplasma gondii*, an obligate intracellular protozoa. (See also Chapter 68, "Parasitic Infections of the Central Nervous System.") About one-third of the population is seropositive for *T gondii* by adulthood. The primary mode of transmission is the fecal-oral route through the ingestion of oocytes or cysts in feline feces, contaminated food, or uncooked meat.

Neurologic symptoms are secondary to the development of focal parenchymal abscess or abscesses and

Table 65.3 • Neurologic Complications of Highly Active Antiretroviral Therapy (HAART)

Drug		
Class	**Example**	**Potential Neurologic Complication**
Nucleoside analogue	Zidovudine	Myalgia Myopathy (related to mitochondrial toxicity) Neuropathy (related to mitochondrial toxicity; the combination of didanosine and stavudine carries the highest risk)
Non-nucleoside reverse transcriptase inhibitor	Nevirapine	Hepatotoxicity leads to hepatic encephalopathy Headache Nightmares Confusion Mood changes
Protease inhibitor	Ritonavir	Headache Circumoral and limb paresthesia
CCR5 inhibitor	Maraviroc	Musculoskeletal symptoms
Integrase inhibitor	Raltegravir	Headache Myositis

consist of headache, seizures, hemiparesis, hemianopia, aphasia, or ataxia. Subacute encephalitis can also ensue.

Neuroimaging of a patient with toxoplasmosis shows 1 or more ring-enhancing lesions with a predilection for the basal ganglia. About two-thirds of patients have multiple lesions at presentation, unlike patients with HIV-associated central nervous system (CNS) lymphoma, who usually present with a solitary lesion. Imaging findings help distinguish between neurotoxoplasmosis and lymphoma: Lymphoma has greater thallium uptake on thallium single-photon emission computed tomography and greater glucose and methionine metabolism on positron emission tomography than neurotoxoplasmosis. Polymerase chain reaction for *T gondii* in the cerebrospinal fluid (CSF) has a specificity of more than 95%, but sensitivity is variable. Lumbar puncture may be contraindicated if a focal mass lesion is present.

Treatment is with pyrimethamine, sulfadiazine, and folinic acid. HAART should be initiated and maintenance therapy continued until the CD4 cell count is more than 200/μL. Patients should then receive lifelong prophylaxis with trimethoprim-sulfamethoxazole.

Cryptococcal Meningitis

Cryptococcal meningitis is caused by *Cryptococcus neoformans*, an encapsulated yeast. It was a frequent cause of meningitis in AIDS before HAART. (See also Chapter 67, "Fungal Infections of the Central Nervous System.") Cryptococcal meningitis rarely occurs in patients with CD4 cell counts greater than 100/μL.

Cryptococcosis is characterized by chronic basilar meningitis with slow onset of altered mentation, cranial neuropathies, behavioral changes, and seizures leading to coma. Headache and nuchal rigidity are absent because of the mild inflammatory reaction.

MRI may be normal or may show sulcal or basilar leptomeningeal enhancement or nonspecific T2 hyperintensities.

CSF analysis shows a mild mononuclear pleocytosis with slightly increased protein and decreased glucose concentration. CSF fungal cultures have high sensitivity and specificity but take several weeks to grow. Increased serum and CSF cryptococcal capsular polysaccharide antigen titer is faster and can be diagnostic. India ink stain is no longer used routinely.

Histologic examination shows leptomeningeal inflammatory infiltrates and enlarged perivascular cystic spaces (cryptococcal cysts) filled with encapsulated cryptococci or budding yeast (Figure 65.2).

Treatment is with amphotericin B followed by fluconazole.

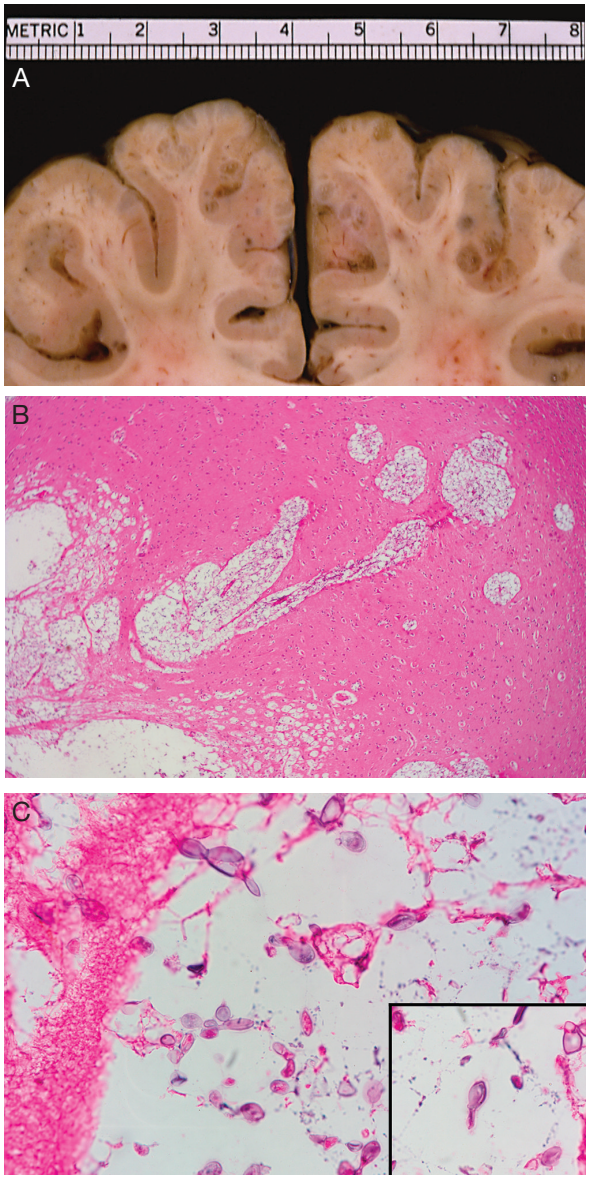

Figure 65.2 *Cryptococcosis.*
A, Typical macroscopic appearance of multiple small intraparenchymal gelatinous cysts involving the cerebral cortex. B, Parenchymal lesions are cystic spaces, often appearing as enlarged perivascular spaces, filled with colonies of cryptococci. C, Higher magnification shows encapsulated organisms, which appear as round basophilic structures.
(Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

Other Viral Infections

Patients with HIV infection may be more susceptible to progressive multifocal leukoencephalopathy (PML) and cytomegalovirus (CMV) infection. In addition, patients with HIV infection may have primary CNS lymphoma related to Epstein-Barr virus infection. For additional

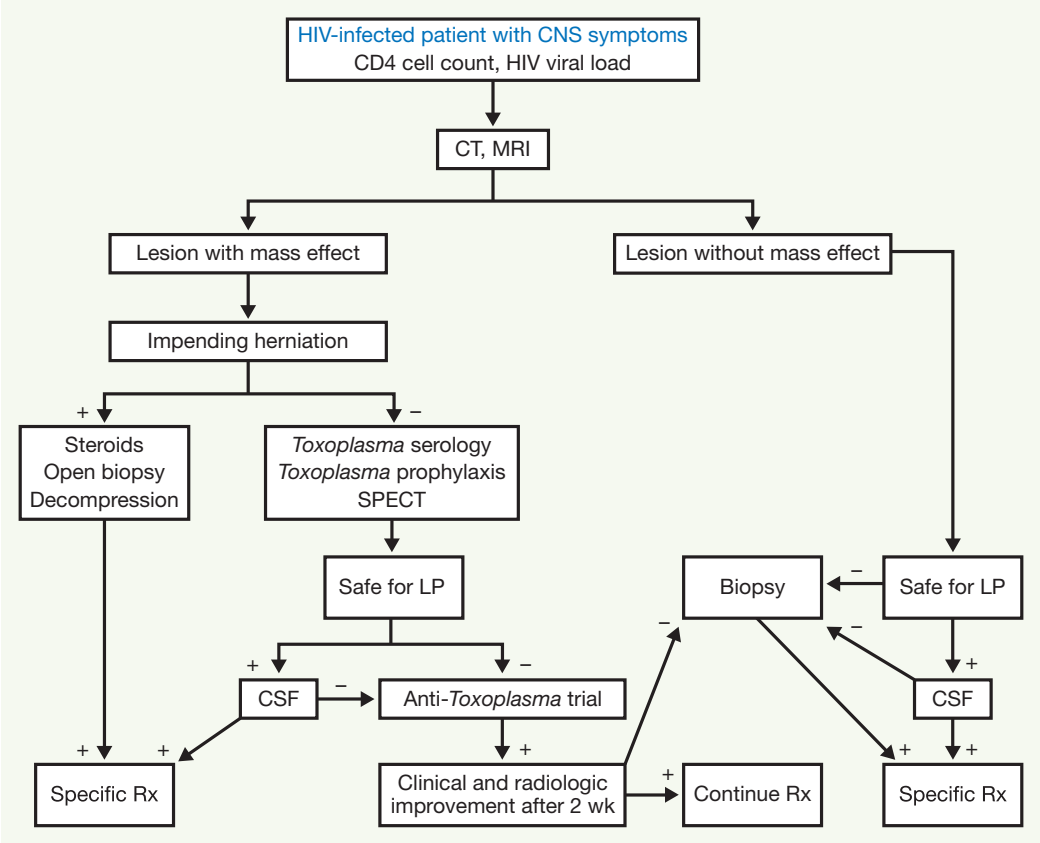

Figure 65.3 *Approach to Patients With HIV Infection and a CNS Mass Lesion.*
CNS indicates central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; HIV, human immunodeficiency virus; LP, lumbar puncture; MRI, magnetic resonance imaging; Rx, treatment; SPECT, single-photon emission computed tomography.

details, see Chapter 64, "DNA and RNA Viral Infections of the Nervous System."

- Neuroimaging of a patient with toxoplasmosis shows 1 or more ring-enhancing lesions with a predilection for the basal ganglia.
- Imaging findings help distinguish between neurotoxoplasmosis and lymphoma: Lymphoma has greater thallium uptake on thallium single-photon emission computed tomography and greater glucose and methionine metabolism on positron emission tomography than neurotoxoplasmosis.

Approach to Patients With HIV Infection and CNS Disease

When evaluating a patient with known HIV infection, it is helpful to consider the clinical syndromes directly related to HIV in addition to opportunistic infections and complications of HIV therapy. The most common diseases associated with advanced HIV infection include toxoplasmosis, CMV encephalitis, primary CNS lymphoma, PML, and HIV dementia.

If a patient has a known HIV infection and a CNS mass lesion with mass effect, considerations generally include toxoplasmosis, primary CNS lymphoma, and other infections (bacterial or fungal) common in the immunosuppressed. For a patient with known HIV infection and a CNS mass without mass effect, considerations may include PML, HIV dementia or encephalopathy, or CMV encephalitis. MRI with a contrast agent is important for the differential diagnosis. A common approach to the diagnosis and treatment of these entities is shown in Figure 65.3.

- When evaluating a patient with known HIV infection, it is helpful to consider the clinical syndromes directly related to HIV in addition to opportunistic infections and complications of HIV therapy.

HTLV-1 Infection

Tropical spastic paraparesis results from the HTLV-1 infection. Transmission of this virus, similar to transmission of HIV, may be vertical (mother to child), sexual, or parenteral. Intravenous drug users are at increased risk for this condition. Myelopathy develops in only 1 in 250 patients infected with HTLV-1.

Patients typically present with a slowly progressive myelopathy primarily affecting the thoracic segments. The bladder is often affected. HTLV-1 may also be associated with a demyelinating polyneuropathy and ataxia.

66 Bacterial Infections of the Nervous System

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Introduction

Bacterial infections of the nervous system manifest themselves in several ways, most of which are neurologic emergencies. This chapter reviews the classic syndromes of meningoencephalitis and focal infection (cerebritis or abscess) as well as the syndromes of neurosyphilis, tuberculosis, botulism, leprosy, Lyme disease, Whipple disease, ventricular shunt infections, rickettsiosis, and diphtheria.

Acute Bacterial Meningitis

Overview

Acute bacterial meningitis is a neurologic emergency. The syndrome of bacterial meningitis consists of the subacute onset of headache, meningismus, fever, and depressed level of consciousness. These features are considered sensitive for the condition; 95% of patients have 2 of the 4 features of fever, stiff neck, altered mental status, or headache, but only 45% have all 4. An awareness of acute bacterial meningitis is of great importance to the practicing neurologist since outcome is dependent on rapid diagnosis and administration of antibiotics.

Epidemiology

The overall incidence of acute bacterial meningitis in developed countries is estimated to be about 5 per 100,000 annually. The most common agents associated with sporadic community-acquired disease include *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae*. They are thought to enter the bloodstream or the leptomeninges (or both) after nasopharyngeal and respiratory infection. *Listeria monocytogenes* is thought to account for about 8% of community-acquired acute bacterial meningitis and is typically acquired from contaminated food. Other risk factors for a *Listeria* infection include age older than 50 years, pregnancy, diabetes mellitus, immune suppression or compromise, or other chronic illness. The development of the *Haemophilus* b conjugate vaccine dramatically reduced the incidence of *Haemophilus* in children as a cause of meningitis and likely contributed to the shift in peak incidence of acute bacterial meningitis from childhood to adulthood. The pneumococcal and meningitis vaccines have decreased overall incidence but, for different reasons, are not as likely to have had as great an impact as the *Haemophilus* b conjugate vaccine.

Diagnosis

If a patient presents with signs and symptoms suggesting bacterial meningitis, evaluation and management should be expeditious. Blood cultures should be performed.

The clinical history and physical examination are of great importance, but confirmation of diagnosis is by cerebrospinal fluid (CSF) analysis. Performing neuroimaging before lumbar puncture in all suspected cases remains a matter of discussion, but noncontrast computed tomographic neuroimaging is recommended to exclude an intracranial mass effect before lumbar puncture when there are 1) signs of elevated intracranial pressure (papilledema), 2) focal or lateralizing neurologic signs, 3) signs potentially associated with herniation (coma), 4) new-onset seizures, or 5) an immune compromised state.

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PCR, polymerase chain reaction

Lumbar puncture for CSF analysis should include glucose and protein concentrations, white blood cell count with differential blood count, Gram staining, and bacterial culture. The classic CSF formula for acute bacterial meningitis includes hypoglycorrhachia (ratio of CSF glucose to serum glucose <0.3), a neutrophilic pleocytosis, elevated protein level, and positive Gram staining or culture. Bacterial antigen testing has fallen out of favor but is still used by some laboratories. Polymerase chain reaction (PCR) studies can show bacterial infection but are not widely available for rapid diagnosis. Identification of bacteria and their antimicrobial sensitivity is best performed with a culture, which can take 48 to 72 hours. Deviations from the classic CSF formula can exist, including lymphocytic predominance or only mild hypoglycorrhachia. Gram stain and culture can be uninformative if performed more than 6 hours after the initiation of antimicrobial therapy, at which point the diagnosis depends on the clinical syndrome and the CSF formula. The differential diagnosis of culture-negative meningitis cases includes tuberculous meningitis, fungal meningitis, viral meningitis, and drug- or chemical-induced meningitis, all which can mimic bacterial meningitis according to clinical and CSF findings.

Pathology may show leptomeningeal exudates with predominantly polymorphonuclear cells (Figure 66.1).

Treatment

The choice of empirical antibiotics depends on the likely etiologic organisms (Table 66.1). In adults 35 years or older, *S pneumoniae* is most likely. *Neisseria meningitidis* is just as likely in patients aged 11 to 34 years, and *H. influenzae* can occur at any age (accounting for ≤10% of all cases) but is more frequent in patients from infancy to 11 years. Newborns are most likely to be infected by group B streptococci.

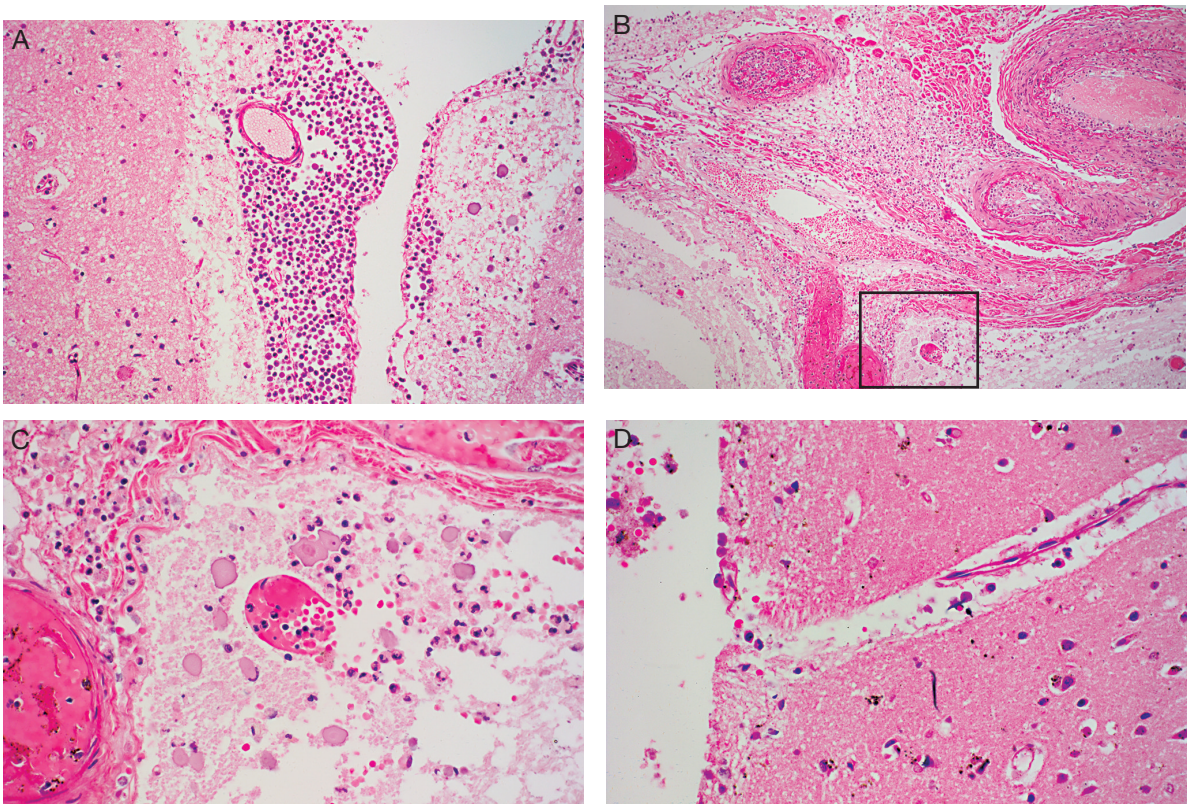

Figure 66.1 *Acute Bacterial Meningitis.*
A and B, Histopathology is characterized by leptomeningeal exudates, consisting predominantly of polymorphonuclear cells with strands of fibrin, and infiltration of the walls of leptomeningeal and cortical arteries and veins, sometimes superimposed with thrombosis of these blood vessels (as in B). C, Higher magnification of the box in B shows polymorphonuclear cells penetrating disrupted walls of a small cortical vein that has undergone fibrinoid necrosis. D, Polymorphonuclear cellular infiltrates also invade Virchow-Robin spaces and infiltrate cortical blood vessels.
(Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 66.1 • Empirical Antibiotic Therapy for Bacterial Meningitis

Patient Population	Therapy
Pediatric (1 mo to 18 y)	Ceftriaxone 50 mg/kg every 12 h intravenously *or* Cefotaxime 150 mg/kg every 8 h intravenously *and* Vancomycin 15 mg/kg every 6 h intravenously *plus* Dexamethasone 0.15 mg/kg every 6 h
Adults with community–acquired disease	Ceftriaxone 2 g every 12 h intravenously *or* Cefotaxime 3 g every 6 h intravenously *and* Vancomycin 1 g q every 12 h intravenously (until sensitivities of organism are known) *and* Dexamethasone 10 mg 4 times daily for 4 days
Adults who are alcoholic or elderly	*above plus* For *Listeria* species, use ampicillin, 2 g every 4 h intravenously
Adults who have had a neurosurgical procedure, shunt infection, or head trauma	Cefepime 2 g every 8 h *plus* Vancomycin (above dosages) *plus* Meropenem, 1 g every 8 h

Empirical treatment of bacterial meningitis is based on the use of a third- or fourth-generation cephalosporin and vancomycin. Patients with risk factors for an infection with *Listeria* species should be treated with ampicillin in addition to the other antibiotics. For patients with upper airway, middle ear, or mastoid bacterial infections, which can be caused by anaerobic bacteria, metronidazole should be added. The initial antibiotics should be continued until sensitivity results are obtained from blood or CSF cultures. Duration of therapy depends on the suspected bacterium, but therapy typically lasts 7 to 21 days (Table 66.2).

Adjunctive dexamethasone helps in treating pneumococcal meningitis in adults (Table 66.1). The landmark study had too few cases of *N meningitidis* or *H influenzae* infection to prove benefit in those infections. Adjunctive corticosteroids help prevent hearing loss in children with acute bacterial meningitis, but mortality benefit has not been shown. There is no compelling evidence for the use of adjunctive corticosteroids in neonates with acute bacterial meningitis. The concern about corticosteroid use is that antimicrobials might not penetrate the blood-brain barrier as well, but there is no direct evidence that a clinically significant effect exists. Corticosteroids likely help patients by diminishing the inflammatory response that adversely affects the meninges, brain parenchyma, and vasculature.

Table 66.2 • Bacterial Meningitis Treatment Duration

Infectious Agent	Duration of Therapy, d
Streptococcus pneumoniae	10–14
Listeria monocytogenes	>21
Neisseria meningitides	7
Staphylococcus	Variable
Gram-negative bacilli	21
Group B streptococci	14–21

Acute bacterial meningitis can be complicated by hydrocephalus, subdural effusion (Figure 66.2), status epilepticus, cerebral venous sinus thrombosis (Figure 66.3), or vasculitis. Cerebral venous sinus thrombosis and vasculitis can cause acute infarctions (Figure 66.4).

- The syndrome of bacterial meningitis consists of the subacute onset of headache, meningismus, fever, and depressed level of consciousness. These features are considered sensitive for the condition; 95% of patients

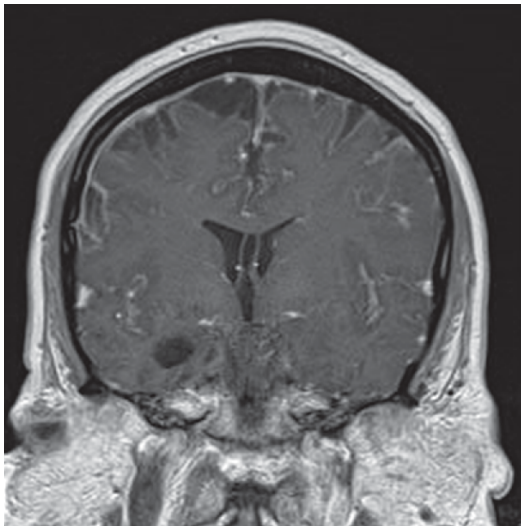

Figure 66.2 *Acute Bacterial Meningitis With Hydrocephalus and Subdural Effusion.*
Contrast-enhanced magnetic resonance image of the brain (T1 sequence, coronal section) shows several findings characteristic of acute bacterial meningitis, including diffuse pachymeningeal and leptomeningeal thickening and contrast enhancement, hydrocephalus, and parasagittal septated empyema.

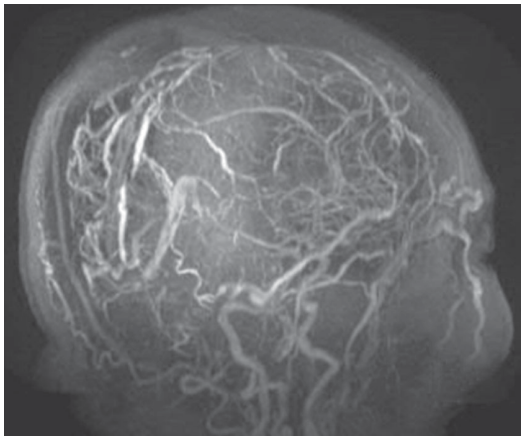

Figure 66.3 *Acute Bacterial Meningitis With Cerebral Venous Sinus Thrombosis.*
Magnetic resonance venography of the brain shows diffuse cerebral venous sinus thrombosis. The straight sinus is the only one that appears patent.

have 2 of the 4 features of fever, stiff neck, altered mental status, or headache, but only 45% have all 4.
- The most common agents associated with sporadic community-acquired acute bacterial meningitis includes *S pneumoniae, N meningitidis*, and *H influenzae*.

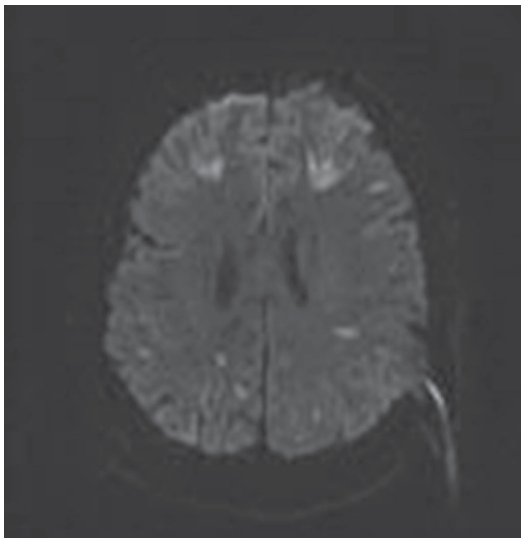

Figure 66.4 *Acute Bacterial Meningitis With Acute Infarctions.*
Magnetic resonance imaging of the brain (diffusion-weighted imaging [DWI] sequence, axial section) shows numerous focal DWI hyperintensities indicating restricted diffusion related to diffuse cerebral venous sinus thrombosis (see Figure 66.3).

- Empirical treatment of bacterial meningitis is based on the use of a third- or fourth-generation cephalosporin and vancomycin. Patients with risk factors for an infection with *Listeria* species should be treated with ampicillin in addition to the other antibiotics.
- Adjunctive dexamethasone helps in treating pneumococcal meningitis in adults.
- Adjunctive corticosteroids help prevent hearing loss in children with acute bacterial meningitis, but mortality benefit has not been shown.

Chronic Bacterial Meningitis

Overview

Chronic bacterial meningitis differs clinically from acute bacterial meningitis. Chronic bacterial meningitis is often more indolent and nonspecific; is characterized by more than 4 weeks of headache, mild meningismus, and recurrent low-grade fever; and is more commonly complicated by cranial neuropathy.

Epidemiology

Of the many bacteria that cause chronic bacterial meningitis, the most common worldwide is *Mycobacterium tuberculosis*, particularly in regions where the disease is endemic. Other causative agents include *Treponema pallidum, Coxiella burnetii, Francisella tularensis, Ehrlichia chaffeensis, Anaplasma phagocytophilum, Brucella* species, *Leptospira* species, *Borrelia* species, and *Actinomyces* species.

Diagnosis

Diagnosing chronic bacterial meningitis is more difficult than diagnosing acute bacterial meningitis because the microorganisms involved in the chronic disease are difficult or impossible to culture. Contrast-enhanced magnetic resonance neuroimaging can be helpful in showing meningeal inflammation. Lumbar puncture for CSF analysis is diagnostically important for culturing the pathogenic organism. Most commonly, a mononuclear pleocytosis with hypoglycorrhachia and elevated protein suggests *M tuberculosis*. Serologic tests on blood and CSF become much more important for confirming the etiologic cause when other chronic bacterial organisms are involved.

Cerebritis, Abscess, and Empyema

Overview and Epidemiology

Focal purulent infection of brain parenchyma is referred to as *cerebritis*. When rapid liquefactive central necrosis and a rind of inflammation develop, the infection is referred to

as a *brain abscess*. When infection develops in the subdural space, it is referred to as a *subdural empyema* (Figure 66.5).

Risk factors for development of bacterial abscess or empyema include active otitis media or mastoiditis, neurosurgical intervention, chronic illness, immunocompromised state, or congenital cardiac and vascular malformations. Organisms that cause brain abscess and subdural empyema include streptococci, staphylococci, Enterobacteriaceae, *Bacteroides* species, and anaerobes.

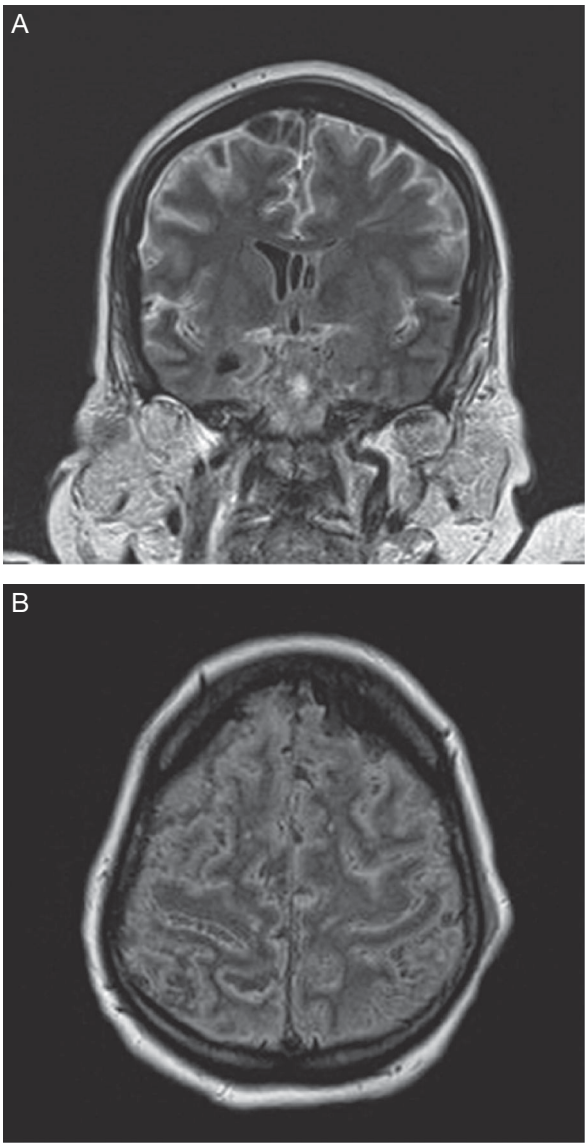

Figure 66.5 *Subdural Empyema.*
A and B, Magnetic resonance imaging of the brain (T2 fluid-attenuated inversion recovery [FLAIR] sequence, coronal and axial sections) shows bilateral subdural empyema and the T2 FLAIR hyperintensity associated with the purulent material within the bihemispheric sulci.

Clinical Features

Patients with a brain abscess can present with many of the same symptoms of bacterial meningitis, which is in part why neuroimaging is recommended for patients who have headache, fever, and focal neurologic deficit. Abscesses are particularly epileptogenic, and patients may present with seizure. Fever occurs in only half of patients with brain abscess; thus, the absence of fever should not eliminate abscess from the differential diagnosis for a patient with headache and focal neurologic deficit.

Diagnosis

Diagnosis is made by recognizing the clinical syndrome and finding evidence on neuroimaging, preferably with contrast-enhanced magnetic resonance imaging (MRI), but contrast-enhanced computed tomography can be suggestive as well. In addition to a ring-enhancing lesion on MRI, diffusion-weighted imaging and apparent diffusion coefficient sequences show bright restricted diffusion within the lesion, separating this finding from other ring-enhancing lesions such as a neoplasm (Figure 66.6). CSF analysis cannot be used to diagnose bacterial abscess. In the presence of a space-occupying lesion, lumbar puncture can be dangerous because of the potential for herniation. However, CSF analysis may be required when focal viral encephalitis must be distinguished from abscess.

Treatment

Antimicrobial therapy depends on the suspected organisms, but typically a third- or fourth-generation cephalosporin antibiotic is the mainstay with vancomycin if there is a need to cover for staphylococcal infection. Metronidazole is added if anaerobic infection is suspected. If the patient has concomitant pneumonia and immunosuppression, *Nocardia* species should be suspected and the treatment of choice is trimethoprim-sulfamethoxazole. Image-guided stereotactic aspiration can be performed to assist in identifying the microorganism, but this is case dependent. Most treatment regimens involve at least 6 to 8 weeks of intravenous antibiotics.

Spinal Epidural Abscess

Spinal epidural abscess is a distinct clinical phenomenon. Patients present with a subacute progressive neurologic decline localizable to the spinal cord, fever, and new-onset back pain. Spread is typically from infection of the disk space or osteomyelitis of the vertebral body. Myriad microorganisms are implicated, with *Staphylococcus aureus* present in about half of all isolates. Risk factors include those for abscess in other parts of the central nervous system, such as intravenous drug use.

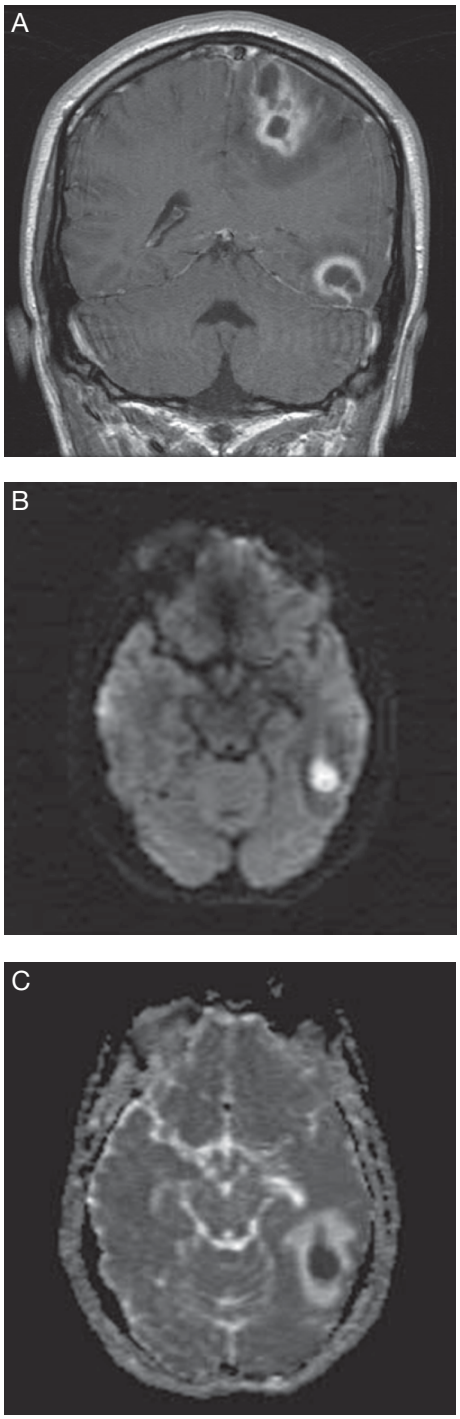

Figure 66.6 *Intracerebral Abscess.*
A, B, and C, Magnetic resonance imaging (MRI) of the brain (T1 sequence with contrast agent) shows multifocal, septated, and lobular ring lesions of a patient with intracerebral abscesses (A). Axial diffusion-weighted imaging (B) and apparent diffusion coefficient sequences (C) show intense restricted diffusion within the core of the abscess, which is a characteristic finding on MRI that helps to distinguish abscess from tumor in equivocal clinical situations.

Diagnosis depends on a high degree of awareness and MRI neuroimaging (Figure 66.7). Nonspecific serologic biomarkers, such as elevated erythrocyte sedimentation rate and C-reactive protein level, may be present. Diagnosis usually requires aspiration for identification of the organism. Management is decided on a case-by-case basis, sometimes with antibiotics alone and sometimes with surgical therapy in combination with medical therapy. Duration of therapy depends on the organism isolated. Typical organisms warrant 6 to 8 *weeks* of intravenous antimicrobial therapy, much like treatment of intracranial abscess,

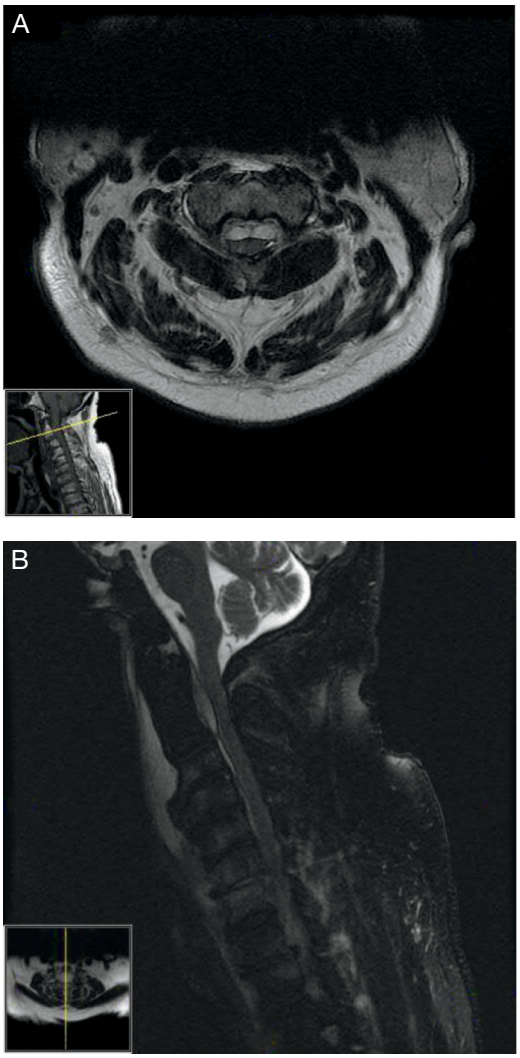

Figure 66.7 *Spinal Epidural Abscess.*
A and B, Magnetic resonance imaging of the cervical spine. A, The axial T1-weighted image shows the mass effect of a ventral epidural abscess on the cervical spinal cord. B, The sagittal T2-weighted image shows a ventral epidural abscess just posterior to the C2 and C3 vertebral bodies.

whereas a tubercular abscess demands 6 to 9 *months* of treatment.

- Organisms that cause brain abscess and subdural empyema include streptococci, staphylococci, Enterobacteriaceae, *Bacteroides* species, and anaerobes.

Neurosyphilis

Overview and Epidemiology

Syphilis infection of the nervous system is caused by *T pallidum*. Neurologic complications of syphilis are uncommon now compared with the era before antibiotics.

Clinical Features and Diagnosis

The major clinical syndromes of neurosyphilis include meningovascular syphilis, tabes dorsalis, and general paresis (also called dementia paralytica).

The meningovasculitis caused by syphilis includes an infectious arteritis that affects small and medium-sized vessels. Infarction of the brain or spinal cord may occur. Meningovascular syphilis causes neurologic complications, including hydrocephalus, arteritis, seizures, and polyradiculoneuropathy. The CSF abnormalities in symptomatic meningitis include a white blood cell count of 200 to 400/µL and protein levels of 100 to 200 mg/dL.

Tabes dorsalis is a syphilitic syndrome of lemniscal (eg, posterior column of the spinal cord) and dorsal root ganglion destruction leading to a sensory ataxia and anesthesia with diminished or absent tendon reflexes. The spinal cord findings are also clinically associated with ocular abnormalities, including Argyll Robertson pupil (ie, pupil is unreactive to light or ciliospinal stimuli and constricts to accommodation and convergence). (See alsoChapter 38, "Myelopathies.")

General paresis, or dementia paralytica, is a dementing illness associated with dysfunction of episodic memory and executive function, personality changes, and neuropsychiatric symptoms. General paresis is a potentially reversible cause of dementia. Although the pathologic findings are associated with diffuse gray matter brain parenchymal inflammation, CSF abnormalities are more subtle, with an elevated CSF protein level being most sensitive but nonspecific. CSF serology is very helpful.

The more relevant clinical syndromes in the current era of antibiotics and human immunodeficiency virus are those of asymptomatic neurosyphilis and symptomatic meningitis. *Asymptomatic neurosyphilis* is associated with CSF abnormalities, including modest monocytic pleocytosis (eg, white blood cell count <100/µL), elevated CSF protein level, and VDRL test reactivity. These abnormalities are usually noted in human immunodeficiency virus–positive patients who have other physical (but no neurologic) manifestations of syphilis. This condition warrants treatment to prevent irreversible neurologic complications. *Symptomatic meningitis* is characterized by the clinical symptoms of meningitis (eg, headache, nausea, nuchal rigidity, and fever) and robust CSF meningeal inflammation. A focal inflammatory change that may occur in the brain is called gumma because of the texture of lesion.

Treatment

Neurosyphilis is treated with large doses of intravenous penicillin (typically 20–24 million units daily), and sometimes with adjuncts such as probenecid, for 10 to 14 days. An alternative strategy includes the use of ceftriaxone for a similar duration.

- The major clinical syndromes of neurosyphilis include meningovascular syphilis, tabes dorsalis, and general paresis (also called dementia paralytica).
- Tabes dorsalis is a syphilitic syndrome of lemniscal (eg, posterior column of the spinal cord) and dorsal root ganglion destruction leading to a sensory ataxia and anesthesia with diminished or absent tendon reflexes.

Tuberculosis

Overview and Epidemiology

Mycobacterium tuberculosis is a gram-positive aerobic bacterium spread by inhalation of aerosolized droplets. It may then spread hematogenously to extrapulmonary sites, including the central nervous system and spine.

Clinical Features

Patients with tuberculosis may present to a neurologist when it affects the central nervous system and results in a subacute to chronic meningitis, when it causes radiculomyelitis, or when it affects vertebral bodies of the spine (Pott disease).

Patients with chronic meningitis may present with nonspecific symptoms of fatigue, malaise, and fever. They often have mental status changes and become confused and disoriented; the condition can progress to coma if untreated. Patients may have accompanying meningismus, headache, nausea, and vomiting. Cranial nerves, most commonly cranial nerve VI, may be affected, and hydrocephalus and cerebral infarctions can occur.

Tuberculomas and tuberculosis abscesses may cause focal neurologic deficits. Neuroimaging is useful for detecting these lesions.

Spinal tuberculosis affecting the spinal cord or roots is rare. It is often accompanied by imaging findings of leptomeningeal enhancement of the spinal cord or nerve roots.

Pott disease is vertebral involvement of tuberculosis. It most commonly affects the thoracic and lumbar regions. Tuberculosis results in softening and collapse of the vertebrae, producing kyphosis, pain, and myelopathic symptoms. Fever may also be present.

Diagnosis

Purified protein derivative may be helpful, but it yields both false-positive and false-negative results. Chest radiographs may show lymphadenopathy.

CSF examination may show lymphocytic pleocytosis and decreased glucose and increased protein levels. An acid-fast bacilli smear can be performed, but it has low sensitivity. CSF PCR for mycobacterium can be performed.

Treatment

Isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin are used to treat meningitis. Surgical resection may be required for tubercular abscesses with mass effect and in select patients with Pott disease.

- Patients with tuberculosis may present to a neurologist when it affects the central nervous system and results in a subacute to chronic meningitis, when it causes radiculomyelitis, or when it affects vertebral bodies of the spine (Pott disease).

Botulism

Botulism is caused by a neurotoxin produced by a few species of *Clostridium* (most commonly *Clostridium botulinum*). Botulism results in a paralytic syndrome of dysfunction at the level of the neuromuscular junction. The clinical features, diagnosis, and treatment of botulism are covered in Chapter 8, "Neuromuscular Disease in the Neuroscience Intensive Care Unit."

Leprosy

Overview and Epidemiology

Leprosy, also called Hansen disease, is a multisystem mycobacterial infection caused by *Mycobacterium leprae*. Leprosy is characterized classically by the physical findings of changes in skin pigmentation, nodular deposits in the skin and ear lobes, loss of body hair, painless skin wounds, and infection with enlargement of the peripheral nerves. The superficial peripheral nerves are affected early in the disease course. Cutaneous nerves in the coolest body regions are affected first.

Mycobacterium leprae is the only known bacterial organism that routinely infects peripheral nerves. The bacterium specifically binds to a target antigen, α-dystroglycan, at the G domain of the α subunit of laminin. This protein internalizes the organism to the Schwann cell. After binding the mycobacterium, the cell is induced to divide, also amplifying the number of organisms. The bacillus proliferates at low temperatures (27ºC-30ºC), which are cooler than body core temperature. The nerve tropism and low-temperature requirements create the basis for the major neurologic features of the disease. Nerve damage is principally in the cool areas of the body: skin, anterior one-third of the eye, testes, and nerves. It does not occur in the warmer, deeper tissues in major organs. Brain and spinal cord are not affected.

Clinical Features

Leprosy has 3 main clinical manifestations, depending on host resistance. The organism is the same for all 3 types. *Tuberculoid leprosy* occurs in patients with high resistance and is primarily a granulomatous reaction of the skin, where there are few organisms. Cutaneous nerve endings are destroyed, and the lesion is typically anesthetic.

For the second type, *lepromatous leprosy*, there is no evidence of human immunity. The organisms proliferate to large numbers, with constant bacterial replication. During this process and frequently after treatment has begun, an immune reaction, called erythema nodosum leprosum, can occur. This reaction causes neuritis, orchitis, iritis, and painful skin nodules and leads to infarction and ulceration in the most severe circumstances.

A third type of leprosy exists between the extremes of tuberculoid and lepromatous leprosy. This type, called *borderline leprosy* or *intermediate leprosy*, is inherently unstable. It may tend toward lepromatous leprosy with more organisms or toward tuberculoid leprosy with fewer organisms and more immune reaction.

Diagnosis and Treatment

Diagnosis is made by examining full-thickness skin biopsy specimens from active lesions to screen for invasion of bacilli in cutaneous nerves or by performing PCR for *M leprae* DNA in the tissue.

Treatment is with dapsone and rifampicin with or without clofazimine for 6 to 24 months, depending on the extent of infection.

- Leprosy, also called Hansen disease, is a multisystem mycobacterial infection caused by *M leprae*. Leprosy is characterized classically by the physical findings of changes in skin pigmentation, nodular deposits in the skin and ear lobes, loss of body hair, painless skin wounds, and infection with enlargement of the peripheral nerves.

Lyme Disease

Overview and Epidemiology

Lyme disease affecting the nervous system, called neuroborreliosis, is caused by the tick-borne spirochete,

Borrelia burgdorferi. It is a multisystem disease that most typically affects the skin (erythema chronicum migrans) and joints (polyarthralgias) but also affects the peripheral and central nervous systems. The pattern of neurologic illness caused by Lyme disease is somewhat analogous to what is noted in syphilis: Distinct neurologic manifestations of early disease are associated with lymphocytic meningitis and separate neurologic problems that arise indolently with chronic, untreated disseminated disease.

Clinical Manifestations

Early neuroborreliosis, which typically occurs weeks to months after a tick bite, is characterized by the triad of meningitis, cranial neuritis (typically facial), and radiculoneuritis. When cranial nerves are affected in neuroborreliosis, the facial nerve is involved about 80% of the time, but involvement of other cranial neuropathies has been reported. The radiculoneuritis of Lyme disease can be difficult to diagnose because it clinically masquerades as a garden-variety mechanical radiculopathy, but the presence of a painful radiculopathy (especially after a known tick bite), meningitis, and cranial neuropathy is suggestive.

Focal encephalitis and encephalomyelitis are relatively rare acute neurologic problems that are associated with Lyme disease and result from direct infection. Patients with focal encephalitis present with seizures or focal neurologic deficits corresponding to the affected brain parenchyma. Patients with encephalomyelitis can present with lesions that appear inflammatory on MRI neuroimaging and with inflammatory CSF (including oligoclonal bands and an elevated immunoglobulin G index).

The chronic neurologic symptoms of untreated, disseminated Lyme disease include an axonal polyneuropathy (sensory and motor) and subacute cognitive disturbance. More subtle symptoms and signs, such as fatigue and mild encephalopathy, are not considered part of the neurologic syndrome and are more likely attributable to systemic inflammation.

Diagnosis

Diagnosis is made by having a high degree of clinical awareness (especially in endemic areas) and testing for anti-*Borrelia* antibodies, especially immunoglobulin M. Testing for antibodies can be negative early in the disease. Convalescent serology is necessary. The CSF has a lymphocytic pleocytosis, and *Borrelia*-specific antibodies are found in the CSF. *Borrelia* PCR is available for CSF analysis, but sensitivity is low. MRI of the brain or spinal cord (or both) should be performed if the patient has seizure, focal neurologic deficit, or myelopathic symptoms.

Treatment

Treatment of neuroborreliosis depends on the neurologic presentation. Isolated facial neuritis is typically treated with oral doxycycline, whereas meningitis and polyradiculitis are treated with an intravenous third-generation cephalosporin (eg, ceftriaxone). These drugs are given for 10 to 28 days. Lyme encephalomyelitis requires systemic antibiotics and is exquisitely sensitive to treatment. Neuroborreliosis polyneuropathy is not quite as treatment responsive.

- When cranial nerves are affected in neuroborreliosis, the facial nerve is involved about 80% of the time, but involvement of other cranial neuropathies has been reported.
- The chronic neurologic symptoms of untreated, disseminated Lyme disease include an axonal polyneuropathy (sensory and motor) and subacute cognitive disturbance.
- Treatment of neuroborreliosis depends on the neurologic presentation. Isolated facial neuritis is typically treated with oral doxycycline, whereas meningitis and polyradiculitis are treated with an intravenous third-generation cephalosporin (eg, ceftriaxone).

Whipple Disease

Overview

Whipple disease is a rare gastrointestinal tract illness caused by *Tropheryma whipplei* and characterized by abdominal pain, diarrhea, weight loss, and arthralgias. The neurologic manifestations, which typically appear late in the disease process, are protean. Cognitive dysfunction, cerebellar ataxia, and conjugate vertical gaze palsy are the most common neurologic manifestations of Whipple disease. Seizures, other oculomotor palsies, hemiparesis, meningoencephalitis, central sleep disorder, and syndrome of inappropriate secretion of antidiuretic hormone have been noted.

A characteristic movement disorder, oculomasticatory myorhythmia, is diagnostic of neurologic involvement in Whipple disease. This finding is a continuous, rhythmic, conjugate movement of the eyes with concomitant rhythmic contraction of the muscles of mastication. Skeletal muscles are occasionally involved, in which case the disorder is termed oculofacioskeletal myorhythmia.

Diagnosis and Treatment

Definitive diagnosis of Whipple disease requires duodenal biopsy and demonstration of macrophages with periodic acid–Schiff stain. PCR of CSF, however, can be fairly suggestive and, at the very least, is more frequently positive for *T whipplei* in patients with neurologic disease due to Whipple disease than in those with Whipple disease but no neurologic signs.

Treatment requires an initial course of intravenous ceftriaxone or meropenem followed by 1 year of

trimethoprim-sulfamethoxazole. Treatment of the disease can lead to dramatic recovery within several weeks, but the neurologic complications are more difficult to treat than the gastrointestinal symptoms.

- Cognitive dysfunction, cerebellar ataxia, and conjugate vertical gaze palsy are the most common neurologic manifestations of Whipple disease.
- A characteristic movement disorder, oculomasticatory myorhythmia, is diagnostic of neurologic involvement in Whipple disease.
- Definitive diagnosis of Whipple disease requires duodenal biopsy and demonstration of macrophages with periodic acid–Schiff stain.

Rickettsiosis

Overview and Epidemiology

Rocky mountain spotted fever is a tick-borne illness caused by the obligate intracellular aerobe *Rickettsia rickettsii*. In spite of its moniker, rickettsiosis is not limited to the western United States and is reported throughout the Western hemisphere. It is a rare infection, however, with an estimated annual incidence of about 2/1,000,000.

Clinical Features

Patients are infected after a painless tick bite, which only 33% to 50% of patients recall receiving. They present with nonspecific symptoms such as fever, rash, and headache; neurologic symptoms are infrequent at presentation, which is often within days after the tick bite. With untreated disease, however, seizure, meningismus, headache, encephalopathy, cranial neuropathy, and coma are possible.

Diagnosis and Treatment

Diagnosis is difficult and requires a high degree of awareness in the proper clinical and seasonal settings (eg, spring or summer). Immunofluorescence serology is highly sensitive but only after 7 to 10 days of infection, and treatment should be started before then. Other findings may include hyponatremia, renal failure, thrombocytopenia, mild transaminitis, and mildly inflammatory CSF (white blood cell count <100/μL, with a neutrophilic or lymphocytic predominance; protein about 200 mg/dL; and a normal glucose level).

Rickettsiosis is potentially fatal but imminently treatable. Standard treatment is with doxycycline for 7 to 14 days.

Diphtheria

Overview and Epidemiology

Patients with diphtheria usually present with a pharyngeal infection that is caused by *Corynebacterium diphtheriae*. Certain virulent strains carrying a plasmid can emit an exotoxin that has neurologic toxicity. Diphtheria is now a rare infection in the developed world because of the routine vaccination of children, although outbreaks have occurred in regions where vaccination has lapsed. Before the vaccine was available, diphtheria was a major cause of morbidity and mortality among children worldwide.

Clinical Features

The clinical hallmark of diphtheria is the thick pharyngeal membrane associated with the infection. Neurologic complications are relatively rare in patients with diphtheria (estimated to be present in about 5% of all cases), but they are clearly associated with increasing severity of respiratory and systemic disease.

The most common neurologic findings include local neuropathies (eg, lower cranial neuropathies) that cause dysphagia. With more severe disease, due to wide dissemination of exotoxin, neuropathy can be diffuse and range from mild paresis to the locked-in syndrome of quadriplegia.

Treatment

Neurologic illness can be reversible with treatment of the infection and supportive measures. Treatment is with systemic delivery of antitoxin and antibiotics. The recommended antibiotics include erythromycin or penicillin G.

Ventricular Shunt Infections

Ventricular shunts can be broadly classified as internalized (eg, ventriculoperitoneal or ventriculoatrial) and externalized (eg, external ventricular drain or an Ommaya reservoir). Infection occurs with an estimated 5% to 15% of all shunts placed.

For internalized shunts, infection occurs most frequently in the early weeks or months after placement. Serial revisions and prior infections predict future infections. When the proximal (ventricular) end is infected, it is typically from skin flora including coagulase-negative staphylococci (which cause half of infections) and *Staphylococcus aureus* (which cause one-third of infections). Distal infections, typically associated with bowel rupture or other causes of peritonitis, can be caused by any of the enteric bacteria. External drains are infected typically by skin flora and associated local soft tissue infection.

Infection can be difficult to detect clinically. Patients infrequently present with obvious signs that suggest infection (eg, fever or meningitis). Sometimes the diagnosis is suspected only with shunt failure and elevated intracranial pressure. Furthermore, there are no individual CSF biomarkers that reliably predict ventricular shunt infection other than culture. One study suggested that CSF pleocytosis with more than 10% neutrophils was about 90%

sensitive. Blood and CSF cultures are important for the diagnosis and speciation that direct antimicrobial therapy.

Treatment requires removal of the infected hardware, placement of an external ventricular drain, and administration of systemic antimicrobials. Given the commonality of skin flora as a causative agent, vancomycin is the standard empirical treatment until culture sensitivity is determined. If an enteric source of infection is suspected, broad-spectrum antibiotics with anaerobic coverage are recommended. A fourth-generation cephalosporin to cover nosocomial gram-negative microorganisms is also recommended. In the rare case when a device cannot be removed, treatment may rely on intraventricular antibiotics. Vancomycin and gentamicin are the most commonly used antimicrobials in that situation, but their intraventricular use has not been studied.

- There are no individual CSF biomarkers that reliably predict ventricular shunt infection other than culture.

67 Fungal Infections of the Central Nervous System

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Introduction

Fungal infections in the central nervous system (CNS) are encountered clinically in both inpatients and outpatients. These infections are identified more readily in patients with immunosuppressive conditions, but select fungal pathogens are occasionally diagnosed in immunocompetent patients as well. An example is a recent outbreak of fungal meningitis caused by epidural injection of contaminated batches of corticosteroids. Compared with most bacterial and viral infections of the CNS, fungal infections can be more challenging to diagnose and treat. This chapter reviews 3 groups of fungi involved in CNS infections: yeasts, dimorphic fungi, and molds.

Yeasts

Cryptococcus species and *Candida* species are common yeast organisms that may cause CNS infection. The details of these organisms are reviewed below and summarized in Table 67.1.

Cryptococcus neoformans and *Cryptococcus gattii*

Overview and Epidemiology

Cryptococcus species is an encapsulated fungus acquired through inhalation, with subsequent pulmonary infection. CNS cryptococcal disease develops from hematogenous dissemination and causes meningitis. *Cryptococcus neoformans* and *C gattii* are the predominant pathogens causing human disease.

Cryptococcus neoformans is the more commonly encountered cryptococcal species and has been identified worldwide. *Cryptococcus neoformans* has been frequently encountered in soils contaminated with pigeon and chicken excrement. CNS disease from *C neoformans* is especially common in patients with immunologically advanced human immunodeficiency virus (HIV) infection (usually the CD4 T-lymphocyte count is <100/μL). Cryptococcal disease is well documented among patients who are not infected with HIV: patients receiving

Table 67.1 • Clinical Features and Management of Central Nervous System Yeast Infections

Feature	*Cryptococcus*	*Candida*
Clinical features	Meningitis Meningoencephalitis Rarely mass lesions	Meningitis Cerebral abscess Shunt and wound infections
Diagnostic testing	CSF examination Cryptococcus antigen in serum and CSF Brain imaging India ink stain of CSF	Brain imaging CSF examination Fungal CSF cultures
Treatment	Induction therapy with amphotericin B (see Table 67.2)	Induction therapy with amphotericin B

Abbreviation: CSF, cerebrospinal fluid.

Abbreviations: CNS, central nervous system; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; IRIS, immunologic reconstitution inflammatory syndrome; MRI, magnetic resonance imaging; PCR, polymerase chain reaction

long-term systemic corticosteroids, patients who received an organ transplant, and patients who have hematologic malignancies, rheumatologic diseases, hepatic cirrhosis, poorly controlled diabetes mellitus, or chronic renal disease. Several monoclonal antibody therapies have also been associated with cryptococcal infection, including infliximab, efalizumab, adalimumab, and alemtuzumab. The calcineurin inhibitors used for immunomodulation in solid organ transplant have mild antifungal activity and may confer some protection against cryptococcal infection.

Cryptococcus gattii has been more recently identified and can produce CNS infection in healthy, immunocompetent persons in addition to those who are immunosuppressed. *Cryptococcus gattii* is associated with select trees, including eucalyptus, and is endemic in Oceania, Southeast Asia, parts of Latin America, southern California, and Hawaii. It has also been more recently identified in outbreaks at Vancouver Island, British Columbia, Canada, and in the states of Washington and Oregon.

Clinical Features

Cryptococcus species is the most common cause of fungal meningitis and meningoencephalitis. Hydrocephalus is a frequent complication. Less common complications of CNS cryptococcosis include vasculitis and the presence of 1 or more granulomatous masses, called cryptococcomas, in the cerebrum or cerebellum.

Patients with cryptococcal meningitis generally present with headache and fever from a subacute or chronic syndrome occurring over weeks to months. They may have altered mentation, progressive fatigue and lethargy, memory loss, and nausea and vomiting. Neck stiffness and photophobia are less common than in meningitis caused by bacteria.

Diagnosis

The diagnosis of cryptococcal meningoencephalitis is typically made through specific laboratory testing of blood and cerebrospinal fluid (CSF), with supporting clinical findings. Although radiologic findings for cryptococcal meningitis are not specific, magnetic resonance imaging (MRI) of the head may show leptomeningeal enhancement, mass lesions consistent with cryptococcomas, hydrocephalus, or cerebral edema. Cryptococcal antigen (CrAg) testing, by either enzyme immunoassay or latex agglutination, of both the serum and the CSF should be performed. Serum CrAg is usually positive for disseminated disease and for CNS disease. Serum CrAg testing can be used as a screening tool for CNS or systemic cryptococcal disease, but it cannot be used by itself to exclude infection. This polysaccharide antigen assay has a sensitivity and specificity of more than 93%, and higher CrAg titers at diagnosis typically correlate with higher organism burdens.

CSF analysis is usually abnormal, with an elevated CSF leukocyte count and monocyte predominance, elevated protein, low glucose, and a positive test for CrAg. Compared with HIV-negative patients, immunologically advanced HIV-coinfected patients often have a lower CSF leukocyte count (which can be normal or near normal), lower average total protein, and, less commonly, hypoglycorrhachia. Additionally, HIV-coinfected patients commonly have a higher average CSF CrAg titer (>1:512), a higher incidence of positive *C neoformans* cultures concurrently from other sites (eg, blood and lymph nodes), and a higher likelihood of normal results from imaging of the head. India ink staining of the encapsulated *C neoformans* in CSF can provide quick identification, with a sensitivity of about 50% in HIV-negative patients and more than 80% in HIV-infected patients.

Fungal culture remains the gold standard for confirming the diagnosis, but growth requires 3 to 7 days. In addition to CSF, blood cultures for *C neoformans* from immunosuppressed patients are commonly positive.

Treatment

The treatment of cryptococcal meningoencephalitis depends on immunologic host factors, including HIV infection and organ transplant status. Detailed treatment recommendations for cryptococcal disease have been published by the Infectious Diseases Society of America (updated in 2010); primary therapies are outlined in Table 67.2. Optimal treatment in the induction phase of treatment generally consists of combination therapy with an amphotericin B product and flucytosine. Fluconazole is the preferred azole in the more prolonged continuation and maintenance phases.

Poor prognostic factors with cryptococcal meningoencephalitis include altered or suppressed mentation at presentation, CSF opening pressure of more than 200 mm H_2O, CSF leukocyte count less than 20/μL, CSF glucose less than 40 mg/dL, high CSF CrAg titer (>1:1,024), positive India ink smear, and concurrent positive fungal culture growth from extraneural sites.

Cerebral cryptococcomas typically require an extended induction phase of antifungal therapy (≥6 weeks) followed by consolidation and maintenance treatment periods of 6 to 18 months. Overall duration of therapy is guided by the clinical and radiologic response to antifungals; however, some cryptococcomas may persist radiologically for prolonged periods.

Management of hydrocephalus and elevated CSF pressure associated with cryptococcal infection is a vital component of successful therapy. Repeated lumbar punctures, a temporary external ventricular drain, or, rarely, ventriculoperitoneal shunts may be required.

For HIV-infected patients who are not taking antiretroviral therapy, consultation with an HIV expert is recommended for the selection and timing of antiretroviral therapy. The optimal timing for initiating antiretroviral therapy after starting therapy for cryptococcal disease is unclear. The risks of

Table 67.2 • First-Line Treatment Regimens for Cryptococcal Meningoencephalitis[a,b]

Patient Population	Duration
HIV-infected patients	
Induction therapy	
Liposomal AmB (3–4 mg/kg daily) or ABLC[c] (5 mg/kg daily, with renal function concerns) plus flucytosine (25 mg/kg every 6 h)[d,e]	2 wk
Consolidation therapy	
Fluconazole (400 mg daily)	8 wk
Maintenance therapy	
Fluconazole (200 mg daily)	≥1 y or indefinitely[f]
Organ transplant recipients	
Induction therapy[g]	
Liposomal AmB (3–4 mg/kg daily) or ABLC[c] (5 mg/kg daily) plus flucytosine (25 mg/kg every 6 h)[e]	2 wk
Consolidation therapy	
Fluconazole (400–800 mg daily)	8 wk
Maintenance therapy	
Fluconazole (200–400 mg daily)	6–12 mo
Non-HIV–infected, nontransplant patients[h]	
Induction therapy	
Liposomal AmB (3–4 mg/kg daily or ABLC[c] (5 mg/kg daily) plus flucytosine (25 mg/kg every 6 h)[e]	≥2–4 wk[i]
Consolidation therapy	
Fluconazole (400–800 mg daily)[j]	8 wk
Maintenance therapy	
Fluconazole (200 mg daily)	6–12 mo

Abbreviations: ABLC, amphotericin B lipid complex; AmB, amphotericin B; HIV, human immunodeficiency virus.
[a] For detailed treatment recommendations including alternative therapies, see Clin Inf Dis 2010;50:291–322.
[b] Monitor cerebrospinal fluid opening pressure; multiple lumbar punctures may be needed.
[c] Amphotericin B deoxycholate has also been recommended as first-line therapy, but lipid-based amphotericin B products are more commonly used out of concerns for higher rates of amphotericin B deoxycholate–associated toxicities.
[d] Begin highly active antiretroviral therapy 2–10 weeks after the start of initial antifungal treatment. Monitor for immunologic reconstitution inflammatory syndrome.
[e] Flucytosine serum peak concentrations should be 50–100 μg/mL (drug toxicity is encountered more frequently when serum peak concentrations >100 μg/mL).
[f] Suppressive therapy can be stopped (during effective highly active antiretroviral therapy) in HIV-infected patients with CD4 cell counts greater than 100/μL and undetectable (or very low) HIV viral loads for 3 months or more after completing at least 12 months of antifungal therapy. Restart antifungal suppressive therapy if CD4 cell counts decrease to less than 100/μL.
[g] Immunosuppressive management may require sequential reductions.
[h] Limited-duration data.
[i] Four weeks are reserved for patients with meningitis who have no neurologic complications, who have no significant underlying diseases or immunosuppression, and for whom the cerebrospinal fluid culture performed at the end of 2 weeks of treatment does not yield viable yeasts; otherwise, a longer course can be considered. Some providers, however, favor the same 2-week induction regimen as outlined for HIV-infected and transplant patients.
[j] A higher dosage of fluconazole (800 mg daily) is recommended if the 2-week induction regimen was used and if renal function is normal.

promoting immunologic reconstitution inflammatory syndrome (IRIS) must be balanced with the risks of progressive HIV-associated morbidity and mortality. A patient's condition should be stable with antifungal therapy before combination antiretroviral drug therapy is started.

Candida Species

Overview and Epidemiology

Candida species are part of the normal microbial flora throughout the gastrointestinal tract and genitourinary tract. Collectively, they cause the most common fungal infection in humans and are the fourth most common cause of bloodstream infections. *Candida* species produce biofilms, and infection of intravascular lines and ventricular shunts are common. Risk factors for invasive candidiasis are listed in Box 67.1. Many species of *Candida* have been identified to produce infection; however, *Candida albicans* is most commonly recovered in culture. Other *Candida* species encountered include *Candida glabrata, Candida krusei, Candida parapsilosis, Candida tropicalis,* and *Candida dubliniensis.* Species identification is important because antifungal drug susceptibility varies with different species.

As yeasts, *Candida* species replicate by budding, but some species are pleomorphic and can have pseudohyphae filaments that, on direct microscopy, have the false appearance of a mold. Granulomatous inflammation is the typical pathologic reaction to *Candida* infection.

Box 67.1 • Risk Factors for Invasive Candidiasis

- Central venous catheters and other prosthetic endovascular materials
- Prolonged antibacterial therapy
- Parenteral nutrition
- Colonization by *Candida* species in multiple nonsterile body sites
- Abdominal surgery involving the bowel
- Prolonged hospital stay in an intensive care unit
- Immunosuppressive conditions, including neutropenia, hematologic malignancies, HIV infection, solid organ transplant, hematologic stem cell transplant, corticosteroids and other immunomodulatory drugs, diabetes mellitus, renal failure
- Extensive burn wounds
- Age younger than 1 y (especially premature neonates) or older than 65 y
- Intravenous drug use

Abbreviation: HIV, human immunodeficiency virus.

Clinical Features and Diagnostic Strategies

Patients with CNS candidiasis may present with meningitis, cerebral abscesses, shunt infections, or postoperative or posttraumatic wound infections. Meningitis from *Candida* species may result from hematogenous spread or through neurosurgical procedures, including craniotomies and implantation or manipulation of CSF shunts. Chronic meningitis over weeks to months is the typical clinical presentation and can resemble that of meningeal tuberculosis or cryptococcosis. Headache, fever, and depressed mentation are common. Evaluation of the CSF typically shows a leukocyte pleocytosis with a lymphocytic or a neutrophilic predominance. Fungal stains and cultures are commonly negative; sometimes additional CSF sampling is required.

Ventricular devices and CSF shunts infected with *Candida* species may produce minimal or nonspecific clinical symptoms and with only mildly abnormal CSF parameters. Fungal stains and cultures may be more readily positive when samples are collected through the infected device.

Multiple cerebral microabscesses can develop during systemic candidemia. Candidal microabscesses are predominantly located in the gray matter structures of the brain; however, they can occur anywhere in the CNS and often are encountered concurrently in other organ systems as well. Decreased mentation is a common presenting symptom. Cerebral microabscesses may develop alone or in association with *Candida* meningitis. If disseminated candidiasis with multifocal candidal microabscesses or meningitis is suspected, additional clinical examination of the fundi and skin may identify characteristic lesions. Routine blood cultures may identify *Candida* species in acute disseminated disease; however, the sensitivity is less than in bacterial infection.

Treatment

For treatment of CNS candidal infections, induction therapy with a lipid-based amphotericin product (eg, AmBisome or Abelcet) is preferred in combination with oral flucytosine. For patients intolerant of these amphotericin B products, fluconazole (for susceptible *Candida* species) can be given with or without flucytosine. Induction therapy should continue until there is significant improvement in both the patient's clinical symptoms and the CSF findings (including cell counts and negative CSF fungal cultures). After induction therapy, continuation therapy with fluconazole monotherapy is typically sufficient for susceptible *Candida* species. Duration of therapy is variable and generally continues until there is full clinical improvement, normalization of CSF pleocytosis and, when applicable, radiologic resolution of the lesions (usually weeks to months).

Treatment of brain abscesses requires longer durations of therapy. Infected ventricular shunts and other involved foreign material should be removed. Antifungal susceptibility should be checked to optimize therapy. The vast majority of *C albicans, C parapsilosis, C tropicalis,* and *C dubliniensis* are susceptible to fluconazole. *Candida krusei* and *C glabrata*, however, are resistant to fluconazole. Voriconazole can be used for fluconazole-resistant *Candida* species; like fluconazole, it penetrates the blood-brain barrier well.

- *Cryptococcus neoformans* has been frequently encountered in soils contaminated with pigeon and chicken excrement. CNS disease from *C neoformans* is especially common in patients with immunologically advanced human immunodeficiency virus (HIV) infection (usually the CD4 T-lymphocyte count is <100/μL).
- *Cryptococcus* species is the most common cause of fungal meningitis and meningoencephalitis.
- CrAg testing, by either enzyme immunoassay or latex agglutination, of both the serum and the CSF should be performed.
- India ink staining of the encapsulated *C neoformans* in CSF can provide quick identification, with a sensitivity of about 50% in HIV-negative patients and more than 80% in HIV-infected patients.
- Patients with CNS candidiasis may present with meningitis, cerebral abscesses, shunt infections, or postoperative or posttraumatic wound infections.
- For treatment of CNS candidal infections, induction therapy with a lipid-based amphotericin product (eg, AmBisome or Abelcet) is preferred in combination with oral flucytosine.

Dimorphic Fungi

Overview

The dimorphic fungi exist as filamentous mycelia in the natural environment and as yeast or endospores in mammals. Members of this group that are associated more frequently with CNS infections include *Coccidioides* species, *Histoplasma capsulatum, Blastomyces dermatitidis*, and *Sporothrix schenckii* (Table 67.3). Some of these fungi have also been called *endemic fungi* in reference to the select geographic locations where they are highly prevalent. The primary means of exposure to dimorphic fungi is inhalation of the spores with subsequent development of pulmonary infection and occasional disseminated disease. Necrotizing granulomatous tissue inflammation is the usual pathologic finding. Patients who have immunosuppressive conditions and are exposed to dimorphic fungi are at increased risk of hematogenous disseminated CNS disease.

Coccidioides immitis and *Coccidioides posadasii*

Overview and Epidemiology

Coccidioidomycosis is limited to the western hemisphere and is endemic in the Southwestern United States (including the southern Central Valley of California, Arizona, and Texas), northern Mexico, and parts of Central and South America. *Coccidioides immitis* and *C posadasii* produce disease in humans with similar clinical presentations. In addition to immunosuppression, persons of African and Filipino descent are at increased risk of disseminated disease. Pulmonary coccidiomycosis in various degrees is the most common clinical presentation, but CNS disease is a well-recognized complication. Symptoms of CNS coccidioidomycosis typically develop weeks to months after the onset of pulmonary disease, although occasionally CNS disease may be the solitary clinical presentation.

Clinical Features

Chronic meningitis is the most common clinical presentation of CNS coccidioidomycosis, with fever, headache, occasional meningismus, and cognitive changes. The basilar leptomeninges are typically involved. Hydrocephalus, the most common complication of meningitis in coccidioidomycosis, occurs in up to 40% of patients and may be a presenting manifestation of early CNS infection or a later manifestation of chronic disease. Vasculitis is another recognized complication of coccidioidomycosis and can result in cerebral infarctions. The manifestation of vasculitis correlates with the severity of meningeal inflammation. Less common findings in CNS coccidioidomycosis include encephalitis, spinal arachnoiditis, cerebral mass lesions, fungal abscesses, and vascular aneurysms.

Diagnosis

The CSF examination typically shows a lymphocytic pleocytosis, but occasionally neutrophils may predominate. Eosinophils may also be present in the CSF and should raise suspicion for CNS coccidioidomycosis. As in other fungal infections, the CSF protein level is typically elevated, and the glucose level is usually decreased.

Histoplasma capsulatum

Overview and Epidemiology

Histoplasma capsulatum var *capsulatum* is endemic along the Ohio and Mississippi River valleys and in the Mid-Atlantic and South-Central United States. Outside the United States, *Histoplasma* infections have been identified in Canada (Quebec and Ontario) and in the warmer

Table 67.3 • Clinical Features and Diagnosis of Dimorphic Fungal Central Nervous System Infections

Feature	Coccidioidomycosis	Histoplasmosis	Blastomyocosis	Sporotrichosis
Regions where endemic	Southwestern United States (California, Arizona, and Texas)	Ohio and Mississippi river valleys, Mid-Atlantic and South-Central United States	Ohio and Mississippi river valleys, Great Lakes region, St Lawrence River basin	Regions with warm climates
Clinical features	Pulmonary disease Chronic meningitis (commonly basilar leptomeninges) Hydrocephalus (common)	Pulmonary disease (mediastinal adenopathy) Chronic meningitis (basilar leptomeninges) Rarely mass lesion	Pulmonary disease Cutaneous lesions Bone disease Genitourinary disease Chronic meningitis	Chronic meningitis
Diagnosis	Isolation of organism from any affected fluid or tissue (eg, sputum, skin) CSF: lymphocytic pleocytosis, elevated protein, decreased CSF glucose (eosinophils in coccidioidomycosis) Serum and CSF fungal serology CSF and tissue fungal culture CSF and tissue PCR to detect *Histoplasma capsulatum, Blastomyces dermatitidis*, and *Coccidioides immitis* Antigen detection by ELISA from urine, serum, or CSF for histoplasmosis and blastomycosis			

Abbreviations: CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.

climates of Mexico, Central and South America, and regions of Africa, East Asia, and Australia.

Clinical Features

Pulmonary histoplasmosis with associated hilar and mediastinal adenopathy is the most common syndrome. CNS involvement, including involvement of the brain or spinal cord (or both), has been documented in 10% to 20% of patients with disseminated histoplasmosis; however, only about 25% of patients with known CNS involvement have neurologic symptoms.

Chronic meningitis is the most common clinical manifestation of CNS histoplasmosis, with headache, fever, cranial nerve deficits, seizures, and alterations in mental status. The basilar meninges are often involved, and symptoms may be present from weeks to months. Hydrocephalus may also occur. An intracranial histoplasmoma can appear as a mass lesion and may be mistaken for a neoplasm. Cerebral or spinal cord lesions may be isolated, or they may be present with coinciding meningitis.

Diagnosis

Evaluation of the CSF typically shows a leukocytic pleocytosis with a lymphocytic predominance, elevated protein level, and often a decreased glucose level. CSF abnormalities with isolated histoplasmomas are commonly less abnormal than those seen with meningeal involvement.

Blastomyces dermatitidis

Overview and Epidemiology

Blastomyces dermatitidis has a geographic preponderance in the South-Central and Great Lakes regions of the United States and in the Mississippi, Ohio, and St Lawrence river basins. CNS blastomycosis is relatively rare, accounting for 5% to 10% of cases of disseminated and extrapulmonary disease. Infection may occur after exposure to decaying plant material, especially in wet environments.

Clinical Features and Diagnosis

Blastomycosis syndromes that may occur concurrently with CNS infection include pulmonary, cutaneous, bone, and genitourinary disease. Meningitis, spinal epidural abscess, intracranial mass lesions, and meningoencephalitis have all been reported.

Radiologic findings with either computed tomography (CT) or MRI of the head are not specific and may show isolated or combined features of leptomeningeal enhancement and solitary or multiple mass lesions. Pathologic reactions in the leptomeninges are typically necrotizing granulomas. *Blastomyces* has a propensity for producing a desmoplastic or fibrotic additional reaction in the leptomeninges or a pachymeningitis that can sometimes be identified with MRI of the head.

Meningitis caused by *B dermatitidis* may be associated with either a lymphocyte-predominant or a neutrophil-predominant pleocytosis in the CSF along with elevated protein and decreased glucose levels. When CNS blastomycosis is suspected, isolation of *B dermatitidis* from another site (eg, lung, skin) strongly supports the diagnosis. CSF serology is incompletely sensitive (estimated to be 60% to 70%), but if the results are positive, they are helpful. There is some cross-reactivity of antibodies to *Blastomyces* and *Histoplasma*.

Sporothrix schenckii

Overview and Epidemiology

Sporothrix schenckii can be found around the world in decaying vegetation, plant products, and soil, but infections tend to occur more frequently in warmer climates. Infection is an occupational hazard for florists, gardeners, and others who have exposure to select animals. The infection may occur either through traumatic cutaneous inoculation or through inhalation into the lungs. CNS infection with *S schenckii* is uncommon but may develop in the setting of disseminated hematogenous disease.

CNS infections from *S schenckii* have been reported most commonly when patients have immunosuppressive conditions, including HIV infection; however, infections in immunocompetent patients have also been reported. Immunosuppressed patients with CNS sporotrichosis commonly present with findings of disseminated disease, including cutaneous, lymphatic, bone, and concurrent pulmonary involvement.

Clinical Presentation and CSF

Patients typically present with chronic meningitis or meningoencephalitis is the typical presentation and associated with a wide range of symptoms with durations of weeks to many months. CSF evaluation typically shows a lymphocytic-predominant leukocytic pleocytosis; however, a neutrophilic-predominant pleocytosis occasionally occurs.

Diagnosis of Dimorphic Fungal CNS Disease

Diagnosing CNS coccidioidomycosis, histoplasmosis, blastomycosis, and sporotrichosis can be challenging. Staining of the CSF is commonly negative for fungi. Meningeal or parenchymal tissue biopsy commonly shows granulomatous inflammation. Gomori methenamine silver tissue staining of *C immitis* and *C posadasii* may show large (20–80 µm) round spherules containing many small endospores or only endospores from a ruptured spherule. Large (5–15 µm) broad-budding yeast with a thickened cell wall is characteristic of *B dermatitidis.* On staining, *H capsulatum* is a small (2–5 µm) yeast, whereas *S schenckii* has a more elongated cigar or oval shape. The diagnosis of dimorphic fungal CNS

disease is confirmed with a positive culture from either CSF or tissue biopsy; however, multiple large-volume CSF samples may need to be submitted for culture.

Serum serologies for *Histoplasma, Blastomyces*, and *Coccidioides* have a relatively low sensitivity and do not readily discriminate between active disease and prior infection. Serologic cross-reactivity occasionally occurs between select fungal species. The simultaneous appearance of both H and M precipitation bands on immunodiffusion testing is suggestive of active histoplasmosis. CSF serologic tests that are positive for these fungi provide more specific and supportive evidence for active CNS infection.

Other tests include polymerase chain reaction (PCR) and antigen testing. PCR testing is available from select laboratories and can be performed on CSF and tissue. In cases of fungal meningitis, PCR to detect *H capsulatum, B dermatitidis*, and *C immitis* from CSF in cases of fungal meningitis has shown a sensitivity comparable to that of culture and a specificity of more than 98%. Antigen detection by enzyme-linked immunosorbent assay (ELISA) from urine, serum, and CSF can be performed for *H capsulatum* and *B dermatitidis* both to diagnose an infection and to assess the response to therapy. As noted above, the diagnosis of fungal infection from another site (eg, lung or blood) may obviate the need for more invasive testing if CSF testing is inconclusive. Thus, chest radiography and (when appropriate) sputum analysis may facilitate evaluation of the causal dimorphic fungal pathogen.

Treatment of Dimorphic Fungal CNS Disease

The treatment of CNS coccidioidomycosis, histoplasmosis, blastomycosis, and sporotrichosis depends on the clinical presentation and the fungal species. Treatment options for each of the dimorphic fungi are listed in Table 67.4. Generally, treatment should be undertaken with an infectious diseases specialist. A lipid-based amphotericin B product is recommended as initial therapy for most CNS fungal infections with the exception of coccidioidomycosis. Fluconazole and voriconazole have much higher penetration through the blood-brain barrier than the other azoles and the amphotericin products; however, their activity against *H capsulatum* and *S schenckii* is inferior to that of other agents. As with treatment of cryptococcal disease, immunologically advanced HIV-infected patients who have recently started effective antiretroviral therapy may experience IRIS, which can be mistaken for clinical progression of fungal disease and usually is managed symptomatically.

- The primary means of exposure to dimorphic fungi is inhalation of the spores with subsequent development of pulmonary infection and occasional disseminated disease.
- Patients who have immunosuppressive conditions and are exposed to dimorphic fungi are at increased risk of hematogenous disseminated CNS disease.
- Coccidioidomycosis is limited to the western hemisphere and is endemic in the Southwestern United States (including the southern Central Valley of California, Arizona, and Texas), northern Mexico, and parts of Central and South America.
- Chronic meningitis is the most common clinical presentation of CNS coccidioidomycosis, with fever, headache, occasional meningismus, and cognitive changes.
- Eosinophils may also be present in the CSF and should raise suspicion for CNS coccidioidomycosis.

Table 67.4 • Treatment of Dimorphic Fungal Central Nervous System Disease

Fungal Pathogen	Induction Therapy	Continuation Therapy
Coccidioides species	Fluconazole 800–1,200 mg daily until a significant clinical response is apparent	Fluconazole 400–600 mg daily indefinitely[a] Alternatives: lipid-based amphotericin B product; voriconazole, itraconazole[b]
Histoplasma capsulatum[c]	Lipid-based amphotericin B product 5 mg/kg daily is recommended as initial therapy for 4–6 wk	Itraconazole[b] 200 mg twice daily for ≥1 y Alternatives: high-dose fluconazole or voriconazole
Blastomyces dermatitidis[c]	Lipid-based amphotericin B product 5 mg/kg daily is recommended as initial therapy for 4–6 wk	Fluconazole 600–800 mg daily, itraconazole[b] 200 mg orally daily, or voriconazole 200 mg orally daily can be used for ≥1 y
Sporothrix schenckii	Lipid-based amphotericin B product 5 mg/kg daily is recommended as initial therapy for 4–6 wk	Itraconazole[b] 200 mg twice daily for ≥1 y

[a] Patients with central nervous system coccidioidomycosis who respond favorably to oral azole therapy should continue with azole therapy indefinitely to avoid clinical relapse of infection.
[b] Serum itraconazole levels should be monitored periodically to ensure adequate enteric absorption.
[c] Monitoring urine *Histoplasma* or *Blastomyces* antigens during therapy can help ensure appropriate response and establish duration of therapy.

- *Histoplasma capsulatum* var *capsulatum* is endemic along the Ohio and Mississippi River valleys and in the Mid-Atlantic and South-Central United States.
- When CNS blastomycosis is suspected, isolation of *B dermatitidis* from another site (eg, lung, skin) strongly supports the diagnosis.
- Large (5–15 µm) broad-budding yeast with a thickened cell wall is characteristic of *B dermatitidis*.
- The diagnosis of dimorphic fungal CNS disease is confirmed with a positive culture from either CSF or tissue biopsy; however, multiple large-volume CSF samples may need to be submitted for culture.
- In cases of fungal meningitis, PCR to detect *H capsulatum, B dermatitidis*, and *C immitis* from CSF in cases of fungal meningitis has shown a sensitivity comparable to that of culture and a specificity of more than 98%. Antigen detection by ELISA from urine, serum, and CSF can be performed for *H capsulatum* and *B dermatitidis* both to diagnose an infection and to assess the response to therapy.

Molds

Aspergillus Species

Overview and Epidemiology

Aspergillus is a filamentous fungus encountered worldwide. Human exposure occurs through the inhalation of spores; occasionally, though, direct exposure to an open wound or intravenous catheter serves as a portal of entry. Among the many species of *Aspergillus, Aspergillus fumigatus* is most commonly associated with invasive disease.

Although allergic and saprophytic forms of aspergillosis exist, invasive aspergillosis is the most worrisome form of disease and typically occurs in patients with significant immunosuppressive conditions. Pulmonary and sinus disease are common presentations; however, the angioinvasion tropism for blood vessels readily leads to disseminated disease.

Risk factors for invasive aspergillosis are listed in Box 67.2. Conditions and medications associated with prolonged neutropenia are highly associated with invasive mold disease.

Box 67.2 • Risk Factors for Invasive Aspergillosis

Hematologic stem cell transplant
Hematologic malignancies, including leukemia, lymphoma, and myeloma
Myelodysplastic syndrome
Myeloablative chemotherapy
Solid organ transplant
Immunologically advanced HIV infection (AIDS)
Long-term corticosteroid use
Chronic granulomatous disease
Diabetic ketoacidosis (for mucormycosis disease)

Abbreviation: HIV, human immunodeficiency virus.

Clinical Presentation

Invasive aspergillosis of the CNS is uncommon but carries the highest mortality of any site. CNS aspergillosis can develop by either hematogenous dissemination from the lungs or by direct extension from a progressive invasive sinus infection. Cerebral abscesses usually develop from disseminated *Aspergillus* infection, they may be solitary or multifocal, and they are more common than cerebellar abscesses. *Aspergillus* is an invasive vascular fungus, so patients may present with intracerebral hemorrhage or, more rarely, cerebral infarction. Meningitis is an uncommon presentation. Progressive extension of invasive rhinosinusitis can result in direct frontal lobe invasion with associated tissue necrosis and in vascular or sinus thrombosis. Orbital coinfection is not uncommon through direct extension. Presenting symptoms of patients with *Aspergillus* brain abscesses are similar to the symptoms of other infections and include headache (which may be chronic and progressive), motor weakness, new paresthesias, new seizures, and alterations in mental status.

Patients with invasive sinus disease with CNS extension may report sinus pain and congestion, headache, visual changes, and photosensitivity. Vascular thrombosis and unilateral proptosis may develop. Progressive invasive aspergillosis sinusitis may extend through the cribriform plate to the base of the frontal lobe. Cerebral cortical and subcortical infarction can develop with associated hemorrhage. Specific sinus and orbital CT more clearly identify bone destruction, and MRI can clarify meningeal and parenchymal involvement.

Diagnosis

An *Aspergillus* CNS abscess may be highly suspected in a patient with disseminated disease if invasive aspergillosis is confirmed in another location. However, direct histologic examination of tissue and positive culture growth are required to make a definitive diagnosis. *Aspergillus* is rarely detected in the CSF. With Gomori methenamine silver staining and histologic examination of tissue, *Aspergillus* hyphae have characteristically septate, 45° branching; however, other select molds (eg, *Fusarium* species and *Scedosporium* species) can have a similar appearance under the microscope (Figure 67.1). *Aspergillus* typically grows well in fungal cultures, allowing for confirmation of the fungal species. Fungal blood cultures are typically negative for *Aspergillus*, even with

overwhelming disseminated infection. Supplemental blood tests such as the serum galactomannan assay or the Beta-D-glucan assay may support the diagnosis when positive, but a negative result should not exclude the diagnosis of invasive CNS aspergillosis. The galactomannan assay can also be performed on CSF.

Treatment

Successful treatment of CNS aspergillosis typically requires a combination of surgical débridement and antifungal therapy. The rapid progression of invasive sinus disease in a neutropenic host is well recognized and is an urgent indication for débridement. Multiple débridements and endoscopic nasal reinspections are generally required. Voriconazole is the antifungal agent of choice and penetrates well into the CSF and brain tissue. An amphotericin B lipid complex can be used in patients intolerant of voriconazole. Other agents, including posaconazole, itraconazole, and the echinocandin class of antifungals, are active against most *Aspergillus* species, but collectively they do not penetrate well into the brain and are generally reserved for salvage and combination therapies. Data supporting the successful use of combination antifungal therapy for CNS aspergillosis are lacking, but combination therapy can be considered for patients with progressive and refractory disease. Duration of therapy is based on clinical and radiologic disease resolution and generally requires months of antifungal therapy.

Agents of Mucormycosis

Overview and Epidemiology

The agents of mucormycosis, members of the Zygomycetes class, collectively compose another group of filamentous molds with global distribution. They can be isolated in the environment from various soils, decaying vegetation, animal material, and various foods. This group includes many pathogenic fungi, but *Mucor* species and *Rhizopus* species are the pathologically dominant organisms. Similar to aspergillosis, invasive mucormycosis typically occurs in notably immunosuppressed patients and generally after an inoculum of inhaled spores. Occasionally, mucormycosis occurs through direct trauma or ingestion as well. Sinus and pulmonary disease are the predominant forms of mucormycosis, but any organ can be involved. There is a similar angioinvasive tropism with the mucormycosis group as with *Aspergillus* species, producing tissue ischemia, infarction, hemorrhage, and abscess. Cavernous sinus thrombosis can develop if mucormycosis extends beyond the nasal and sinus regions.

Clinical Features

The 3 predominant forms of CNS mucormycosis are rhinocerebral infection (the most common form, which also includes rhino-orbital-cerebral mucormycosis), disseminated mucormycosis with multifocal CNS involvement, and

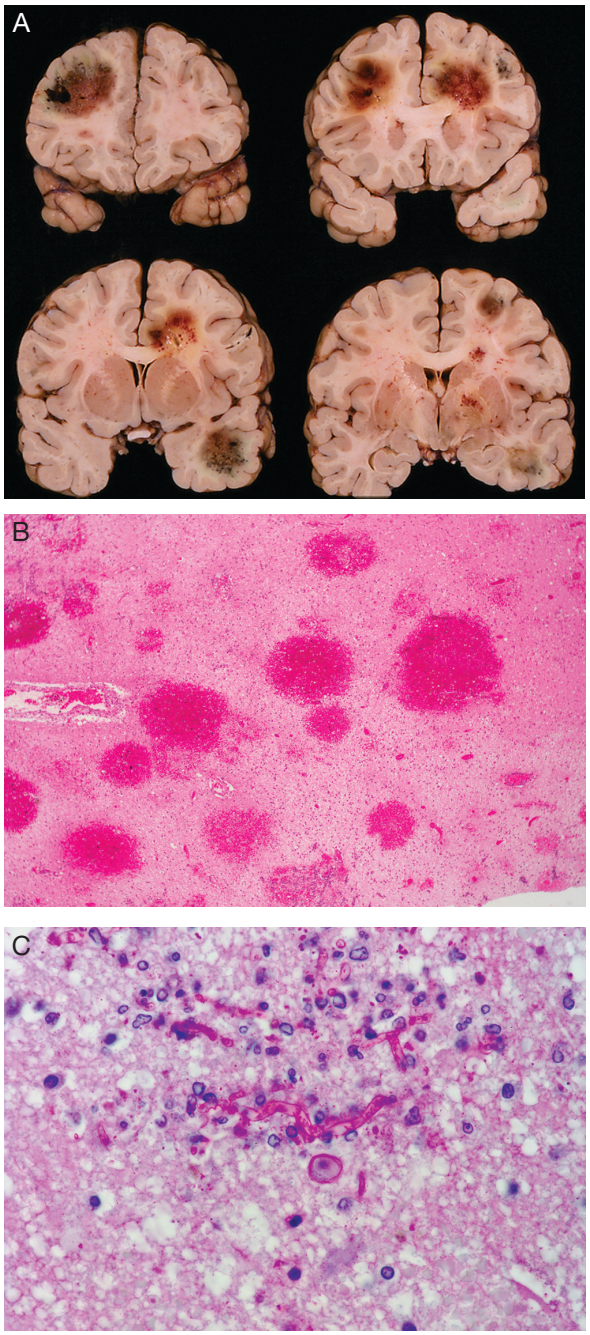

Figure 67.1 *Aspergillosis.*
A, Multiple hemorrhagic and necrotic mass lesions are characteristic of cerebral aspergillosis. B, Numerous microscopic hemorrhages occur from invasion of blood vessels. C, Numerous hyphae are seen at high magnification. (Periodic acid–Schiff stain.)
(Adapted from Tracy JA, Mowzoon N. Neurology of infectious diseases. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 589–626. Used with permission of Mayo Foundation for Medical Education and Research.)

Box 67.3 • Risk Factors for Invasive Mucormycosis

- Acute myeloid leukemia
- Hematologic stem cell transplant
- Prolonged neutropenia from myeloablative chemotherapy
- Myelodysplastic syndrome
- Diabetic ketoacidosis
- Solid organ transplant
- Long-term corticosteroid use
- Iron overload
- Iron chelation therapy with deferoxamine (but not with deferasirox or deferiprone)
- Intravenous drug use

isolated CNS mucormycosis. Risk factors for development of mucormycosis are listed in Box 67.3. Like patients with invasive aspergillosis, patients who have hematologic malignancies (especially acute myeloid leukemia and prolonged neutropenia) or who have received a transplant are especially at risk for all forms of mucormycosis. Diabetic ketoacidosis, however, is a significant risk factor for the development of rhinocerebral mucormycosis disease. Uncontrolled acidosis, often corresponding to elevated serum iron concentrations, propagates invasive rhinocerebral mucormycosis.

Diagnosis

Diagnosing CNS mucormycosis can be challenging. There are no antigen assays or licensed PCR tests approved. Tissue biopsies should be obtained for histologic examination and culture. Morphologically, agents of mucormycosis have typically broad, nonseptate or pauciseptate, irregularly shaped hyphae with characteristic 90° branching. Despite these features, agents of mucormycosis can appear similar to other select molds, and confirmation by culture is required. The lack of septations causes frequent breakage of hyphae during the homogenization process in the laboratory, and subsequently there is no growth on cultures. Therefore, early communication with the laboratory about the suspicion of mucormycosis can enable proper handling of the tissue sample for optimal culture growth.

Treatment

Treatment of CNS mucormycosis is challenging and requires a combination of medical and surgical therapy. Early and aggressive surgical débridement of contiguous rhinocerebral disease is crucial for both diagnostic confirmation and successful outcome. A lipid-based amphotericin B product (eg, AmBisome or Abelcet) is generally recommended. For patients intolerant of lipid-based amphotericin B, oral posaconazole can be used (as the only alternative antifungal agent with activity against this group) but requires a high-fat meal for optimal enteric absorption. Combination therapy with lipid-based amphotericin B and posaconazole or with lipid-based amphotericin B and caspofungin can be considered for serious or refractory cases. Typically, duration of therapy is weeks to months until there is complete clinical resolution (including follow-up endoscopic nasal and sinus inspections) and complete radiologic resolution of disease. Finally, immunomodulatory factors, including poorly controlled diabetes mellitus, neutropenia, and use of immunosuppressive medications, should be corrected to facilitate a more active immunologic response against the fungus.

- Although allergic and saprophytic forms of aspergillosis exist, invasive aspergillosis is the most worrisome form of disease and typically occurs in patients with significant immunosuppressive conditions.
- *Aspergillus* is an invasive vascular fungus, so patients may present with intracerebral hemorrhage or, more rarely, cerebral infarction.
- Similar to aspergillosis, invasive mucormycosis typically occurs in notably immunosuppressed patients and generally after an inoculum of inhaled spores.
- Cavernous sinus thrombosis can develop if mucormycosis extends beyond the nasal and sinus regions.
- The 3 predominant forms of CNS mucormycosis are rhinocerebral infection (the most common form, which also includes rhino-orbital-cerebral mucormycosis), disseminated mucormycosis with multifocal CNS involvement, and isolated CNS mucormycosis.

68 Parasitic Infections of the Central Nervous System

SHAMIR HAJI, MD; ALLEN J. AKSAMIT JR, MD

Introduction

Parasitic infections make up a small but important subset of central nervous system (CNS) infections. Although necessary to be considered in the comprehensive differential diagnosis for patients presenting with suspected neurologic infections, these conditions are particularly important where parasitic infections are endemic and for immunocompromised patients. Among the most common parasitic infections of the CNS are neurocysticercosis, echinococcosis (hydatid cyst), toxoplasmosis, amebic meningoencephalitis, and cerebral malaria. They are covered in this chapter in more detail.

Neurocysticercosis

Epidemiology and Life Cycle

Neurocysticercosis is the most common parasitic disease of the CNS. It is attributed to infection by the larval stage of the parasite *Taenia solium*, more commonly known as the pork tapeworm. The disease is particularly important in areas where it is endemic, including Central and South America and Southern and Eastern Asia where pork consumption is common and hygiene is not ideal. This condition deserves consideration in patients who have migrated from those regions.

The most important route of transmission is fecal-oral. Eating undercooked pork with larval forms produces intestinal tapeworm infection in humans but not neurologic disease. Eggs shed in human stool and subsequently ingested by porcine animals, leads to larval forms in porcine muscle, completing the life cycle (Figure 68.1). Human neurocysticercosis develops when humans ingest the eggs shed by other humans because of poor hygiene. The larval forms then migrate from the intestine to other organs, especially the brain.

Cysticerci develop 3 to 8 weeks after the ingestion of eggs. Multiple sites, both neural and extraneural, can be involved, and hosts can remain asymptomatic for many years as the *Taenia* larvae evade destruction by the host immune system. Eventual larval death leads to cystic lesion degeneration and host granulomatous inflammation, often manifesting clinically as seizures and radiographically with edema or contrast enhancement (or both). Cystic lesions can fully resolve or form calcified granulomas, which are often associated with recurrent seizures. Cystic and calcified lesions in various stages of degeneration can be present in the same host simultaneously.

Clinical Manifestations

Neurocysticercosis is often subdivided into parenchymal and extraparenchymal subtypes. Lesions of the parenchymal subtype are often found at the corticomedullary junction and are sometimes referred to as cellulose forms. Lesions of the extraparenchymal subtype, referred to as racemose forms, include subarachnoid, intraventricular, intraocular, and spinal disease and are often associated with large cysts. In patients with neurocysticercosis, parenchymal involvement is most often associated with seizures caused by cysticerci in

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; CT computed tomography; ELISA, enzyme-linked immunosorbent assay; GAE, granulomatous amebic encephalitis; HIV, human immunodeficiency virus; Ig, immunoglobulin; IRIS, immune reconstitution inflammatory syndrome; MRI, magnetic resonance imaging; PCR, polymerase chain reaction

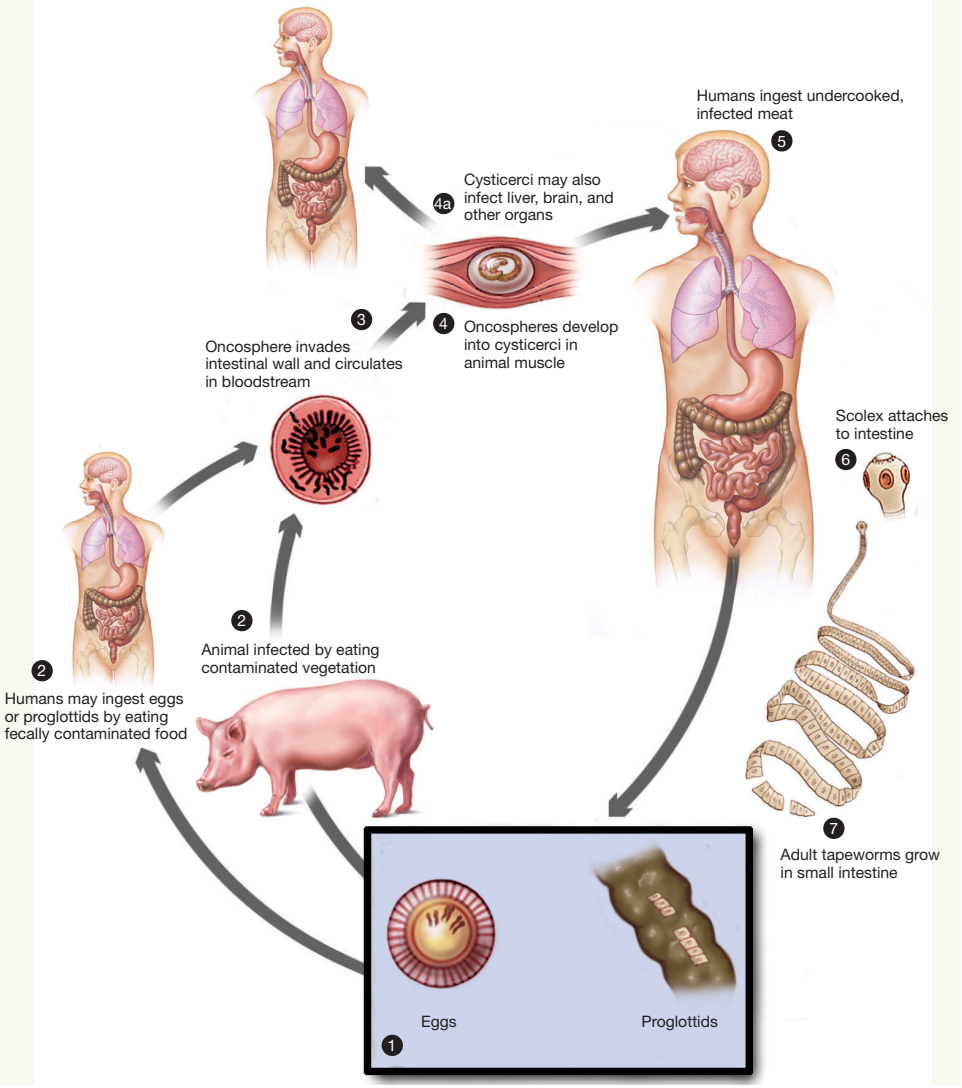

Figure 68.1 *Life Cycle of* Taenia solium.
1) Eggs or proglottids of T solium *passed from human feces survive in the environment. 2) Pigs or humans may ingest the eggs or proglottids from fecally contaminated food. The eggs hatch and release oncospheres. 3) Oncospheres invade the intestinal wall of the animal and spread to striated muscle through the bloodstream. 4) Here they develop into cysticerci, a larval stage. 4a) Cysticerci may also infect liver, brain, and other organs. 5) Humans ingest undercooked meat infected with cysticerci. 6) Protoscolices from the cysticerci are released in the human intestine, attach to the wall, and become the heads of adult tapeworms. 7) Adult tapeworms produce proglottids. The proglottids mature, become gravid, and detach, passing through the stool. Eggs from the gravid proglottids are released in the stool.*
(Adapted from Centers for Disease Control and Prevention. [Internet]. Atlanta (GA): DPDx – Laboratory identification of parasitic diseases of public health concern: cysticercosis. [cited 2015 Jan 7]. Available from: http://www.cdc.gov/dpdx/cysticercosis/index.html.)

the cerebral cortex and less often by cysticerci in the brainstem, cerebellum, or basal ganglia. In contrast, extraparenchymal disease manifestations can include hydrocephalus due to cystic obstruction of the foramina or aqueduct, mass effect, or arachnoiditis if the subarachnoid space is involved.

Clinical presentations therefore are variable and largely dependent on the location and quantity of parasitic lesions, ranging from seizures and headache with parenchymal involvement to altered mental status and signs of elevated intracranial pressure with extraparenchymal disease. Patients may also present with encephalitis due to diffuse cerebral edema with multiple inflamed degenerating lesions. Focal neurologic symptoms, meningeal signs, and fever are less likely.

Diagnosis

The diagnosis is often made from the history, including emigration from or travel in an area where the disease is endemic, clinical presentation, and brain imaging with either

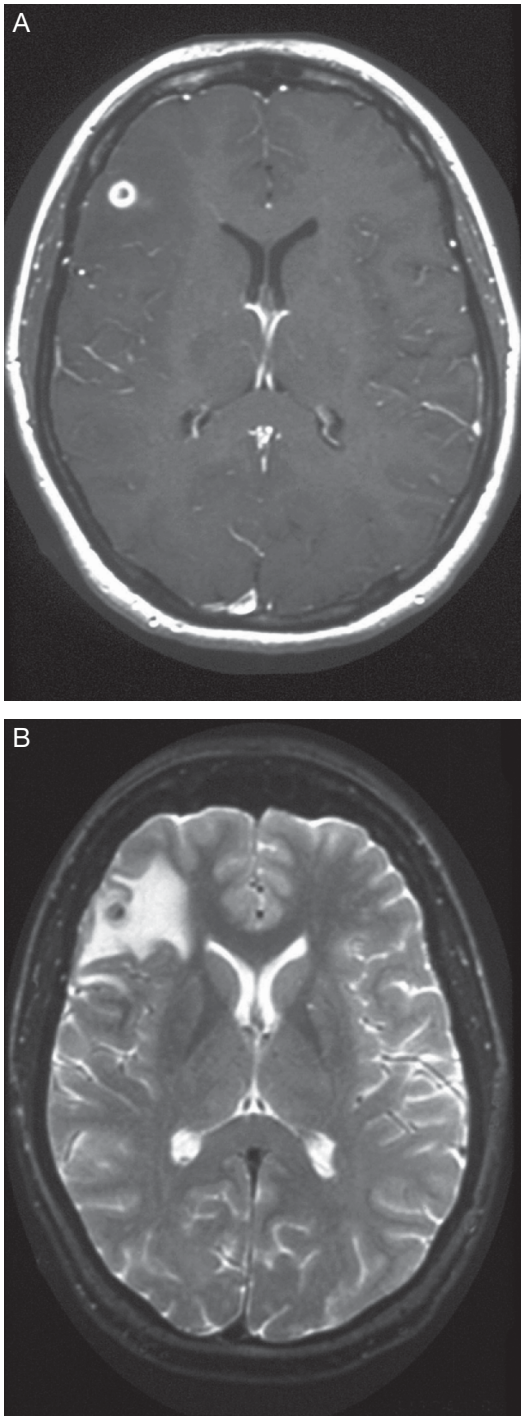

Figure 68.2 *Cysticercosis Abscess (Globose Form). A, Magnetic resonance image (MRI) (T1-weighted, gadolinium-enhanced image) demonstrates a ring-enhancing lesion in the right frontal lobe with associated edema. This suggests a host immune response to a live or dying organism. B, The surrounding edema demonstrated on T2-weighted MRI has a similar implication.*

computed tomography (CT) or magnetic resonance imaging (MRI) (or both) (Figure 68.2). Lesions can be either viable or degenerating. Viable lesions are characterized by nonenhancing, circular, hypodense and variably sized cystic masses. Degenerating lesions show an intense host reaction with increased wall density and accompanying contrast enhancement or edema (or both). Late changes are associated with calcification and resolution of edema. Imaging findings highly suggestive of neurocysticercosis include parenchymal or extraparenchymal lesions, which can be either single or multiple, appear cystic or calcified, and be associated with perilesional edema or enhancement (or both).

Hydrocephalus, leptomeningeal enhancement, and parenchymal brain calcifications may also be evident. The presence of a bright nodule within the cyst cavity is suggestive of a scolex and is radiographically pathognomonic for neurocysticercosis.

Funduscopic examination can occasionally lead to direct visualization of cysticerci in the retina and can therefore be invaluable. Posttreatment or spontaneous resolution of imaging findings is also suggestive of the diagnosis.

In diagnostically challenging cases without definitive neuroimaging findings, adjunct testing can be important. Antibody detection of *T solium* is available with enzyme-linked immunosorbent assay (ELISA), although enzyme-linked immunoelectrotransfer blot assay provides higher sensitivity and specificity. Both serum and cerebrospinal fluid (CSF) evaluations are available, but serum evaluation is preferred because of its increased sensitivity. The presence of serum antibodies does not prove that brain disease is related to cysticercosis. Antibodies can persist for several years after the death of the parasites and may therefore not always indicate active disease. Antigen testing may be useful. Other laboratory assessments and CSF examinations provide little additional information. Brain biopsy is rarely necessary.

Treatment

The cornerstone of neurocysticercosis treatment includes either albendazole or praziquantel, although albendazole is preferred because it has a more favorable pharmacokinetic profile. Antiparasitic therapy carries a significant risk of disease exacerbation due to death of the organism and inflammation. The presence of suspected live cysticerci warrants simultaneous treatment with corticosteroids. Given the predilection for seizures in patients treated for neurocysticercosis, especially in patients with multiple degenerating parenchymal lesions, an anticonvulsant is often added for prophylaxis. Appropriate agents include phenytoin, carbamazepine, and levetiracetam. Surgical or endoscopic intervention may be indicated if patients have hydrocephalus or herniation. The prognosis largely depends on the location and quantity of cysticerci and on the degree of

inflammation. Hosts with multiple lesions have a poorer prognosis than those with a single enhancing lesion.

- Neurocysticercosis is attributed to infection by the larval stage of the parasite *T solium*, more commonly known as the pork tapeworm.
- In patients with neurocysticercosis, parenchymal involvement is most often associated with seizures caused by cysticerci in the cerebral cortex and less often by cysticerci in the brainstem, cerebellum, or basal ganglia.
- Imaging findings highly suggestive of neurocysticercosis include parenchymal or extraparenchymal lesions, which can be either single or multiple, appear cystic or calcified, and be associated with perilesional edema or enhancement (or both).
- The cornerstone of neurocysticercosis treatment includes either albendazole or praziquantel, although albendazole is preferred because it has a more favorable pharmacokinetic profile.
- Given the predilection for seizures in patients treated for neurocysticercosis, especially in patients with multiple degenerating parenchymal lesions, an anticonvulsant is often added for prophylaxis.

Hydatid Cyst

Epidemiology and Life Cycle

Echinococcosis is a potentially lethal parasitic disease most commonly caused by the larval stages of *Echinococcus granulosus* and *Echinococcus multilocularis*, although other species of this tapeworm can also produce infection in humans. Disease states can be subclassified into either cystic echinococcosis (caused by *E granulosus*) or alveolar echinococcosis (caused by *E multilocularis*) depending on the infecting organism. Areas where cystic echinococcosis is endemic include the Mediterranean, Middle East, South America, Australia, and southern Africa, whereas the alveolar form tends to occur most frequently in North America, Central Europe, Turkey, Russia, and China.

Echinococcosis is thought to be acquired in childhood, with latency periods of up to 50 years. Humans are the intermediate host and are infected by the ingestion of parasitic eggs in contaminated food or water. The initial phase of the primary infection with cystic echinococcosis is often asymptomatic, and the subsequent clinical features often appear years later and are dependent on the sites of dissemination and the lesion size. This condition is usually self-limited and remains undiagnosed in many asymptomatic patients. In contrast, alveolar echinococcosis is less likely to be clinically silent, although findings can be nonspecific and often involve constitutional symptoms and hepatomegaly. The lungs and the liver are affected most frequently, with the liver often involved in both cystic echinococcosis and alveolar echinococcosis.

Echinococcosis is usually disseminated hematogenously, either through primary inoculation or secondary spread, leading to the development of cystic lesions containing hydatid fluid, more commonly known as hydatid cysts. Cerebral involvement is rare but can be found in 2% to 4% of all cases of echinococcosis; most are accompanied by lesions in the liver or lung. Symptoms often result from mass effect within organs, obstruction of flow, or complications of rupture. Specifically, in the CNS, manifestations can include seizures, signs of increased intracranial pressure (including headache and focal neurological deficits), and compressive symptoms if the spinal cord is involved.

Diagnosis and Treatment

A combination of imaging and serologic studies is often most informative for making the diagnosis of both cystic echinococcosis and alveolar echinococcosis. Laboratory assays are often more sensitive and specific for the alveolar form. Given the frequency of hepatic involvement, ultrasonography in combination with ELISA can help confirm the diagnosis. In rare cases, percutaneous aspiration or biopsy may be necessary for diagnostic confirmation.

The most common location for cystic echinococcosis lesions is within the brain parenchyma, although other possible sites are the subarachnoid space, epidural space, ventricles, and spinal cord. Single unilocular or multilocular lesions are often identified—the presence of multiple daughter cysts is pathognomonic for hydatid disease. Typical MRI findings include spherical, well-demarcated, thin-walled, homogenous, and CSF-isointense cystic lesions with an occasional thin rim of contrast enhancement. Perilesional cerebral edema may be present. Partial to complete calcification of the cyst may occur; dead cysts are often characterized by a thick, calcified wall. Magnetic resonance spectroscopy may be useful diagnostically, with pyruvate and succinate peaks being important markers of identification and viability of cysts.

Characteristic imaging findings in alveolar echinococcosis include multilocular or single cystic lesions with partially calcified walls that are variable and irregular in thickness and are poorly demarcated from surrounding tissue; they often contain multiple irregular cysts. Peripheral calcification and perilesional edema are typical.

Given the risk of anaphylactic reaction and dissemination with cyst rupture, treatment options for cerebral hydatid disease are primarily surgical. Particular care is needed to ensure that cysts are removed intact. Anthelmintic agents and injection of cysts with either formalin or hypertonic saline can reduce cystic size.

- Echinococcosis is thought to be acquired in childhood, with latency periods of up to 50 years. Humans are the intermediate host and are infected by the ingestion of parasitic eggs in contaminated food or water.

- Given the risk of anaphylactic reaction and dissemination with cyst rupture, treatment options for cerebral hydatid disease are primarily surgical. Particular care is needed to ensure that cysts are removed intact.

Toxoplasmosis

Epidemiology and Life Cycle

Toxoplasmosis is a parasitic disease due to macrophage infection by the intracellular protozoan *Toxoplasma gondii*. It most commonly affects immunocompromised hosts, particularly patients with human immunodeficiency virus (HIV) infection, and, less frequently, patients who have other forms of T-cell immune defects. In the majority of immunocompetent hosts, the infection remains asymptomatic in the CNS and skeletal muscle tissue. Toxoplasmosis has a worldwide distribution and is usually acquired by oral ingestion of tissue cysts or oocysts from contaminated water or undercooked food. Feline exposure increases risk of infection. After initial inoculation, a latent cystic form remains in the tissues until reactivation and rupture. Reactivation often occurs with immunosuppression and results in acute illness.

Clinical Manifestations

Parasitic cystic lesions in toxoplasmosis often create abscesses in the cerebral cortex, hippocampus, and basal ganglia. Clinical presentations after CNS infection are variable and often involve headache, seizures, focal neurologic findings (including cranial nerve palsies), and symptoms of mass effect and elevated intracranial pressure. Although fever can occur, it is not usually present.

Diagnosis

The diagnosis of toxoplasmosis is typically made on the basis of the clinical syndrome, imaging findings, and laboratory assessments, including peripheral blood and CSF polymerase chain reaction (PCR) testing, both of which have high sensitivity and specificity for detection. Toxoplasmosis is a reactivation infection, so serum anti-*Toxoplasma* immunoglobulin (Ig)G antibodies are usually present in patients with encephalitis, although IgM antibodies are usually absent. The absence of serum antibodies can be used as a screening tool to argue against, but not exclude, *Toxoplasma* causing a mass lesion.

CSF analysis may show a mild mononuclear pleocytosis with an elevated protein level. PCR studies have a high specificity and are definitive for the diagnosis when positive, although the sensitivity is incomplete.

Biopsy is usually reserved for patients who do not improve, clinically or radiographically, with an appropriate treatment. Deep gray matter or white matter cerebral sites, including the thalamus and basal ganglia, are most often involved, with less frequent involvement of the brainstem and cerebellum. Rarely, the corpus callosum is involved, with an appearance similar to that of a glioblastoma. Multiple unencapsulated lesions are often present with accompanying perilesional edema, but solitary lesions are occasionally seen.

CT and MRI are key in making the radiographic diagnosis, although MRI is preferred because of its higher sensitivity. Pertinent findings in toxoplasmosis include the presence of multiple ring-enhancing lesions, subcortical involvement, and eccentric target signs (Figure 68.3). Studies in the acute phase of infection may show small foci of nodular enhancement in the periventricular and subpial regions with minimal adjacent edema. On MRI T2-weighted and fluid-attenuated inversion recovery imaging, a target sign may be present, with central hyperintensity that indicates likely necrosis. Perilesional hyperintensity representing edema is common, and postcontrast images often show ring enhancement. Magnetic resonance spectroscopy can also be informative, often showing lipid and lactate peaks, which correlate with the anaerobic and acellular environments within an abscess.

Treatment

Presumptive diagnosis in the presence of a high clinical suspicion usually warrants empirical treatment. Therapy includes pyrimethamine, sulfadiazine, and folinic acid. Clindamycin should be used in patients allergic to sulfa drugs. Correct empirical treatment should decrease the multitude and size of the lesions, lessen the perilesional edema, and decrease the mass effect in 10 to 14 days, when a follow-up scan of the head is suggested. Full resolution is expected within 6 months. Patients may have residual calcification and leukomalacia. Adjunctive corticosteroids may be beneficial in patients who have radiographic evidence of elevated intracranial pressure, midline shift, or early clinical deterioration with therapy.

The response to appropriate treatment is often rapid, with clinical improvement often preceding radiographic improvement. Therapy should continue for 6 weeks, followed by secondary prophylaxis in persistently immunosuppressed patients. Rarely, treatment may result in a paradoxical worsening due to immune reconstitution inflammatory syndrome (IRIS). Worsening of imaging findings may accompany these situations. When patients are being treated for toxoplasmosis, a diagnosis of lymphoma should be considered if patients show no improvement within 2 weeks after treatment initiation.

Special considerations for HIV-infected patients who have toxoplasmosis include paradoxical worsening of

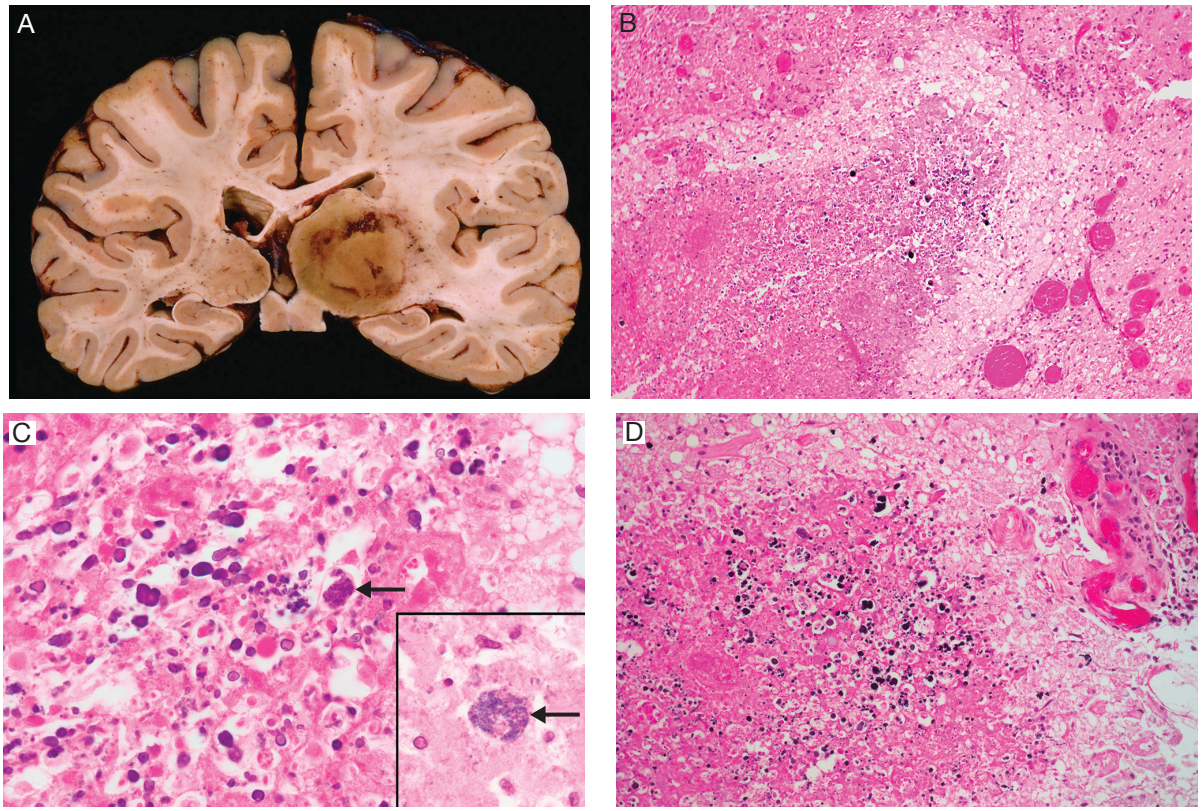

Figure 68.3 *Cerebral Toxoplasmosis.*
A, Typical macroscopic appearance of toxoplasmic parenchymal abscess (resembling a gold coin), with foci of hemorrhagic necrosis. B, Toxoplasmic abscess with nonspecific features of central necrosis surrounded by a rim of neovascularization, vasogenic edema, and inflammatory infiltrates. Toxoplasma *organisms are usually found at advancing edges of the lesion. C and D, Higher magnification shows typical histologic features of aggregates of* Toxoplasma *organisms at the outer edge of the abscess, including microcysts containing* Toxoplasma gondii *bradyzoites (C, arrows) or free organisms of tachyzoites.*

radiographic and clinical findings with IRIS, which can occur as CD4 counts improve after antiretroviral therapy has begun. Treatment of both HIV infection and toxoplasmosis should be continued with adjunct corticosteroid therapy as necessary. Primary prophylaxis should be provided for clinically asymptomatic patients who have CD4 cell counts less than100/μL and positive *T gondii* IgG antibodies. Therapy can be discontinued after CD4 cell counts rise to greater than 200/μL for 3 or more months.

- Toxoplasmosis has a worldwide distribution and is usually acquired by oral ingestion of tissue cysts or oocysts from contaminated water or undercooked food. Feline exposure increases risk of infection.
- Parasitic cystic lesions in toxoplasmosis often create abscesses in the cerebral cortex, hippocampus, and basal ganglia.
- The diagnosis of toxoplasmosis is typically made on the basis of the clinical syndrome, imaging findings, and laboratory assessments, including peripheral blood and CSF PCR testing, both of which have high sensitivity and specificity for detection.
- Pertinent findings in toxoplasmosis include the presence of multiple ring-enhancing lesions, subcortical involvement, and eccentric target signs.
- When patients are being treated for toxoplasmosis, a diagnosis of lymphoma should be considered if patients show no improvement within 2 weeks after treatment initiation.

Cerebral Amebiasis

Overview

Free-living amebas are protozoa that can survive and replicate without a host. Although CNS infection is relatively uncommon and mainly occurs in males in their second to fourth decade of life, the most important organisms that cause clinically significant cerebral disease in humans include *Naegleria, Acanthamoeba*, and *Balamuthia*.

Acute Amebic Meningoencephalitis

Epidemiology

Naegleria fowleri and *Acanthamoeba* are freshwater organisms that cause primary amebic meningoencephalitis. Patients with this rare form of necrotizing encephalitis present with an acute, fulminant and rapidly progressive disease that is often rapidly fatal. *Naegleria fowleri* is found worldwide, usually in warm freshwater. Inoculation occurs with inhalation or direct olfactory contact with water and is usually related to swimming in contaminated water. Invasion occurs through the cribiform plate into the subarachnoid space. Intracerebral dissemination occurs rapidly, often within hours. Previously healthy children or young adults are most likely to be affected.

Clinical Manifestations

The clinical manifestation of acute amebic meningoencephalitis is similar to that of fulminant meningitis and often includes headache, fever, neck stiffness, nausea, and vomiting. Progressive deterioration occurs and can include seizures, cranial nerve palsies, and coma.

Diagnosis

CSF findings often include a hemorrhagic pleocytosis, an elevated opening pressure and protein level, and a low glucose level, which are similar to findings in bacterial meningitis. For suspected acute amebic meningoencephalitis, wet mount preparations should be evaluated for free-swimming organisms.

Although not widely available, PCR performed on CSF can provide a definitive diagnosis. Imaging findings are often nonspecific but can include evidence of basilar meningeal enhancement with exudates, edema, hydrocephalus, and cisternal obliteration. Infarctions with necrosis can occur, especially in basilar locations (including the orbitofrontal regions and basal ganglia) because of obliteration of perforating vessels. Microscopic findings include evidence of hemorrhage and necrosis of the cerebral hemispheres, cerebellum, and brainstem along with purulent exudates involving the leptomeninges. Perivascular *N fowleri* and *Acanthamoeba* trophozoites define the diagnosis but only at autopsy.

Treatment

While the optimal approach to treatment is uncertain, high-dose amphotericin B (intravenously or intrathecally [or both]) is commonly used. In addition, other medications that may be added or used in combination with amphotericin B include rifampicin, fluconazole or miconazole, miltefosine, and azithromycin. The prognosis is usually extremely poor; most patients proceed to coma and death within 4 to 6 days after clinical onset, usually with an elevated intracranial pressure leading to herniation.

Granulomatous Amebic Encephalitis

Epidemiology

Granulomatous amebic encephalitis (GAE) often results from subacute to chronic infection with several species of *Acanthamoeba* or a single species of *Balamuthia, Balamuthia mandrillaris*. Both types of parasites are found worldwide, and entry is usually gained into the host through the respiratory or integumentary systems, followed by hematogenous dissemination and invasion of the CNS. Significant disease occurs most commonly in debilitated or immunocompromised hosts, including patients who have AIDS or who have undergone chemotherapy, although *B mandrillaris* can cause infection in immunocompetent hosts as well.

Clinical Manifestations

Findings are similar with both forms of infection, and hallmarks of the clinical presentation include a long duration of focal neurologic symptoms that are consistent with a chronic, slowly progressive meningoencephalitis. Fever is often absent. Patients with *B mandrillaris* infection may have associated chronic granulomatous cutaneous lesions of the face and nose, which are thought to occur at the site of inoculation.

Diagnosis

Diagnosis of GAE is usually challenging. CSF assessment is often contraindicated because of the risk of herniation; when undertaken, though, CSF assessment may show a moderate pleocytosis with slightly elevated protein level and a low or normal glucose level.

Imaging findings with CT or MRI are notable for the presence of large, solitary, space-occupying or multifocal lesions, although both can be evident simultaneously. Solitary lesions may have a linear gyriform pattern of enhancement that is suggestive of the diagnosis; these lesions are thought to result from inflammation involving the meninges and underlying cortex. Involvement of the diencephalon, thalamus, brainstem, and posterior fossa structures is common. Enhancing punctate lesions of the cerebellar hemispheres and corticomedullary junctions are also seen.

Foci of chronic leptomeningitis may be evident microscopically and are often most prominent adjacent to cerebral lesions. Vasculitis can be present along with evidence of perivascular trophozoites or cysts (or both). A characteristic feature is necrotizing angiitis leading to intralesional hemorrhage.

Definitive diagnosis of *Acanthamoeba* infection requires finding the presence of cysts or trophozoites in brain tissue, whereas definitive diagnosis of *Balamuthia* infection requires positive staining with an indirect immunofluorescence assay of fixed brain tissue. Both are often postmortem diagnoses.

Treatment

An optimal treatment approach for GAE has not been determined, and combination therapy is often necessary. Treatment of GAE from *Acanthamoeba* infection typically includes regimens with either amphotericin B or clotrimazole, whereas treatment of GAE from *Balamuthia* infection has included pentamidine, sulfadiazine, clarithromycin, and fluconazole. Surgical removal of granulomatous mass-like lesions may be necessary. GAE, however, is typically progressive and often fatal within weeks to months after symptom onset, although the progression may be slightly slower in patients with *B mandrillaris* infection.

- *Naegleria fowleri* is found worldwide, usually in warm freshwater. Inoculation occurs with inhalation or direct olfactory contact with water and is usually related to swimming in contaminated water.
- The clinical manifestation of acute amebic meningoencephalitis is similar to that of fulminant meningitis and often includes headache, fever, neck stiffness, nausea, and vomiting.
- For suspected acute amebic meningoencephalitis, wet mount preparations should be evaluated for free-swimming organisms.

Malaria

Overview

Malaria is caused by *Plasmodium* species. When the CNS is involved, the infection is typically due to *Plasmodium falciparum* and rarely *Plasmodium vivax*. Malaria is endemic in tropical and subtropical areas (most commonly, tropical regions of South America, Africa, and Asia). A high clinical suspicion for malaria is raised when patients present with febrile illnesses in these regions.

Epidemiology and Life Cycle

Inoculated sporozoites from a female *Anopheles* mosquito enter the bloodstream and invade the host's liver (Figure 68.4). The incubation period depends on the *Plasmodium* species and the immune status of the person (typical range, 1–2 weeks). The sporozoite then multiplies, forming a

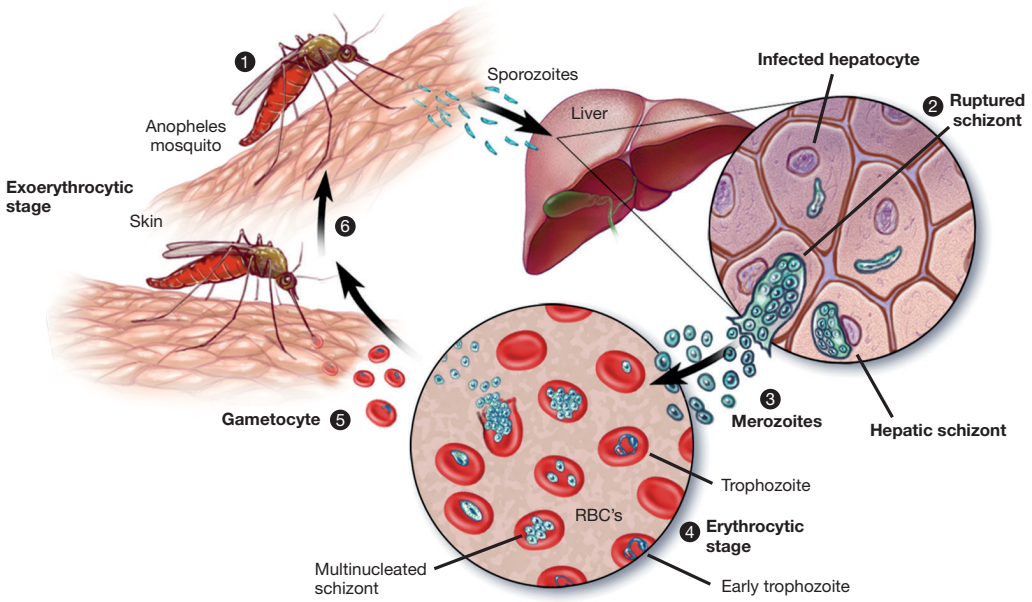

Figure 68.4 *Malaria and* Anopheles *Life Cycle.*
1) Anopheles *mosquito bites a human, and sporozoites are introduced into the bloodstream. 2) Sporozoites spread hematogenously to the liver and infect hepatocytes. 3) In the liver, sporozoites divide to form multinucleated schizonts, which rupture and release merozoites into the blood. 4) Merozoites infect red blood cells. Merozoites may mature into trophozoites and multinucleated schizonts or differentiate into gametocytes. 5) Gametocytes are ingested by the* Anopheles *mosquito and mature in the gut. 6) Sporozoites develop and are transferred to the salivary gland of the mosquito.*
(Adapted from Breman JG. Clinical manifestations of malaria. Post TW, editor. Waltham (MA). UpToDate. c2015 - [cited 2014 Dec 8]. Available from: http://www.uptodate.com. Used with permission.)

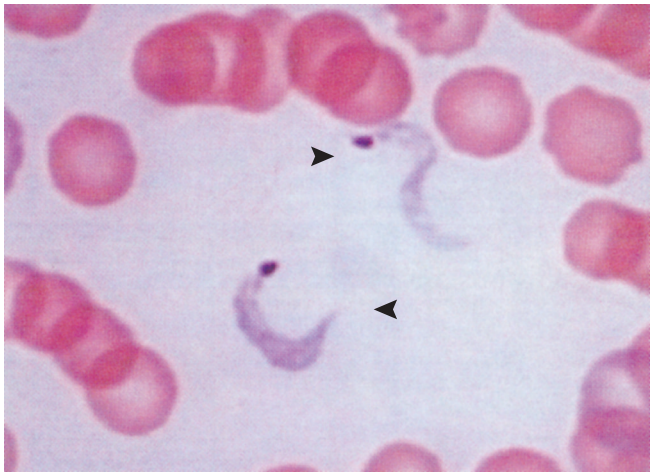

Figure 68.5 *Chagas Disease.*
Thin blood film shows circulating Trypanosoma cruzi *trypomastigotes (arrowheads) in the bloodstream.*
(Adapted from Barreira AA, Nascimento OJM. Peripheral neuropathies in Chagas disease. In: Noseworthy JH, editor. Neurological therapeutics: principles and practice. Vol 2. New York: Martin Dunitz; c2003. p. 1992–8. Used with permission of Mayo Foundation for Medical Education and Research.)

multinuclear body and finally a merozoite. Merozoites rupture, enter other hepatocytes, and reenter the bloodstream, where they invade erythrocytes and form trophozoites. The trophozoites undergo further nuclear division and are transformed into multinuclear schizonts that contain multiple merozoites. When the erythocytes rupture, the merozoites enter the bloodstream and cause an immune reaction with recurrent fevers. Phagocytic cells from the liver and spleen engulf the ruptured erythrocytes, resulting in hepatosplenomegaly.

Patients at higher risk of cerebral malaria include children, elderly patients, pregnant women, patients with a history of splenectomy, and patients with poor nutritional status.

Clinical and Diagnostic Features

General symptoms of uncomplicated malaria include fever, chills, fatigue, headache, nausea and vomiting, diarrhea, arthralgias, and myalgias. Patients may have mild anemia and an enlarged spleen. A peripheral blood smear for trophozoites may show more than 5,000/μL.

Complicated malaria is a more severe form characterized by a large number of trophozoites in the blood (≥100,000/μL). Patients with complicated malaria have more widespread, severe effects on many organs, including the brain. Encephalopathy and seizures may occur with cerebral malaria, and patients may have retinal hemorrhages as well. Patients with cerebral malaria may progress to coma and death without treatment. Other signs and symptoms may include renal failure, hepatic failure, coagulopathy, intravascular hemolysis, respiratory distress, hypoglycemia, and metabolic acidosis.

Treatment

Treatment is usually quinine, quinidine, or artemisinin derivatives. Mortality with cerebral malaria is about 50%. Neurologic complications are common in survivors of cerebral malaria.

- Encephalopathy and seizures may occur with cerebral malaria, and patients may have retinal hemorrhages as well.

Chagas Disease

Overview and Life Cycle

Chagas disease is caused by *Trypanosoma cruzi*. It is prevalent in the southern United States and Central and South America. The organism multiplies in the intestinal tract of the reduviid bug. When this vector takes a blood meal from a human, it also defecates and releases infective trypomastigotes, which enter the bloodstream of the human host. The trypomastigotes transform into amastigotes, multiply, and form pseudocysts in multiple host tissues (skeletal muscle, CNS, and reticuloendothelial cells).

Clinical Features and Diagnosis

In an acute infection, patients may have erythema and swelling at the site of inoculation, cardiac involvement, and, uncommonly, meningoencephalitis. Patients with a chronic infection may have dilated cardiomyopathy, megacolon, and megaesophagus. The diagnosis is made with a peripheral blood smear (Figure 68.5).

69 Prion Disorders: Creutzfeldt-Jakob Disease and Related Disorders

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Introduction

Prion disorders, also known as transmissible spongiform encephalopathies (TSEs), are a group of universally fatal human and animal diseases that cause rapid degeneration of brain neurons (Table 69.1). The essential pathogenesis is called the prion theory: a conformational change of host-derived prion protein (PrP), that propagates further conformational change, which amplifies the process that selectively affects neurons. TSEs may be sporadic, inherited, or spread in an acquired manner like an infectious agent. The acquired manner is least frequent.

This chapter reviews the molecular theory of prions and the pathology, clinical presentation, and management of various prion diseases.

Molecular Theory of Prions

All TSEs result from a proteinaceous infectious particle—that is, a prion—that is not a virus and does not contain any nucleic acid. The cellular isoform of the PrP is encoded by the *PRNP* gene on the short arm of human chromosome 20. PrP is expressed in diverse cell types but is most abundant in neurons. Its precise function is unknown. The normal PrP (PrP^{C}) (*C* indicates cellular) is a membrane-associated protein with primarily an α-helical structure. It is attached to the extracellular surface of the cell membrane by a glycoprotein at its C terminal. The pathogenic form of the PrP (PrP^{Sc}) (*Sc* indicates scrapie) has a β-pleated sheet protein structure. It has the same amino acid sequence as PrP^{C} but differs in that it is resistant to proteolytic digestion and is insoluble to chemical measures that usually solubilize proteins. The pathogenic PrP^{Sc} is thought to bind the normal PrP^{C} and induce a conformational change into PrP^{Sc}, thereby perpetuating conversion to the pathogenic isoform. The prion hypothesis postulates that the conversion of PrP^{C} to PrP^{Sc} may occur spontaneously or result from *PRNP* mutations in familial cases.

Abnormal intracellular aggregation of PrP^{Sc} may affect synaptic transmission and induce dendritic swelling, which may in turn cause pathologic spongiosis, neuronal loss, and gliosis. Extracellular aggregation and polymerization may form the amyloid kuru plaques that are the pathologic hallmark in the type of Creutzfeldt-Jakob disease (CJD) that is called variant CJD (vCJD), in Gerstmann-Sträussler-Scheinker syndrome (GSS), in kuru, and in some cases of sporadic CJD (sCJD).

Strains of prions have been identified. The strains differ in their incubation time of experimental disease, distribution of central nervous system lesions, and resistance to proteolysis. Biochemically, the strains are segregated by their molecular weight after proteolytic digestion (19 kDa vs 21 kDa) and glycosylation patterns (proportion of nonglycosylated, monoglycosylated, and diglycosylated forms).

Abbreviations: BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalographic; fCJD, familial Creutzfeldt-Jakob disease; FLAIR, fluid-attenuated inversion recovery; GSS, Gerstmann-Sträussler-Scheinker syndrome; iCJD, iatrogenic Creutzfeldt-Jakob disease; MRI, magnetic resonance imaging; PrP, prion protein; PrP^{C}, normal (cellular) prion protein; PrP^{Sc}, pathogenic (scrapie) prion protein; sCJD, sporadic Creutzfeldt-Jakob disease; TSE, transmissible spongiform encephalopathy; vCJD, variant Creutzfeldt-Jakob disease

Table 69.1 • Selected Prion Diseases in Humans and Nonhuman Mammals

Mechanism	Prion Diseases in Humans	Prion Diseases in Nonhuman Mammals
Sporadic	Sporadic Creutzfeldt-Jakob disease (sCJD) Sporadic fatal insomnia (sFI)	Scrapie of sheep and goats Chronic wasting disease (CWD) of deer and elk
Genetic	Familial CJD (fCJD) Fatal familial insomnia (FFI) Gerstmann-Sträussler-Scheinker syndrome (GSS)	. . .
Acquired or infectious	Iatrogenic CJD (iCJD) Variant CJD (vCJD) Kuru	CWD Scrapie Bovine spongiform encephalopathy (BSE) (mad cow disease)

Polymorphisms and mutations of the human *PRNP* gene confer increased susceptibility to the various prion diseases. Codon 129 of human *PRNP* codes for either methionine (M129) or valine (V129). Homozygotes (MM or VV) at this location are more susceptible to prion propagation than heterozygotes (MV). The MM genotype occurs in 72% of patients with sCJD and in 100% of patients with vCJD and also increases susceptibility for kuru. The VV genotype occurs in 17% of patients with sCJD and in 50% of patients with iatrogenic CJD (iCJD) (related to human growth hormone). A significant proportion of patients with mutation-associated prion disease do not have a family history of prion disease.

- The pathogenic form of the PrP (PrP^{Sc}) (*Sc* indicates scrapie) has a β-pleated sheet protein structure.
- The prion hypothesis postulates that the conversion of PrP^{C} to PrP^{Sc} may occur spontaneously or result from *PRNP* mutations in familial cases.
- Extracellular aggregation and polymerization may form the amyloid kuru plaques that are the pathologic hallmark of vCJD, GSS, kuru, and some cases of sCJD.

Prion Diseases in Nonhuman Mammals

The first recognized prion disorder was scrapie in sheep in Great Britain in the 18th century. Subsequently, bovine spongiform encephalopathy (BSE) gained worldwide attention from an outbreak in the United Kingdom in the 1980s and the subsequent emergence of vCJD in some people who consumed infected beef. BSE manifests in cattle as apprehension, hyperesthesia, and incoordination; hence, it is called mad cow disease. Chronic wasting disease in deer and elk is endemic in the Midwest and Rocky Mountains of the United States, but chronic wasting disease has not yet been shown to cross the species barrier into humans.

Prion Diseases in Humans

Several prion diseases occur in humans. These include CJD, fatal insomnia, and GSS (Table 69.2). These 3 prion diseases in humans and a fourth, kuru, are reviewed in the remaining sections of this chapter.

Creutzfeldt-Jakob Disease

Epidemiology

Most cases of CJD (85%-90%) are sCJD; the annual incidence is 1 per million in all countries and populations. The remaining 10% to 15% of cases are inherited in autosomal dominant fashion with essentially complete penetrance. Relatively few cases have been reported secondary to accidental inoculation (iCJD or vCJD).

Clinical Features

All forms of CJD are characterized by rapidly progressive dementia. Accompanying features may include ataxia, myoclonus, psychiatric disturbance (psychosis, aggression, and depression), and extrapyramidal signs. Death occurs within 1 year for 80% of patients, with a slightly longer duration of illness in patients with vCJD.

Diagnosis

The diagnosis of CJD is often suspected from the presentation. Ancillary tests may be performed. Cerebrospinal fluid (CSF) analysis can aid in the diagnosis and help rule out mimics. Neuron-specific enolase, 14-3-3 protein, tau protein, and S-100 protein are normally enriched in the cytoplasm of neurons. The protein levels become elevated in CSF as markers of rapid neuronal loss. The levels of these CSF proteins tend to increase during the course of illness. Sensitivity and specificity for sCJD are high but only in the appropriate clinical context. In many other disorders with brain neuronal destruction (eg, stroke and encephalitis) these CSF proteins are elevated. The sensitivity for familial CJD (fCJD) or acquired forms of CJD is much lower. Inflammatory CSF signs (eg, elevated nucleated cell count or total protein >100 mg/dL) are not present in CJD.

Table 69.2 • Clinical and Diagnostic Features of Human Prion Diseases

Feature	Creutzfeldt-Jakob Disease (CJD)	Fatal Insomnia	Gerstmann-Sträussler-Scheinker Syndrome
Age at onset	Seventh decade	Average, 50 y (range, 20–70 y)	40–55 y
Clinical course	8 mo to 1 y	1–2 y	3–10 y
Clinical features	Rapidly progressive dementia Ataxia Myoclonus Psychiatric disturbances	Insomnia Sympathetic hyperactivity Tremor or ataxia	Ataxia Cognitive, pyramidal, and extrapyramidal signs (later)
Diagnostic findings	EEG: nonspecific slow waves (early); periodic sharp waves (late) MRI: cortical ribbon sign (DWI); pulvinar sign (in variant CJD)	EEG: nonspecific slowing	EEG: nonspecific slowing

Abbreviations: DWI, diffusion-weighted imaging; EEG, electroencephalography; MRI, magnetic resonance imaging.

Electroencephalographic (EEG) patterns change with progression of CJD. Nonspecific slow wave abnormalities may be the earliest changes, with more specific periodic sharp wave complexes (usually 1–2 Hz) appearing later. Periodic sharp wave complexes may be diphasic or triphasic, and they often correlate with myoclonic jerks.

Magnetic resonance imaging (MRI) of the brain shows asymmetric T2- and diffusion-weighted increased signal abnormalities in the neocortex, thalamus, caudate, and putamen (Figure 69.1). Diffusion-weighted imaging is the most sensitive sequence for abnormal cortical ribbon sign; the second most sensitive is fluid-attenuated inversion recovery (FLAIR). The pulvinar sign of symmetric T2 hyperintensity in bilateral thalamic pulvinar nuclei is characteristic of, but not exclusive to, vCJD (Figure 69.1).

Histopathology

The brains of patients with CJD have variable macroscopic appearances, ranging from normal to severely atrophic. The defining pathology of CJD is *spongiform change*, which is intracellular vacuolation of neutrophils, primarily in neocortical and deep gray matter. *Spongiosis* is focal

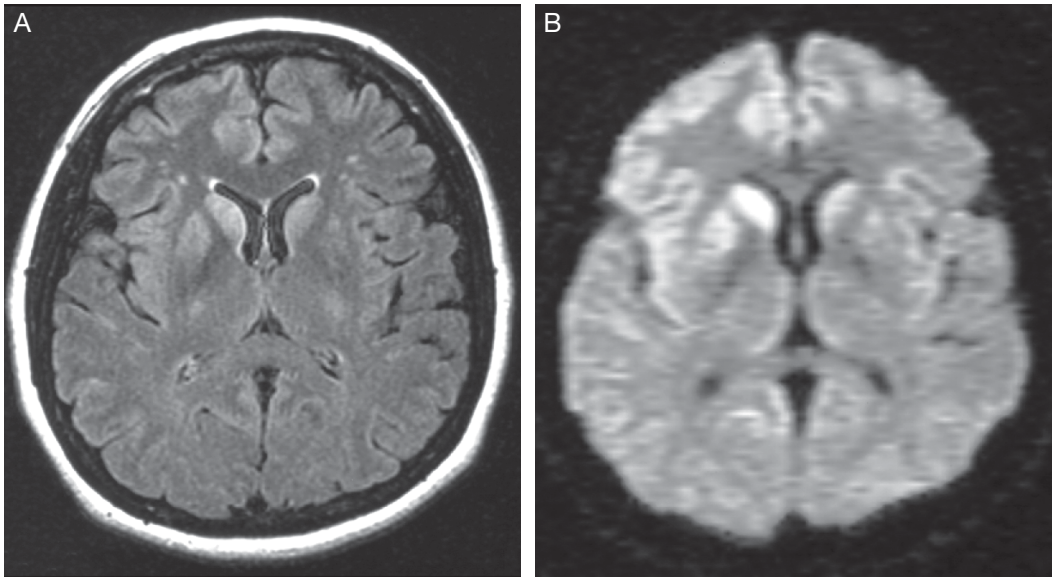

Figure 69.1 *Creutzfeldt-Jakob Disease (CJD).*
Magnetic resonance imaging of the brain from a 54-year-old woman with CJD shows asymmetric increased signal in the caudate and putamen bilaterally. A, Fluid-attenuated inversion recovery imaging. B, Diffusion-weighted imaging. (Adapted from Mowzoon N. Behavioral neurology. Part B: Syndromes of cognitive dysfunction. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 297–332. Used with permission of Mayo Foundation for Medical Education and Research.)

areas of swollen axonal and dendritic processes, which occur primarily at synapses and extracellularly around the perikaryon. *Neuronal loss* (greatest in neocortical layers 3–5) and *reactive gliosis* (ie, reactivation and proliferation of astrocytes) are also present. Amyloid fibrils and plaques are present in most cases of vCJD, GSS, and kuru but in less than 10% of sCJD cases (Figure 69.2).

Sporadic CJD

Rapid-onset dementia is the most common presentation in patients with sCJD. The type of cognitive disturbance is nonspecific. Peak onset is in the seventh decade. Average duration from symptom onset to death is 8 months, with 81% of deaths occurring in the first year. Males and females are affected equally. Early signs are most often loss of memory and concentration, but psychiatric changes and vegetative dysfunction (poor appetite, poor sleep, and poor hygiene) are also common presenting symptoms. Other symptoms that occur over the course of the illness include myoclonus (stimulus-induced [startle] or spontaneous myoclonus), ataxia, and extrapyramidal signs. End-stage CJD is typically marked by akinetic mutism.

Four clinical variants of sCJD have been described (Box 69.1): 1) The Heidenhain variant is characterized by cortical blindness due to primary involvement of the visual cortex. 2) The Brownell-Oppenheimer variant is characterized by early prominent ataxia. 3) The Stern-Garcin variant has early, prominent parkinsonism and other extrapyramidal features from primary involvement of the deep gray matter, including basal ganglia. 4) The more controversial amyotrophic variant has early, prominent lower motor neuron signs.

Familial CJD

Compared with sCJD, fCJD usually has an earlier onset and longer course. Multiple mutations in the *PRNP* gene have been associated with fCJD. Except in patients with E200K *PRNP* mutation, fCJD typically does not manifest periodic EEG abnormalities. The E200K mutation (the most common *PRNP* mutation) may also cause peripheral neuropathy.

Iatrogenic CJD

Transmission of iCJD occurs from human to human by direct inoculation into brain parenchyma or by systemic exposure. Cases of iCJD have been reported from direct nervous system inoculation involving corneal transplants, dural grafts, contaminated surgical instruments, and intracranial EEG electrodes (autoclaved at temperatures below 134°C). Systemic exposure has occurred from cadaveric pituitary hormone and pericardial grafts. Approximately 400 cases of iCJD have been reported from all causes. Direct inoculation, which is associated with a shorter incubation period, causes a clinical course identical to that of sCJD.

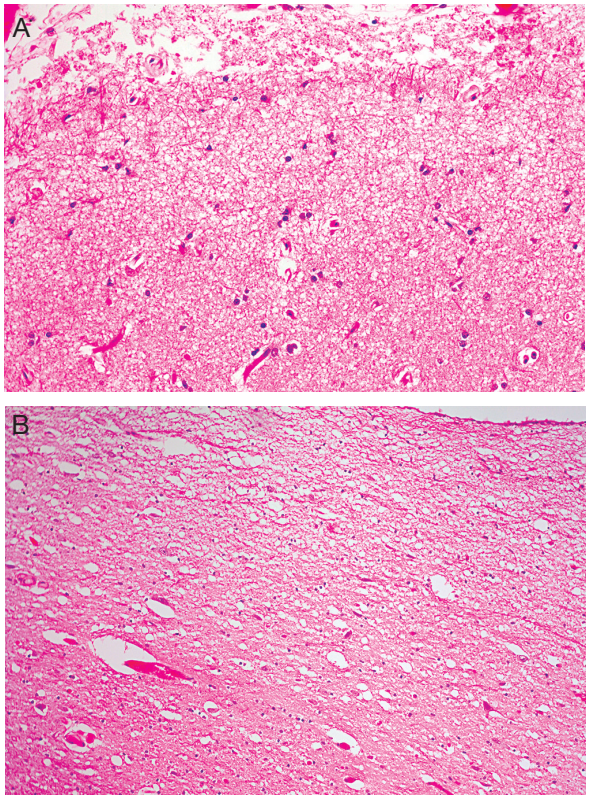

Figure 69.2 *Histopathology of Creutzfeldt-Jakob Disease (CJD).*
A, Spongiosis with coarse vacuolation of the cortex. B, Deep gray matter (thalamus) in advanced CJD.
(Adapted from Mowzoon N. Behavioral neurology. Part B: Syndromes of cognitive dysfunction. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 297–332. Used with permission of Mayo Foundation for Medical Education and Research.)

The CSF 14-3-3 protein level is elevated in most patients. Periodic EEG changes occur in only half the patients.

Variant CJD

In humans, vCJD is thought to be related to BSE. Exposure was first reported in the United Kingdom in 1996, approximately 10 years after the start of the BSE epidemic there. Of the 226 total worldwide cases of vCJD, 173 have occurred in the United Kingdom. The average age at onset is only 28 years, which is younger than for any other CJD type. After an incubation period of 12 to 15 years, the average duration of illness is 14 months. Early clinical manifestations include psychiatric and sensory symptoms (dysesthesias affect a limb more often than the face), with early development of ataxia; later manifestations include myoclonus and dementia. Compared with sCJD, vCJD is less often associated with elevated CSF 14-3-3 protein levels.

Periodic EEG abnormalities have not been reported in vCJD, and MRI shows high signal intensity in the pulvinar of the posterior thalamus (pulvinar sign) in 90% of patients.

Antemortem diagnosis of vCJD can sometimes be made by positive PrP immunohistochemistry on biopsied tonsillar tissue. Histopathology of brain in vCJD is distinguished by florid amyloid plaques surrounded by halos of vacuolation; spongiform changes are more prominent in the thalamus and basal ganglia.

- All forms of CJD are characterized by rapidly progressive dementia. Accompanying features may include ataxia, myoclonus, psychiatric disturbance (psychosis, aggression, and depression), and extrapyramidal signs.
- MRI of the brain shows asymmetric T2- and diffusion-weighted increased signal abnormalities in the neocortex, thalamus, caudate, and putamen. Diffusion-weighted imaging is the most sensitive sequence for abnormal cortical ribbon sign; the second most sensitive is FLAIR.
- The defining pathology of CJD is *spongiform change*, which is intracellular vacuolation of neutrophils, primarily in neocortical and deep gray matter.
- Cases of iCJD have been reported from direct nervous system inoculation involving corneal transplants, dural grafts, contaminated surgical instruments, and intracranial EEG electrodes (autoclaved at temperatures below 134°C).
- Compared with sCJD, vCJD is less often associated with elevated CSF 14-3-3 protein levels. Periodic EEG abnormalities have not been reported in vCJD, and MRI shows high signal intensity in the pulvinar of the posterior thalamus (pulvinar sign) in 90% of patients.
- Antemortem diagnosis of vCJD can sometimes be made by positive PrP immunohistochemistry on biopsied tonsillar tissue.

Box 69.1 • Diagnostic Criteria for Sporadic CJD

Definite CJD

Pathology

Autopsy or biopsy showing spongiosis

Probable CJD

Clinical and ancillary testing

Progressive dementia

and ≥2 *of*

Myoclonus

Visual or cerebellar deficits

Pyramidal or extrapyramidal signs

Akinetic mutism

and ≥1 *of*

EEG: periodic sharp wave complexes

CSF: elevated 14–3-3 protein level

MRI: typical T2 hyperintensity in cortical ribbon or deep gray matter

Possible CJD

Clinical

Progressive dementia

and ≥2 *of*

Myoclonus

Visual or cerebellar deficits

Pyramidal or extrapyramidal signs

Akinetic mutism

Abbreviations: CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; EEG, electroencephalography; MRI, magnetic resonance imaging.

Fatal Insomnia

Fatal insomnia is a syndrome of intractable insomnia, encephalopathy, and dysautonomia. First described in 1992, *fatal familial insomnia* is caused by the D178N *PRNP* mutation with M129 on the mutant allele. When the D178N mutation coexists with V129 on the mutant allele, the clinical phenotype better matches fCJD.

Symptom onset occurs between ages 20 and 70 years (average, 50 years). Disease duration is usually 1 to 2 years. The first clinical manifestation is progressive intractable insomnia, followed by sympathetic hyperactivity (hypertension, tachycardia, and hyperhidrosis). Other features may include mental status changes, tremor, ataxia, myoclonus, and hyperreflexia.

EEG usually shows nonspecific slowing (not periodic sharp waves). Histopathologic examination shows severe neuronal loss and gliosis in the ventral and mediodorsal thalamic nuclei more than the inferior olivary nuclei and cerebellum, with little spongiform change. *Sporadic fatal insomnia* has clinical and pathologic features that are identical to those of fatal familial insomnia but in the absence of a *PRNP* mutation.

- The first clinical manifestation of fatal familial insomnia is progressive intractable insomnia, followed by sympathetic hyperactivity (hypertension, tachycardia, and hyperhidrosis).

Gerstmann-Sträussler-Scheinker Syndrome

GSS has the slowest clinical course of the human prion diseases, with a duration from symptom onset to death ranging from 3 to 10 years. Onset usually occurs between ages 40 and 55 years. Most patients with GSS have early, prominent ataxia; cognitive signs and pyramidal and extrapyramidal signs develop later. Unlike in CJD, myoclonus is rare in GSS. Specific *PRNP* mutations dictate the clinical phenotype.

Ataxic GSS is caused by P102L (most common), G131V, or H187R mutations, and patients present with ataxia and varying degrees of dementia. GSS with pseudobulbar syndrome is caused by the A117V mutation and is characterized by predominant dementia with or without ataxia depending on the residue at codon 129. When the P105L mutation causes GSS, patients present with progressive spastic paraparesis, which may include a clumsy hand; ataxia and cognitive impairment develop later. Several mutations have been associated with GSS with neurofibrillary tangles. When the Y145Stop mutation causes GSS, patients have slowly progressive Alzheimer-like dementia and a disease course as long as 20 years.

Histopathologic examination shows neuronal loss, gliosis, minimal spongiform change, and abundant PrP-amyloid deposits and plaques in the cerebellum.

- GSS has the slowest clinical course of the human prion diseases, with a duration from symptom onset to death ranging from 3 to 10 years.
- Most patients with GSS have early, prominent ataxia; cognitive signs and pyramidal and extrapyramidal signs develop later.

Kuru

Kuru was described in the Fore tribe of New Guinea. It is acquired exclusively through cannibalistic exposure to infected brain tissue—the end of ritualistic cannibalism has nearly eradicated the disease. Although the average duration from symptom onset to death is 12 months, as with other human prion diseases, kuru has a variable latent period from 4.5 months to (rarely) 56 years; hence, the persistent appearance of rare cases. Early clinical manifestations include dysarthria, gait and truncal ataxia, titubation, and postural tremor. Ataxia ultimately predominates, but there may also be emotional lability, psychomotor retardation, and uncontrollable laugher. Histopathologic examination shows the most neuronal loss in the cerebellum and less in the basal ganglia, thalamus, and mesial temporal lobes. Prominent amyloid deposits containing prion protein (called kuru plaques) predominate in the cerebellum.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

XI.1. A 54-year-old man is hospitalized with a fever that began 4 days ago and, on the day of hospital admission, a generalized convulsive seizure. On neurologic examination, he has a mild left hemiparesis. Which of the following could be seen with a diagnosis of cerebral abscess in this patient?
a. Normal protein and glucose levels on cerebrospinal fluid examination
b. Small hyperdense lesion in the central pons on computed tomography of the head
c. Large left cerebellar T2-signal hyperintensity with corresponding diffusion-weighted imaging hypointensity on magnetic resonance imaging of the brain
d. Diffuse slowing, more prominent over the left hemisphere, on electroencephalography
e. Diffuse cerebral hypometabolism on positron emission tomography

XI.2. Polymorphisms and mutations of the human *PRNP* gene are known to confer increased susceptibility to the various prion diseases. Which of the following is most likely in a patient with variant Creutzfeldt-Jakob disease?
a. Valine-methionine genotype at codon 130
b. Methionine-methionine genotype at codon 129
c. Methionine-valine genotype at codon 129
d. Valine-valine genotype at codon 130
e. Methionine-valine genotype at codon 128

XI.3. A 62-year-old man is evaluated for new memory impairment and difficulty using his right hand, both of which have worsened over 4 months. He has a normal sleep-wake cycle. He has no history of travel outside the United States or of dementia in the family. On neurologic examination, he cannot recall any of 4 words after several minutes and cannot demonstrate use of a screwdriver despite normal strength and coordination testing. Which of the following is most likely to be seen at autopsy?
a. Neuronal loss and gliosis, without significant spongiform change, in the thalamic nuclei
b. Neuronal loss and prion protein–amyloid deposits, without significant spongiform change, in the caudate nuclei
c. Spongiform change and neuronal loss that are most severe in the left parietal cortex
d. Prominent amyloid deposits and dense-core plaques in the cerebellum
e. Extensive gliosis and spongiform change in the right occipital lobe

XI.4. A 60-year-old man with a history of alcoholism is brought to the emergency department and is found to be obtunded. He is febrile and has meningismus. Cerebrospinal fluid examination is suggestive of acute bacterial meningitis. Therapy is started with intravenous (IV) vancomycin, ceftriaxone, and dexamethasone. You are asked for a consultation because the patient is not improving clinically. Which of the following additional antimicrobial medications would be most appropriate to add to his management?
a. Amphotericin B IV
b. Ampicillin IV
c. Valacyclovir orally
d. Vancomycin orally
e. Levofloxacin IV

XI.5. Of the following choices, which is the most common cause of meningitis?
a. *Histoplasma*
b. *Coccidioides*
c. *Cryptococcus*
d. *Sporothrix*
e. *Blastomyces*

XI.6. Infection with which of the following fungi is most likely to cause intracerebral hemorrhage?
a. *Candida*
b. *Histoplasma*
c. *Mucor*
d. *Aspergillus*
e. *Sporothrix*

XI.7. Which of the following organisms is transmitted to humans by the reduviid bug?
a. *Trypanosoma cruzi*
b. *Plasmodium falciparum*
c. *Borrelia burgdorferi*
d. *Taenia solium*
e. *Balamuthia mandrillaris*

XI.8. Which of the following statements about amebic meningoencephalitis is most correct?
a. Most patients have clinically silent infections
b. Most patients have mild, self-limited disease
c. Most patients have moderate disease that typically responds well to antimicrobial therapy
d. Most patients have severe disease that typically responds well to antimicrobial therapy
e. Most patients have severe disease and a grave prognosis despite antimicrobial therapy

XI.9. A 57-year-old man who has long-standing human immunodeficiency virus (HIV) seropositivity and has adhered to his regimen for highly active antiretroviral therapy (HAART) is referred to you for evaluation of imbalance over the past 4 months. On examination, he has a mild spastic paraparesis and lower limb vibratory sensory loss. He cannot stand with his eyes closed. Magnetic resonance imaging of his spinal cord is normal. Which of the following is the most likely diagnosis?
a. Varicella zoster myelitis
b. Subacute combined degeneration
c. Coincident hereditary spastic paraparesis
d. Syphilitic myelopathy
e. HIV-associated vacuolar myelopathy

XI.10. A 44-year-old HIV-positive woman presents with slowly progressive, painless proximal muscle weakness. Her electrodiagnostic evaluation showed small, complex motor unit potentials in the proximal muscles. A left vastus lateralis muscle biopsy stained with Gomori trichrome showed prominent mitochondrial proliferation in multiple fibers (ragged red fibers). Which of the following antiretroviral medications is most likely the cause of her syndrome?
a. Didanosine
b. Ritonavir
c. Zidovudine
d. Maraviroc
e. Raltegravir

XI.11. A 30-year-old man is referred to you for evaluation of subacute right-sided facial weakness. On examination, he has severe weakness of all muscles innervated by the right facial nerve. You note a few vesicles around the right external auditory meatus. Which of the following viruses is the most likely causative agent?
a. Cytomegalovirus
b. Herpes simplex 1
c. Epstein-Barr virus
d. Varicella zoster virus
e. Human herpesvirus 6

XI.12. In a 62-year-old man, fever and a shuffling gait developed shortly after a late summer camping trip and were followed by confusion. He was admitted to the hospital after a generalized seizure. He slowly recovers, but on examination 2 weeks later you note a severe flaccid paresis of the right upper limb. Which of the following viruses is the most likely causative agent?
a. Poliovirus
b. West Nile virus
c. Japanese encephalitis virus
d. Eastern equine encephalitis virus
e. Powassan virus

XI.13. You are asked for a consultation for a 48-year-old woman who has a history of recent extensive international travel and who has been admitted to the hospital with recurrent fevers, headache, hepatosplenomegaly, and, now, coma and seizures. After evaluation, you diagnose cerebral malaria. Which of the following medications would be most appropriate to add to her regimen?
a. An artemisinin derivative
b. Amphotericin B
c. Pentamidine
d. Cefepime
e. Albendazole

Answers

XI.1. Answer a.
Roos K, Aksamit AJ Jr, Baldwin KJ, Bartt R, Cho TA, Del Brutto OH, et al. Infectious disease. Continuum: Lifelong Learn Neurol. 2012 Dec;18(6):1243–1496.

XI.2. Answer b.
Wadsworth JD, Collinge J. Molecular pathology of human prion disease. Acta Neuropathol. 2011 Jan;121(1):69–77. Epub 2010 Aug 8.

XI.3. Answer c.
Wadsworth JD, Collinge J. Molecular pathology of human prion disease. Acta Neuropathol. 2011 Jan;121(1):69–77. Epub 2010 Aug 8.

XI.4. Answer b.
Scheld WM, Whitley RJ, Marra CM, editors. Infections of the central nervous system. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; c2004. 939 p.

XI.5. Answer c.
Scheld WM, Whitley RJ, Marra CM, editors. Infections of the central nervous system. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; c2004. 939 p.

XI.6. Answer d.
Scheld WM, Whitley RJ, Marra CM, editors. Infections of the central nervous system. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; c2004. 939 p.

XI.7. Answer a.
Abdel Razek AA, Watcharakorn A, Castillo M. Parasitic diseases of the central nervous system. Neuroimaging Clin N Am. 2011 Nov;21(4):815–41, viii. Epub 2011 Sep 3.

XI.8. Answer e.
Walker MD, Zunt JR. Neuroparasitic infections: cestodes, trematodes, and protozoans. Semin Neurol. 2005 Sep;25(3):262–77.

XI.9. Answer e.
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XI.10. Answer c.
Roos K, Aksamit AJ Jr, Baldwin KJ, Bartt R, Cho TA, Del Brutto OH, et al. Infectious disease. Continuum: Lifelong Learn Neurol. 2012 Dec;18(6):1243–1496.

XI.11. Answer d.
Roos K, Aksamit AJ Jr, Baldwin KJ, Bartt R, Cho TA, Del Brutto OH, et al. Infectious disease. Continuum: Lifelong Learn Neurol. 2012 Dec;18(6):1243–1496.

XI.12. Answer b.
Roos K, Aksamit AJ Jr, Baldwin KJ, Bartt R, Cho TA, Del Brutto OH, et al. Infectious disease. Continuum: Lifelong Learn Neurol. 2012 Dec;18(6):1243–1496.

XI.13. Answer a.
Roos K, Aksamit AJ Jr, Baldwin KJ, Bartt R, Cho TA, Del Brutto OH, et al. Infectious disease. Continuum: Lifelong Learn Neurol.2012 Dec;18(6):1243–1496.

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Section
XII

Pediatric Neurology

Lilly C. Wong-Kisiel, MD, *editor*

70 Malformation of the Brain, Skull, and Spine

LILY C. WONG-KISIEL, MD

Introduction

Abnormal development of the central nervous system is a common cause for developmental delay and epilepsy. Understanding of central nervous system malformation begins with an overview of normal embryology. Genetic advances in embryogenesis have unfolded a complex orchestration of gene expressions in place of the traditional developmental epochs (induction, neurulation, proliferation, migration, organization, synaptogenesis, and myelination). Causes of malformation of the central nervous system are multifactorial. Genetic causes, vitamin excess or deficiency, infections, or teratogens any time during pregnancy may disturb the preprogrammed mechanisms. The major disorders of dysembryogenesis are defined in Table 70.1.

Basic Embryology

The primitive streak is derived from primary ectoderm and gives rise to the mesoderm, which forms between the endoderm and ectoderm layers (Figure 70.1). Hensen node is the end of the primitive streak. Mesodermal cells forming the

Table 70.1 • Definitions of Disorders of Dysembryogenesis

Disorder	Definition
Spina bifida occulta	Defect in the bony components without protrusion of meninges or cord
Meningocele	Defect in overlying bone with protrusion of meninges into defect
Myelomeningocele	Defect in overlying bone with protrusion of meninges and cord into defect
Encephalocele	Defect in skull with resulting herniation of brain and meninges into defect
Anencephaly	Absence of the brain and calvarium covering the brain; sparing of anterior pituitary, eyes, and brainstem
Holoprosencephaly	No evidence of midsagittal fissure, absence of corpus callosum, absence of olfactory bulbs and tracts, varying degrees of fusion of basal ganglia and thalamus, severe facial malformations
Septo-optic dysplasia	Optic nerve hypoplasia and endocrine abnormalities due to hypothalamic–pituitary insufficiency
Microcephaly	Head circumference less than 2 standard deviations of normal
Macrocephaly	Head circumference more than 2 standard deviations above normal
Lissencephaly	Agyric sulci
Band heterotopia	Collections of disorganized gray matter in inappropriate places
Polymicrogyria	Complex set of small gyri that appear fused to each other

Abbreviation: NTD, neural tube defect.

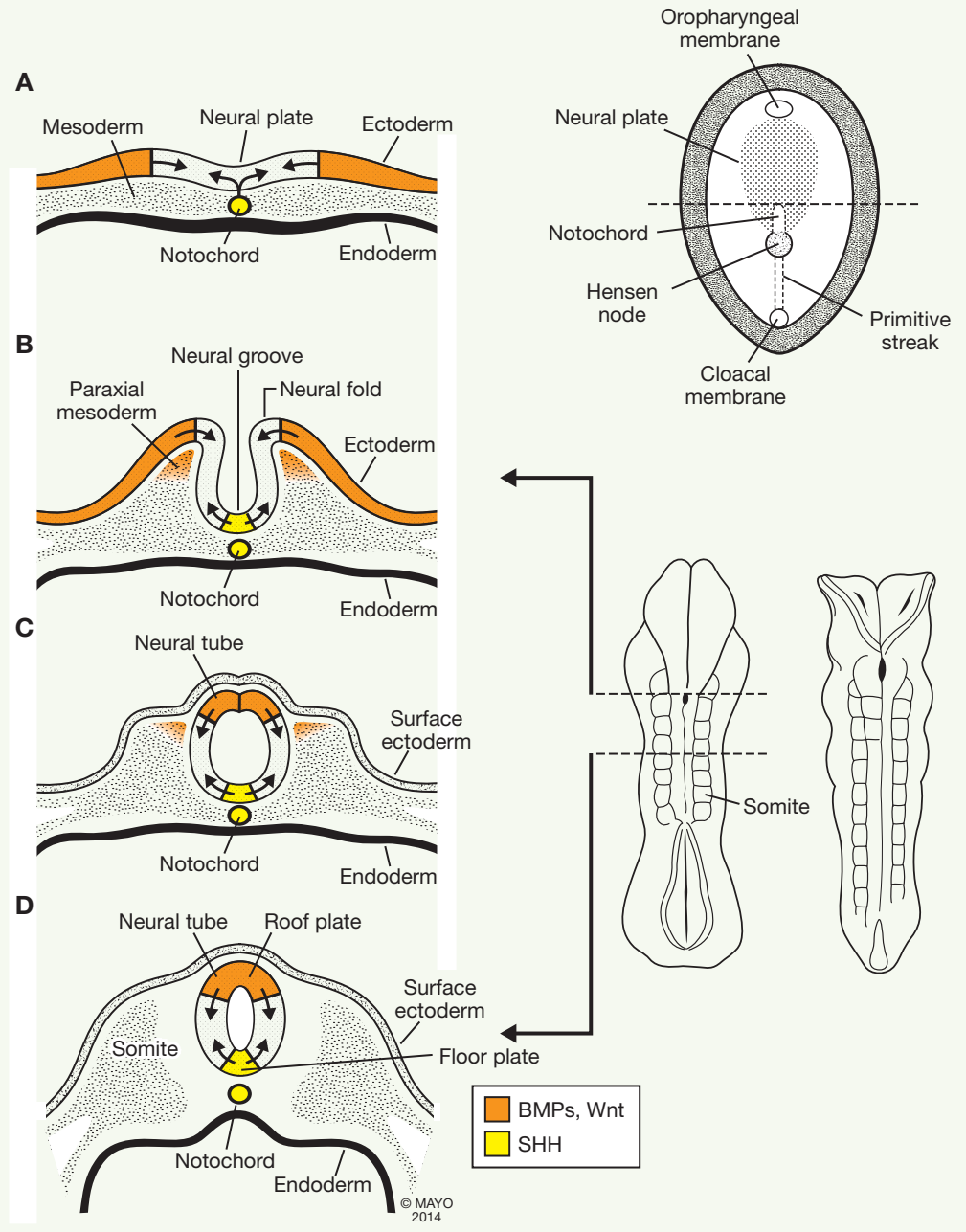


Figure 70.1 *Development of the Neural Tube. Note the signals responsible for the anteroposterior patterning. BMPs and Wnt proteins are important for dorsal patterning and are expressed by dorsal neural tube. SHH is an important ventralizing signal produced by the floor plate and notochord. BMP indicates bone morphogenetic protein, SHH, Sonic Hedgehog.*

(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

notochord give rise to part of the vertebral column and secrete factors involved in induction, which is the transformation of ectoderm to neural plate and results in formation of the neural tube. Neural plate formation occurs during the third week of gestation and becomes columnar epithelium. The rest of the ectoderm becomes skin and neural crest cells. Neurulation begins around the 19th day and continues until the fourth week of gestation, marking the transformation of neural plate into neural tube and the closure of the posterior neuropore. The anterior neuropore closes on

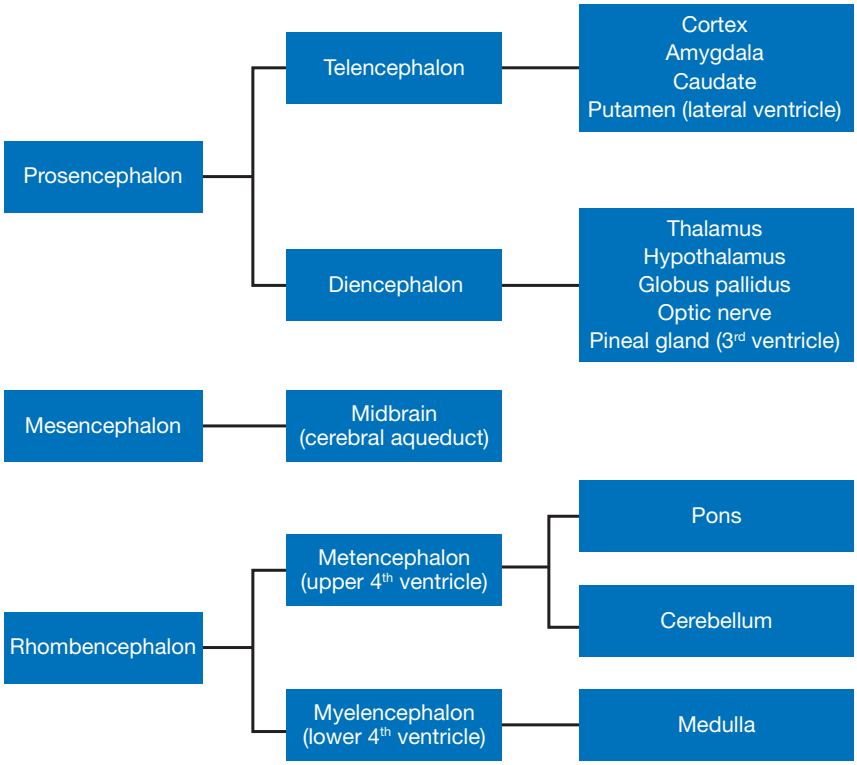


Figure 70.2 *Anatomic Derivatives of Primary Neurulation.*

day 25 after conception and the posterior neuropore, 2 days later. Primary neurulation forms the neural tube, giving rise to brain and spinal cord. Three primary vesicles—forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon)—result from primary neurulation (Figure 70.2). Secondary neurulation is the formation of lower sacral and coccygeal segments, including future conus medullaris and filum terminale.

Dorsoventral patterning of the neural tube evolves from 2 populations of proliferating neuroblasts, separated by sulcus limitans. The dorsolaterally situated alar plates give rise to afferent sensory structures in the brainstem, spinal cord, and dorsal horns. The ventrolaterally situated basal plates give rise to efferent motor structures in the brainstem and anterior horn cells in the spinal cord. The dorsoventral differentiation of the neural tube is dependent on the signaling gradient between proteins secreted from the floor plate and notochord (Sonic Hedgehog) and from the roof plate, dorsal ectoderm, and paraxial mesoderm (bone morphogenic and Wnt). Rostrocaudal patterning of the hindbrain is dependent on homeobox genes, which require retinoic acid.

Development of cerebral cortex begins in the ventricular zone, where neuroepithelial cells proliferate, differentiate into neuronal and glial precursors, and migrate centrifugally along the radial glial cells to the superficial layer of the cortical plate. Microtubule-associated proteins such as doublecortin and LIS1 are essential for migration of cortical neurons. Development of the cerebellar cortex involves granule cells from the neuroepithelium of the rhombic lip and Purkinje cells from ventricular neuroepithelium of the isthmus (junction between the mesencephalon and rhombic lip). Migration of granule neuroblasts is a reelin-independent process and occurs centripetally through the molecular and Purkinje cell to form the internal granule cell layer. Migration of the Purkinje cells is reelin-dependent and occurs centrifugally away from the ventricular zone. Synaptogenesis, apoptosis, and axonal growth result in subsequent dynamic organization in neonatal brain. Myelination of the central nervous system occurs as early as 14 weeks of gestation and continues to adulthood, and the most rapid growth is between birth and 2 years of age.

- Neural plate formation occurs during the third week of gestation and becomes columnar epithelium.
- The anterior neuropore closes on day 25 after conception and the posterior neuropore, 2 days later.

Defects of Neural Tube Closure

Overview and Risk Factors

Major defects of the central nervous system occur in 1 to 2 per 1,000 live births in the general population. Neural tube defects (NTDs) are the most common, estimated at 0.6 per

1,000 births in the United States between 2004 and 2006. NTDs result from faulty neurulation between 25th and 27th days after conception. Open NTDs have exposed neural tissue without cutaneous covering. Closed NTDs are with cutaneous covering. Maternal serum α-fetoprotein screening at 15 to 20 weeks identifies pregnancies at risk for open NTDs, confirmed by ultrasonography.

Chromosomal anomalies (trisomy 13 and trisomy 18), maternal diabetes mellitus, vitamin A deficiency and overuse, folate deficiency, use of anticonvulsants during pregnancy (valproic acid 1%-2% and carbamazepine 0.5%-1%), and polymorphisms in genes encoding folate-dependent enzymes are associated with NTDs. Folate supplementation is recommended for women planning pregnancy or capable of becoming pregnant.

NTDs of Anterior Neuropore Closure

NTDs affecting the cranium result from failure of the anterior neuropore closure. Anencephaly is an open defect of the skull and skin with exposed forebrain and brainstem. Up to 75% of infants with anencephaly are stillborn. Liveborn infants occasionally survive for a few days or weeks. Encephalocele is herniation of the brain through a skull defect that is covered by intact skin. The occiput is the most common location for encephalocele (about 75% of cases). Hydrocephalus is common, and associated malformations involving the optic nerve, brain, and craniofacial structures occur with encephalocele. Occipital encephalocele is associated with chromosomal abnormalities and disorders such as the Meckel-Gruber syndrome (autosomal recessive, occipital encephalocele, polycystic kidneys, liver fibrosis, cleft palate, and polydactyly, usually fatal).

NTDs of Posterior Neuropore Closure

NTDs affecting the spine are generally referred to as *spinal dysraphism*. Myelomeningocele (spina bifida cystica) consists of herniation of spinal cord and meninges through a vertebral defect (Figure 70.3). Myelomeningocele not covered with skin is referred to as myeloschisis. Myelomeningocele with a dilated central canal is myelocystocele. Lumbosacral involvement is the most common and neurologic deficit depends on the level of the lesion. Brain imaging reveals complex malformation of craniovertebral junction, brain, and brainstem (Chiari type II malformation) and associated hydrocephalus in more than 80% of patients with meningomyelocele.

In contrast, meningocele consists of a cutaneous sac with protrusion of meninges without underlying neural tissue. Meningoceles are typically not associated with clinical neurologic manifestations. Spina bifida occulta refers to a defect in vertebral arches with intact meningeal and neural structures. The most common location is in the lumbosacral spine. Cutaneous features of spina bifida are pigmented dermal patch, lump, or coarse dark hair located in the midline of the lower sacral region, and deep dermal sinus tract can be present. Most patients are asymptomatic, but a few patients may have symptoms related to myelodysplasia, tethered cord, or dermal or lipomatous tissue.

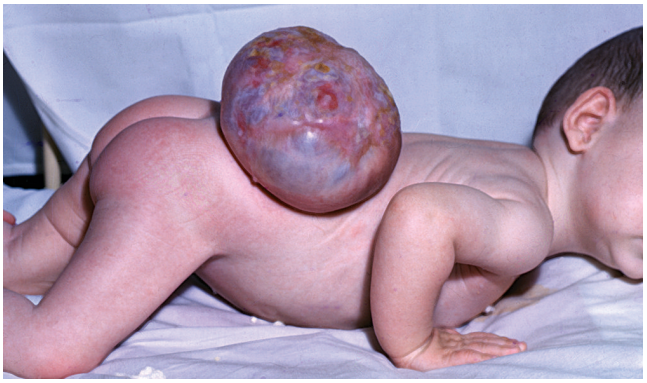


Figure 70.3 *Myelomeningocele (Spina Bifida Cystica). Spinal cord and meninges herniate through a congenital defect in the vertebral arch. It is covered with skin.*
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

Spinal dysraphism can also be due to secondary neurulation. Sacral agenesis, or caudal regression syndrome, presents with failure of the development of the sacral spinal column with associated genitourinary and anorectal anomalies. Maternal diabetes with poor glycemic control increases the risk of sacral agenesis. Diastematomyelia, or duplication of the spinal cord, can have distinct dural covering and bony structures for each split cord or share 1 set of meningeal structure. Clinical features are due to myelodysplasia.

- Maternal serum α-fetoprotein screening at 15 to 20 weeks identifies pregnancies at risk for open NTDs, confirmed by ultrasonography.
- Chromosomal anomalies (trisomy 13 and trisomy 18), maternal diabetes mellitus, vitamin A deficiency and overuse, folate deficiency, use of anticonvulsants during pregnancy (valproic acid 1%-2% and carbamazepine 0.5%-1%), and polymorphisms in genes encoding folate-dependent enzymes are associated with NTDs.
- Myelomeningocele (spina bifida cystica) consists of herniation of spinal cord and meninges through a vertebral defect (Figure 70.3).
- Spina bifida occulta refers to a defect in vertebral arches with intact meningeal and neural structures. The most common location is in the lumbosacral spine.

Disorders of Prosencephalon Development

Holoprosencephaly

Holoprosencephalies are a group of disorders characterized by a failure of differentiation and cleavage of the prosencephalon (Figure 70.4). Three classic forms of increasing severity are described. Alobar holoprosencephaly is a single brain ventricle and no interhemispheric fissure. Semilobar holoprosencephaly has partial separation of the right and left hemispheres. The right and left ventricles are separated in lobar holoprosencephaly but some continuity is present across the frontal cortex. Anosmia due to arhinencephaly (absence of the olfactory bulbs and tracts) occurs in most patients. Associated midline facial anomalies include cebocephaly (single nostril nose), cyclopia (single eye), ethmocephaly (interorbital proboscis), midline cleft lip, and hypotelorism.

Risk factors for holoprosencephaly include maternal diabetes, maternal alcoholism, smoking, drugs (retinoic acid, statins), and intrauterine infections. Genetic causes of holoprosencephaly include trisomy 13, trisomy 18, and single gene mutations (*SHH, ZIC2, SIX3*, and *TGIF*). Smith-Lemli-Opitz syndrome, CHARGE syndrome (coloboma, heart defects, choanal atresia, retardation of growth or development, genital or urinary abnormalities, ear abnormalities), and velocardiofacial syndrome are syndromic causes of holoprosencephaly with normal karyotype.

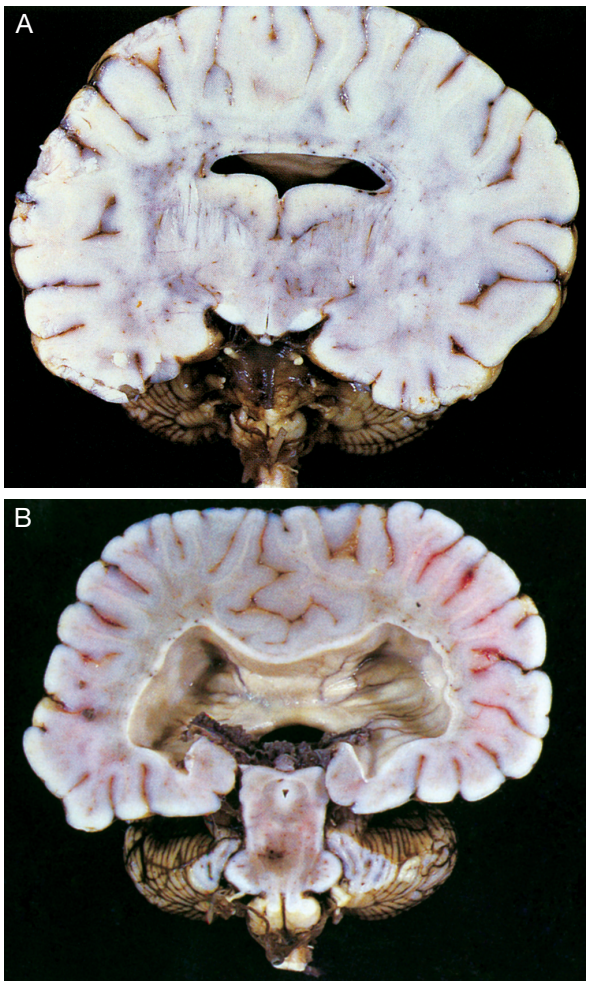


Figure 70.4 *Holoprosencephaly.*
This disorder is characterized by absence of the septum pellucidum and fused thalami and basal ganglia (A) and well-formed occipital horns (B). Despite the appearance of gyral fusion on the surface (not shown), there is a well-formed interhemispheric fissure with a continuous band of cingulate gyrus crossing the midline and resting on the corpus callosum (B).
(Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 288. Used with permission of Mayo Foundation for Medical Education and Research.)

Other Malformations of Midline Structures

Other malformations of midline structures include agenesis of the corpus callosum (Figure 70.5), anomalies of septum pellucidum, and septo-optic dysplasia. Aicardi syndrome is an X-linked triad of infantile spasms, agenesis of the corpus callosum, and chorioretinal lacunes. Septo-optic dysplasia is absence or dysgenesis of the septum pellucidum with hypoplasia of the optic nerve with or without involvement of the optic chiasm and pituitary infundibulum. Hypothalamic-pituitary dysfunction is common in children with malformations of midline structures and should be investigated.

- Septo-optic dysplasia is absence or dysgenesis of the septum pellucidum with hypoplasia of the optic nerve with or without involvement of the optic chiasm and pituitary infundibulum.

Disorders of Cortical Neurogenesis and Migration

Heterotopias are a nodular or laminar group of ectopic neurons due to arrested radial migration. Patients typically present with epilepsy.

Heterotopia can be periventricular (subependymal) (Figure 70.6), focal, or bandlike (Figure 70.7). Periventricular heterotopia may be X-linked due to a filamin-1 (*FLN1*) mutation. Mutations in *DCX* (doublecortin) gene on chromosome X result in anterior dominant subcortical band heterotopia in heterozygous females and lissencephaly in hemizygous males. Affected females can be

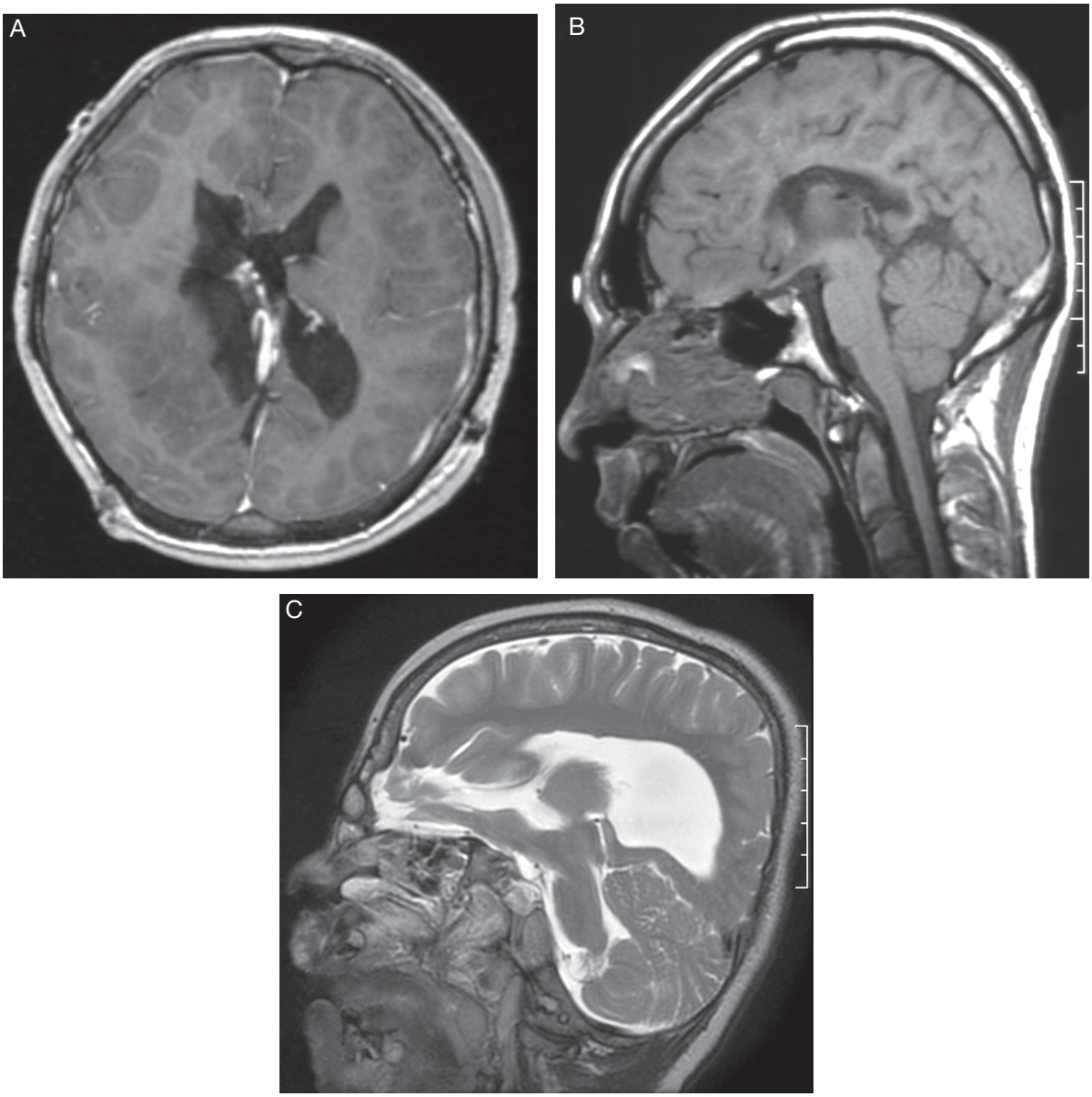


Figure 70.5 *Agenesis of Corpus Callosum on Magnetic Resonance Imaging.*
A and B, Patient with developmental delay and intractable seizures. The T1-weighted, axial (A) and sagittal (B) sequences show colpocephaly due to partial agenesis of corpus callosum (best seen in B). Also note periventricular aggregates of subcortical heterotopic gray matter. C, T2-weighted sagittal image shows colpocephaly in another patient.
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

asymptomatic from band heterotopia. Posterior-dominant subcortical band heterotopias are associated with *LIS1* mutations on chromosome 17.

Polymicrogyria describes multiple small gyri and results from disorder of neuronal organization (Figure 70.8). Syndromes associated with polymicrogyria include Aicardi syndrome.

Focal cortical dysplasia is localized regions of malformed cerebral cortex showing disruption of cortical lamination. Focal cortical dysplasia is among the most frequent epileptogenic malformations amenable to surgical treatment.

Lissencephaly (pachygyria-agyria) is an abnormally smooth cerebral surface and results from aberrant migration of all cortical neurons (Figure 70.9). Clinical presentations include severe epilepsy and mental retardation. Lissencephaly is classified according to imaging and histologic investigations (Table 70.2). Heterozygous deletions of

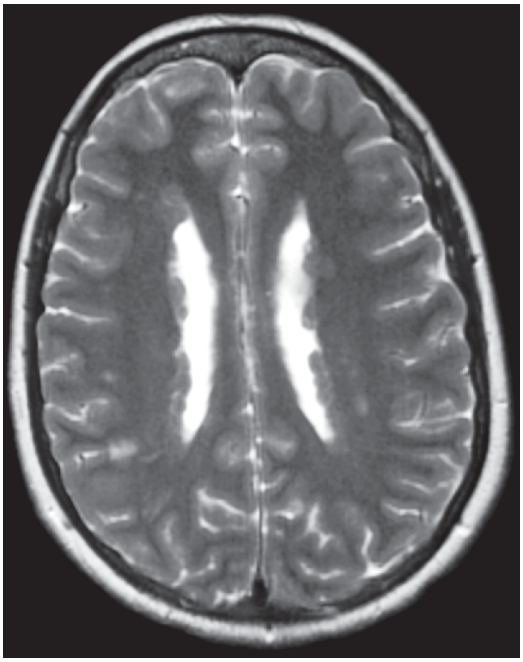


Figure 70.6 *T2-Weighted Magnetic Resonance Image of Bilateral Periventricular Nodular Heterotopia in an Asymptomatic Young Female.*
The nodules are essentially heterotopic gray matter consisting of subependymal neuroepithelial cells that have matured but have not migrated. They are usually present bilaterally.
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

the chromosome 17p13 region including *LIS1* gene cause Miller-Dieker syndrome. Deletions in the reelin gene result in lissencephaly with autosomal-recessive transmission.

- Heterotopias are a nodular or laminar group of ectopic neurons due to arrested radial migration. Patients typically present with epilepsy.
- Lissencephaly (pachygyria-agyria) is an abnormally smooth cerebral surface and results from aberrant migration of all cortical neurons (Figure 70.9).

Other Disorders of Cortical Development

Hemimegalencephaly is characterized by unilateral enlargement and cytoarchitectural abnormalities in 1 cerebral hemisphere. Mental retardation, epilepsy, and motor deficits typically present during the first few months of life. Hemimegalencephaly can occur in isolation or in syndromic form (Proteus syndrome, neurofibromatosis, hypomelanosis of Ito, Klippel-Weber-Trénaunay syndrome, tuberous sclerosis, Beckwith-Wiedemann syndrome, linear sebaceous nevus syndrome, Wilms tumor).

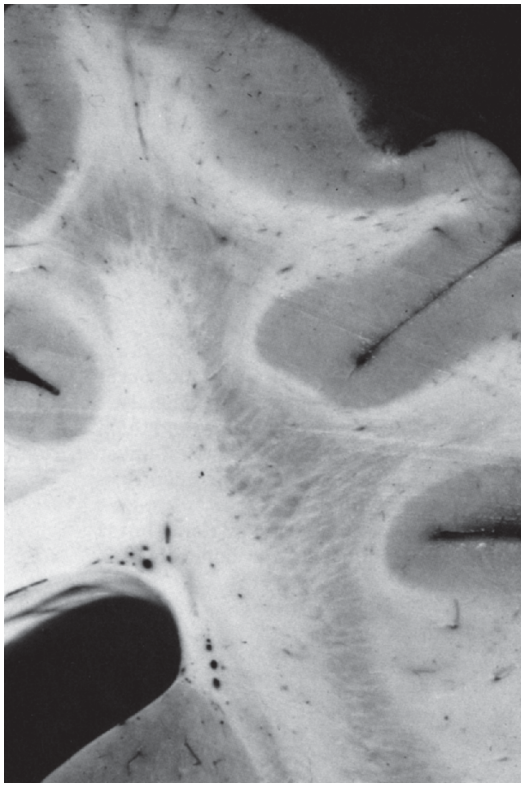


Figure 70.7 *Subcortical Band Heterotopia ("Double Cortex").*
This disorder is likely due to a mutation of the DCX *gene on the X chromosome encoding doublecortin. This occurs through abnormal migration of a group of neurons to form the subcortical band.*
(Adapted from Okazaki H. Fundamentals of neuropathology: morphologic basis of neurologic disorders. 2nd ed. New York [NY]: IGAKU-SHOIN Medical Publishers; c1989. Chapter 8, Perinatal nervous system damage and malformations. p. 275–303. Used with permission.)

Disorders of Hindbrain Development

Dandy-Walker Malformation

Dandy-Walker malformation occurs in 1 in 30,000 and consists of cystic dilatation of the fourth ventricle, cerebellar vermis agenesis, and enlarged posterior fossa. In patients without identifiable multiple malformation syndromes due to a genetic cause such as Walker-Warburg syndrome, multiple brain anomalies such as agenesis of the corpus callosum, heterotopias, and hemimegalencephaly can be present.

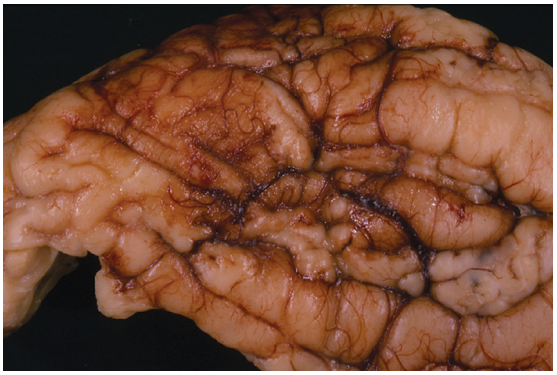


Figure 70.8 *Lateral View of Cerebral Hemisphere With Polymicrogyri.*
This disorder is a migration defect characterized by numerous, small gyri, usually a result of intrauterine ischemic or infectious insult.
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

Joubert Syndrome

Joubert syndrome is aplasia of the cerebellar vermis, distortion of the fourth ventricle, and deformity of the midbrain and aqueduct. Magnetic resonance imaging of the lower midbrain and upper cerebellum shows molar-tooth sign.

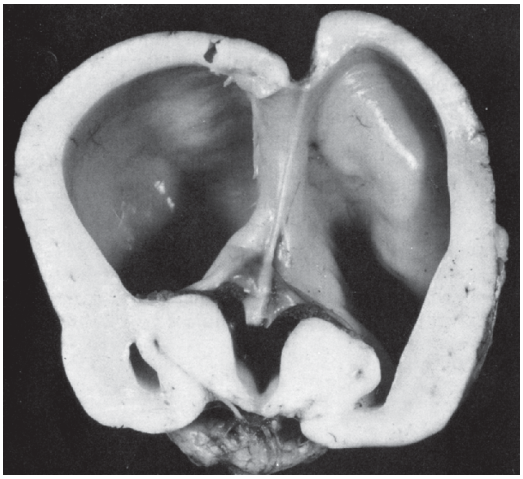


Figure 70.9 *Pachygyria.*
This disorder is a migration abnormality characterized by little evidence of gyral development and secondarily enlarged ventricles.
(Adapted from Okazaki H. Fundamentals of neuropathology: morphologic basis of neurologic disorders. 2nd ed. New York [NY]: IGAKU-SHOIN Medical Publishers; c1989. Chapter 8, Perinatal nervous system damage and malformations. p. 275–303. Used with permission.)

Table 70.2 • Comparison of Type I and Type II Lissencephaly

	Type I	Type II
Macroscopic features	Smooth, largely agyric cerebral cortex	Pachygyria, micropolygyria (cobblestone appearance)
Histologic features	Four-layer cortex	Poorly laminated, disorganized cortex
Associated syndromes	Miller-Dieker syndrome (lissencephaly, microcephaly, epilepsy, craniofacial defects, hypotonia, cardiac defects, and genital abnormalities)	Walker-Warburg syndrome Muscle-eye-brain syndrome Fukuyama muscular dystrophy

The neurologic features include hypotonia, ataxia, developmental delay, intellectual disability, abnormal eye movements, and neonatal breathing dysregulation. These may be associated with multiorgan involvement, mainly retinal dystrophy, nephronophthisis, hepatic fibrosis, and polydactyly.

Pontocerebellar Hypoplasia

Pontocerebellar hypoplasia is characterized by atrophy of the ventral pons and cerebellum, and the cerebellar hemisphere is more affected than the vermis. Severe intellectual deficit, swallow difficulties, seizures, progressive microcephaly, and ventriculomegaly ex vacuo are present. Mutations in the transfer RNA splicing endonuclease complex, which is involved in transfer RNA processing, are responsible for the majority of cases of pontocerebellar hypoplasia.

- Dandy-Walker malformation consists of cystic dilatation of the fourth ventricle, cerebellar vermis agenesis, and enlarged posterior fossa.

Disruptions of the Developing Brain

Schizencephaly and porencephaly are thought to occur from insult to normally developed brain. Schizencephaly describes a cleft between the ventricles and subarachnoid space with associated gray matter heterotopias along the cleft wall (Figure 70.10). Porencephaly describes cystic communication lined by gliotic white matter between the lateral ventricle and the subarachnoid space (Figure 70.11).

- Schizencephaly describes a cleft between the ventricles and subarachnoid space with associated gray matter heterotopias along the cleft wall (Figure 70.10).

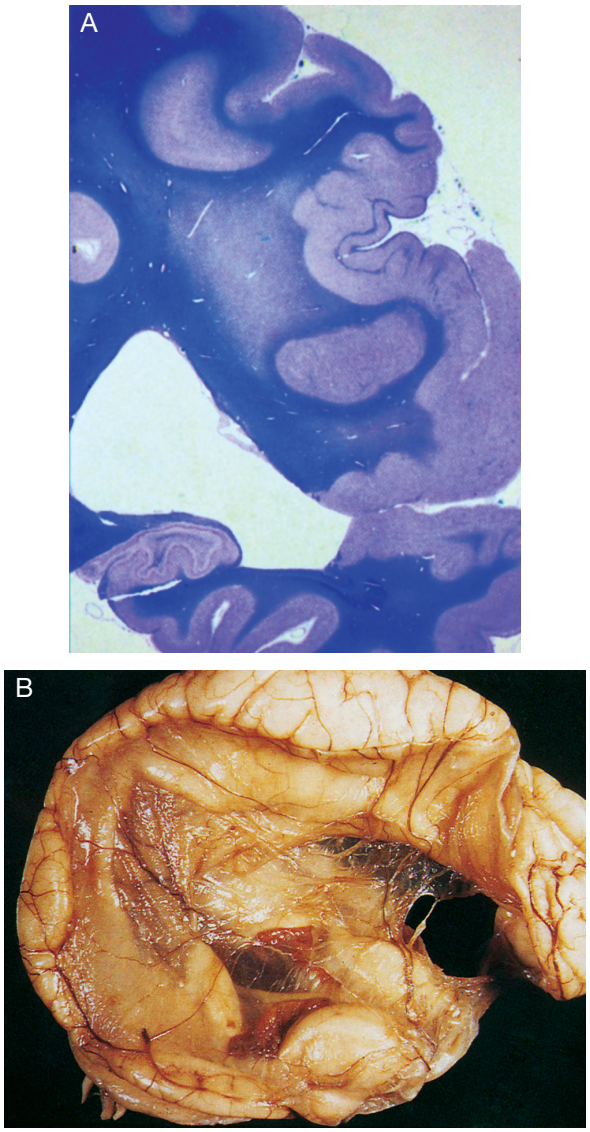


Figure 70.10 *Sporadic Schizencephaly.*
This disorder is usually associated with an in utero ischemic or hypoxic insult. The edges of the clefts are in contact in type I ("closed lip") (A) and separated in type II ("open lip") (B).
(Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 287. Used with permission of Mayo Foundation for Medical Education and Research.)

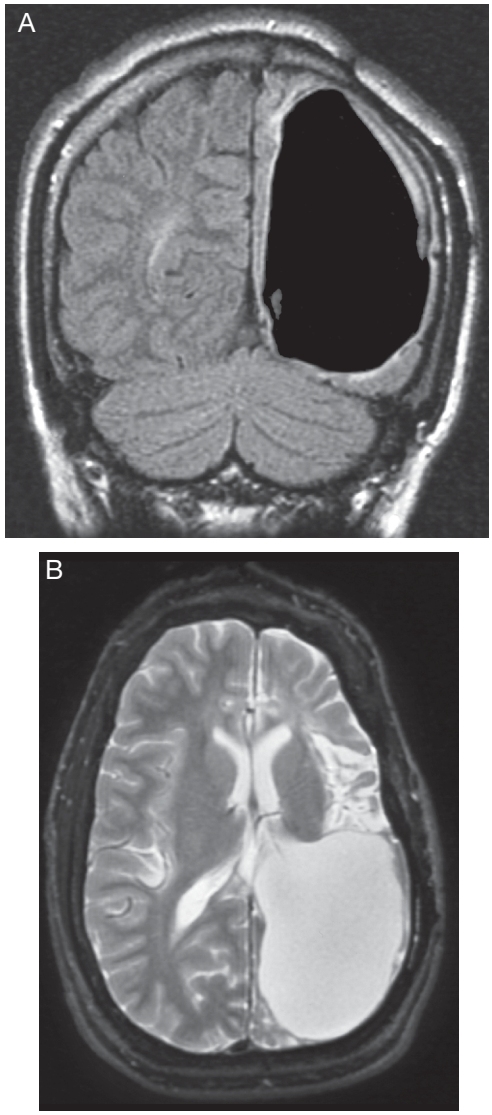


Figure 70.11 *Porencephaly on Magnetic Resonance Imaging.*
A, Coronal fluid attenuation inversion recovery (FLAIR) image. B, Axial T2-weighted image. The lining of the cleft consists of gliotic white matter (compared with the heterotopic gray matter lining the clefts of schizencephalic brains).
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

Defects of the Skull Base and Craniovertebral Junction

Craniovertebral Junction Abnormalities

Craniovertebral junction anomalies include atlantoaxial instability in Down syndrome or fusions of the first vertebral body with occipital bone in Klippel-Feil syndrome. Craniovertebral junction anomalies can result in basilar invagination, compromise the vertebrobasilar arterial system, or occlude cerebrospinal fluid flow. Basilar invagination results in brainstem dysfunctions such as sleep apnea, progressive quadriparesis, and dysfunction of lower cranial nerves. Basilar invagination often occurs with Chiari malformations.

Table 70.3 • Chiari Malformations

Type	Anatomic Abnormality
I	Caudal displacement below foramen magnum
II	Caudal displacement of cerebellar tonsils, cervicomedullary junction, medulla, fourth ventricle, pons
III	Occipital-upper cervical encephalocele with herniation of cerebellum, occipital lobes, pons, medulla
IV	Hypoplasia of cerebellum

Chiari Malformation

Chiari malformations are degrees of herniation of the brainstem and cerebellum through the foramen magnum and different degrees of dysplasia of the nervous system (Table 70.3). Chiari type I malformation is usually an incidental finding (Figure 70.12). Symptomatic patients present with headaches, sleep apnea, or neck pain. Chiari II malformation is associated with beaking of the midbrain tectum, cortical malformation (heterotopias, polymicrogyria), and colpocephaly. Chiari type II malformations are associated with myelomeningocele in more than 90% of cases, and hydrocephalus occurs in up to 80%, requiring surgical intervention (Figures 70.13 and 70.14).

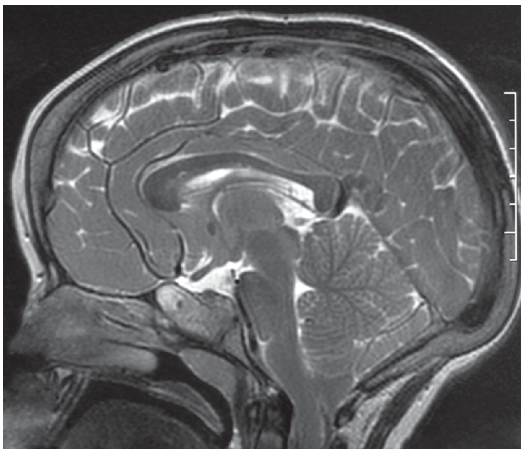


Figure 70.12 *Congenital Chiari Type I Malformation in a 35-Year-Old Woman Who Presented With Headaches.*
The primary manifestation is caudal displacement of the cerebellar tonsils below the foramen magnum.
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

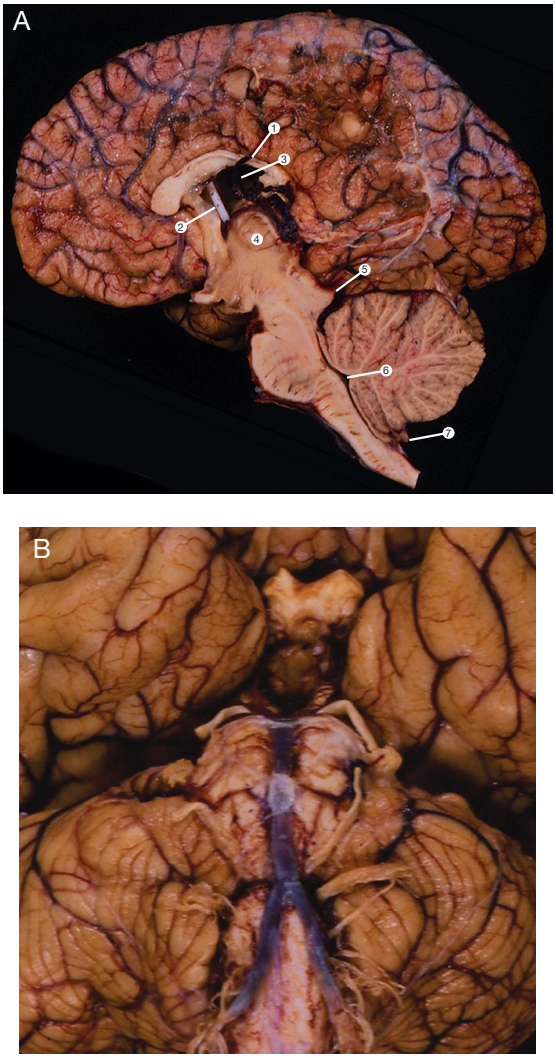


Figure 70.13 *Brain With Chiari Type II Malformation.*
A, Midsagittal view. B, Ventral view. This malformation results in caudal displacement of the medulla, cervicomedullary junction, pons, and fourth ventricle and low cerebellar tonsils (7). The cerebellar tonsils appear "kinked" because of being displaced through the foramen magnum. Note the cephalad displacement and anteromedial extension of the cerebellum around the brainstem (B). Associated findings (A) are beaking of the tectum (5), elongated tubular fourth ventricle (6), enlarged massa intermedia (4), absence of septum pellucidum (3), partial agenesis of corpus callosum (1), myelomeningocele, and hydrocephalus. (2), Cerebrospinal fluid shunt for treatment of hydrocephalus.
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

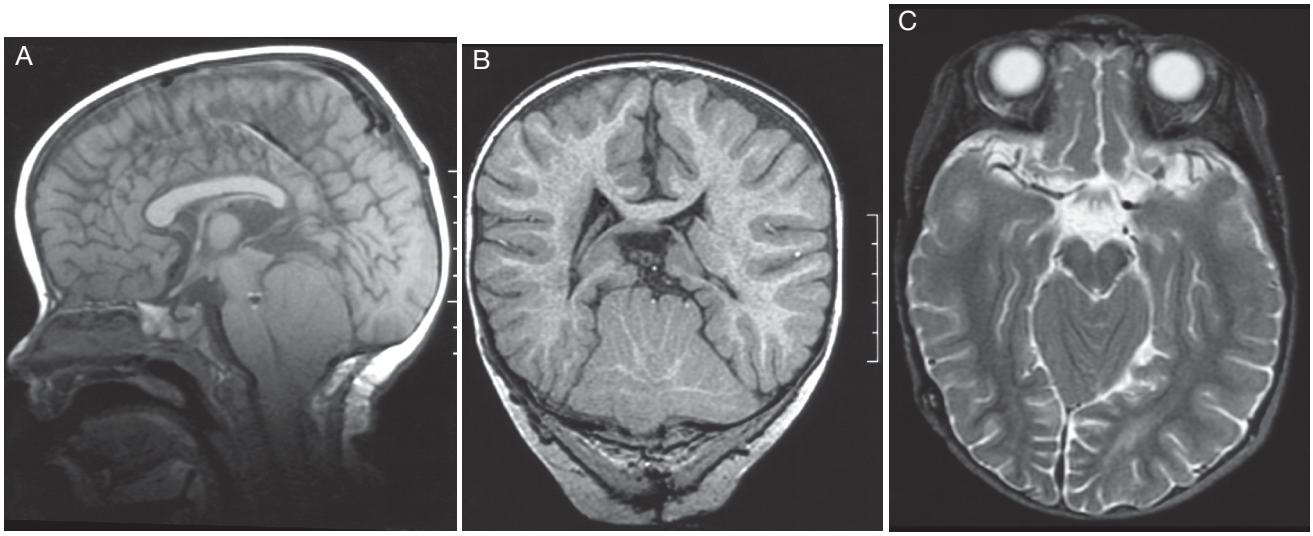


Figure 70.14 *Magnetic Resonance Imaging in Chiari Type II malformation in a 16-Month-Old Infant After Repair of a Myelomeningocele.*
Note cephalad and caudal displacement of the cerebellum, tectal beaking, partial agenesis of the corpus callosum, enlarged massa intermedia, absence of septum pellucidum, and elongated tubular fourth ventricle. A, Sagittal T1-weighted image. B, Coronal T1-weighted image. C, Axial T2-weighted image.
(Adapted from Mowzoon N. Embryology and developmental disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 1–23. Used with permission of Mayo Foundation for Medical Education and Research.)

- Chiari malformations are degrees of herniation of the brainstem and cerebellum through the foramen magnum and different degrees of dysplasia of the nervous system.

Skull Malformation and Craniosynostosis

Head Circumference

Head circumference is about 35 cm for a full-term male infant and 34 cm for a full-term female infant. At 1 year of age, the average head circumference increases by 12 cm—about 6 cm in the first 3 months, 3 cm in the next 3 months, and 3 cm in the third 3 months. Growth faster than the normal rate should be investigated. Macrocephaly is head circumference more than the 98th percentile for age and sex and should be differentiated from megalencephaly, which is large head due to large brain. Macrocephaly is usually familial and due to benign enlargement of subarachnoid spaces. Microcephaly is head circumference less than the second percentile for age and sex.

Macrocephaly

A large head (Table 70.4) can be due to increased volumes of the 3 compartments that fill the skull: brain, cerebrospinal fluid, and blood. The main cause of macrocephaly at birth is hydrocephalus. Hydrocephalus develops from obstruction of cerebrospinal fluid flow or from decreased absorptive function of arachnoid villi. Obstruction of cerebrospinal fluid flow within the ventricular system is referred to as noncommunicating hydrocephalus or obstructive hydrocephalus. The most common site of obstruction in noncommunicating hydrocephalus is the cerebral aqueduct, followed by outlet foramina of the fourth ventricle. Obstruction of cerebrospinal fluid flow outside the ventricular system is referred to as communicating hydrocephalus. Intraventricular or subarachnoid hemorrhage, inflammatory process such as meningitis, and increased venous pressure can compromise the absorptive capacity of the arachnoid villi. Clinical features of hydrocephalus in infants include rapid head enlargement, decreased feeding, irritability, and vomiting. Limitation of up gaze appears as preferential down gaze or down and inward deviation of the eyes. Pharmacologic therapy with acetazolamide to decrease cerebrospinal fluid production may provide time before surgical intervention and can be used if no obstruction is identified. Surgical options for hydrocephalus include third ventriculostomy or shunt placement.

Megalencephaly

Megalencephaly is enlargement of the brain with increased gray and white matter volume. Macrocephaly is present at

Table 70.4 • Differential Diagnosis of Large Head Circumference

Component Increased	Description	Differential Diagnosis
Cerebrospinal fluid	Hydrocephalus	Communicating Congenital Hemorrhage Infection Venous thrombosis or congestion (achondroplasia) Choroid plexus papilloma (cerebrospinal fluid production>absorption) Tumor Malformation or structural: Chiari II malformation, Dandy-Walker malformation, holoprosencephaly, encephalocele, lissencephaly, hydrencephaly Noncommunicating (obstructive) Intraventricular tumor Intraventricular hemorrhage Intraventricular infection or cyst Genetic: X-linked hydrocephalus, osteogenesis imperfecta, craniofacial disorders Metabolic: Hurler syndrome, achondroplasia Malformation: aqueductal stenosis, membranous obstruction of the aqueduct, atresia of the foramen of Monro, arachnoid cysts
	Benign enlargement of the subarachnoid space	
Brain	Megalencephaly (anatomic)	Benign, familial Neurocutaneous disorders Cerebral gigantism Achondroplasia Fragile X syndrome Cowden syndrome Autism spectrum disorder
	Megalencephaly (metabolic)	Lysosomal storage disorders (Tay-Sachs disease, gangliosidosis, mucopolysaccharidosis) Leukodystrophies (Alexander disease, Canavan disease, megalencephalic leukoencephalopathy)
Blood		Brain hemorrhage Arteriovenous malformation or vein of Galen malformation
Bone	Bone marrow expansion Primary bone disorder	Thalassemia Cranial dysplasia
Intracranial pressure		Cyst Tumor Abscess Lead

birth in children with anatomic megalencephaly, whereas children with metabolic megalencephaly are usually normocephalic at birth and megalencephaly develops subsequently. Causes of metabolic megalencephaly include GM_1 and GM_2 gangliosidoses, mucopolysaccharidoses, or leukodystrophies such as Alexander disease and Canavan disease. Growth of the skull occurs with growing brain and occurs at cranial sutures. Craniosynostosis is premature closure of cranial sutures and results in progressive skull deformity, and shape depends on which sutures are involved. Children with craniosynostosis are normocephalic at birth and macrocephaly develops during infancy.

Microcephaly

Primary microcephaly originates from anomalous brain development, whereas secondary microchephaly involves destruction of previously normally formed brain (Table 70.5). Microcephaly at birth indicates a prenatal onset of brain abnormality and does not imply a primary or secondary cause. Primary microcephaly presents with congenital microcephaly, and causes include genetic or chromosomal abnormalities, NTD, disorders of prosencephalon development, and cortical neurogenesis and migration. In general, acquired microcephaly indicates secondary microcephaly, such as due to intrauterine disorders, perinatal brain injury, or postnatal systemic diseases.

Table 70.5 • Differential Diagnosis of Microcephaly (Genetic and Acquired)

Category	Mechanism
Vascular	Anoxic-ischemic
Infectious	Perinatal infection (HSV-1, CMV, VZV, rubella, toxoplasmosis, HIV, syphilis, enterovirus)
Metabolic/endocrine	Maternal diabetes Perinatal hypoglycemia Hypothyroidism Deficient adrenal corticosteroid Deficiency in pituitary function
Medications/drugs	In utero toxin exposure (alcohol, tobacco, marijuana, cocaine, heroin, antiseizure medications, radiation)
Genetic/chromosomal abnormalities	Isolated microcephaly (autosomal recessive, autosomal dominant, and X-linked forms) Trisomy 13, 18, and 21 Smith-Lemli-Opitz syndrome Williams syndrome (7q11.23 deletion) Miller-Dieker syndrome (17p13.3 deletion) Cri du chat syndrome (5p15.2 deletion) Cockayne syndrome Angelman syndrome Phenylketonuria Methylmalonic aciduria Others
Malformation	Neural tube defects Holoprosencephaly Aprosencephaly Lissencephaly Schizencephaly Polymicrogyria Pachygyria
Other	Neuronal ceroid lipofuscinosis

Abbreviations: CMV, cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

- Macrocephaly is head circumference more than the 98th percentile for age and sex and should be differentiated from megalencephaly, which is large head due to large brain.
- Microcephaly is head circumference less than the second percentile for age and sex.
- The main cause of macrocephaly at birth is hydrocephalus.
- Clinical features of hydrocephalus in infants include rapid head enlargement, decreased feeding, irritability, and vomiting. Limitation of up gaze appears as preferential down gaze or down and inward deviation of the eyes.
- Primary microcephaly originates from anomalous brain development, whereas secondary microchephaly involves destruction of previously normally formed brain.

71 Neurologic Development and Developmental Disabilities

KATHERINE C. NICKELS, MD

Introduction

To understand developmental disabilities, one must have a good understanding of normal development throughout childhood. Developmental milestones are typically divided into different domains, such as gross motor, fine motor, language, and social/adaptive skills. Assessment of attained milestones across the developmental domains allows the examiner to evaluate potential cognitive outcome. Emotional development is also important at all ages.

Normal Development

Infancy (Birth–12 Months)

The first 4 weeks of life are considered the neonatal period. Infancy continues throughout the first year of life. In addition to cognitive and emotional development, the first year of life is also marked by evolution of primitive reflexes and postural reactions. Primitive reflexes are stereotyped involuntary movements mediated by the brainstem in response to specific sensory stimuli. They are present in preterm infants and gradually resolve throughout the first year of life with maturation of the nervous system and subsequent development of cortical inhibition. Specific examples of primitive reflexes include Moro, rooting, palmar and plantar grasp, Galant, and asymmetrical tonic neck reflexes. Throughout normal development, these reflexes will present and subsequently resolve within a specific time frame (Table 71.1). All of these reflexes must resolve to allow normal motor development to occur.

Postural reactions are also involuntary motor patterns that present throughout infancy. Unlike primitive reflexes, postural mechanisms respond to multimodality input and appear to be protective, "righting" reflexes that eventually allow the infant to maintain an upright position. Examples of postural reactions include anterior, lateral, and posterior propping as well as the parachute response (Table 71.2). The first year of life is also a time of rapid acquisition of new skills, which allow the child to have increasing independence and ability to explore his or her environment (Table 71.3). Furthermore, infancy is an important period for emotional development. Consistent response by stable adult figures (most often parents) to the needs of the infant promotes secure attachment. This is felt to be essential to later psychological well-being.

Early Childhood (Age 1–5 Years)

Early on, toddlers gain independence through walking and running and are able to explore their environment. They manipulate objects, looking for the effect. They are more likely to imitate adults and older children and participate in pretend play. As they grow older, children also explore socially. They begin to emotionally separate from parents and learn to follow social rules of the classroom and the playground. This is also a time of rapid language acquisition (Table 71.4). As young children grow older, playtime progresses from simple mimicry of daily activities, to pretend play next to another child (parallel play), to more interactive play. This allows children to gradually recognize different emotions and situations in which those emotions would be most appropriate.

School Age (Age 6–11 Years)

Thought processes in school-aged children gradually evolve from magical and pretend play to being more objective, logical, and concrete. This is also a time in which

Abbreviation: CP, cerebral palsy

Table 71.1 • Primitive Reflexes

Reflex	Elicitation Method	Motor Response	Age at Appearance	Age at Disappearance
Moro (startle)	Make sudden noise or perform sudden neck extension	Extension, abduction, then adduction of the upper extremities	Birth, as early as 28 weeks' gestation	3–7 mo
Galant (trunk incurvation)	Stroke 1 side of spinal column from thoracic to sacral region while infant in prone suspension	Truncal incurvature toward the stroked side	Birth, possibly in utero	2–6 mo
Root	Stimulate cheek	Head turn toward the side touched and opening of mouth	Birth, as early as 24 weeks' gestation	Awake: 3–4 mo Asleep: 9–12 mo
Suck	Stimulate lips or place something in mouth	Sucking	Birth, as early as 28 weeks' gestation	Lasts through early childhood, especially during sleep
Palmar grasp	Stimulate palm	Palmar grasp	Birth, as early as 32 weeks' gestation	3–9 mo
Plantar grasp	Stimulate beneath toes	Plantar flexion grasp	Birth, as early as 32 weeks' gestation	9–12 mo
Asymmetrical tonic neck (fencer response)	Turn head to 1 side while infant in supine position	Extension of limbs on the side to which the infant is looking and flexion of opposite limbs	Present at birth	4–9 mo

children gain the ability to learn in the more structured environment of the classroom. Academic and classroom performance is increasingly used to monitor cognitive abilities. For children who are not performing as expected, this is also the age at which formal neuropsychometric testing is often performed.

Table 71.2 • Postural Reactions

Reaction	Description	Age at Appearance
Head righting	In prone position, lift chin from surface, keep face/head in vertical alignment; allows head control	Prone: 2 mo Supine: 3 mo
Protective anterior extension tone	Extend arms anteriorly to maintain balance while sitting; allows independent sitting	4–7 mo
Protective lateral extension tone	Extends arm laterally to maintain balance while sitting; allows independent sitting	6–8 mo
Protective posterior propping	Extend arms posteriorly to prevent falling and allow pivoting while sitting	7–10 mo
Parachute	Extend arms when falling	5–6 mo

Emotionally, this is an important time for development of self-esteem. Children are now able to understand how others perceive them. This may lead to altered perceptions and dissatisfaction with body image. By this age, children also understand rules of the family and community. They are beginning to understand the difference between right and wrong and often seek the approval of parents and other adults. However, children also seek the approval of their peers, and peer pressure often significantly affects behavior. Furthermore, children at this age are now judged socially on the basis of "objective" performance, such as athletic, musical, and academic abilities.

Adolescence (Age 12–18 Years)

Adolescence is an important time of rapid physical changes that may begin as young as 8 years and typically lasts from ages 9 through 20 years. At this age, children are often self-conscious, likely due to increasing self-awareness as well as the changes in their bodies. Influences outside of home and family become of increasing importance. Adolescents identify more with peers than their family and try to conform to social traits and roles. They may overreact to parental questioning. Adolescents have a greater understanding than younger children of the moral and legal ramifications of their actions, although they often engage in risky behaviors. Adolescents begin to analyze the world around them and question extensively. Abstract thought and the ability to reason emerge as the frontal cortex matures. Adolescents develop insight and are able to

Table 71.3 • Developmental Milestones, Age 0–12 Months

Age	Gross Motor	Fine Motor/ Adaptive	Language	Social/Self-help	Emotional
Newborn	Flexor tone	Hands fisted	Cry	Regard faces	Can show distress
1 mo	Briefly lift head in prone position	Visually track to midline	Alert to sound	Regard faces	Can show distress
2 mo	Lift head and chest when prone, some head control in midline	Hands not tightly fisted, visually track past midline	Coo, gurgle, turn head toward sounds	Social smile, recognize parent	Can show distress and enjoyment
3 mo	Head and chest up 90° when prone, support on forearms	Hands open at rest, visually track circularly	Coo	Recognize bottle or breast	Can show pleasure/ happiness and displeasure/anger/ sadness
4 mo	Roll over, pull to sit without head lag	Reach with both arms in unison	Laugh, squeal	Interested in environment	Can show pleasure/ happiness and displeasure/anger/ sadness
6 mo	Sit without support	Raking grasp, unilateral reach, transfer objects	Begin vowel-consonant combination babbling	Recognize strangers	Can show fear
9 mo	Pull to stand, get to sitting independently	Emerging pincer grasp, bang 2 toys together	Indiscriminate "mama" and "dada," understand "no"	Play interactive games (eg, pat-a-cake), wave bye-bye	Stranger anxiety, has favorite toys
12 mo	Cruise or walk independently	Pincer grasp, put things in and pull things out of a container	Specific "mama" and "dada," try to copy words, immature jargoning	Play peek-a-boo (object permanence), help with dressing, imitate activities	Separation anxiety, can demonstrate assertiveness or cautiousness

understand others' perspectives. It is at this stage that children also begin making realistic goals for the future. However, cognitive development is affected by emotionality.

- Primitive reflexes are stereotyped involuntary movements mediated by the brainstem in response to specific sensory stimuli. They are present in preterm infants and gradually resolve throughout the first year of life with maturation of the nervous system and subsequent development of cortical inhibition.
- In early childhood, children begin to emotionally separate from parents and learn to follow social rules of the classroom and the playground.
- As young children grow older, playtime progresses from simple mimicry of daily activities, to pretend play next to another child (parallel play), to more interactive play.
- Adolescents identify more with peers than their family and try to conform to social traits and roles.

Abnormal Development

Overview

Developmental concerns are common reasons for referral to a child neurologist. These concerns may present as early as at birth but often present during early childhood. Knowledge of the normal developmental milestones, as well as the normal range of ages at which they occur, is essential. The child with developmental concerns must be evaluated to determine whether disability exists and, if so, whether development has always been slower than expected versus having plateaued or regressed. Furthermore, it must be determined whether abnormal development extends across all domains or whether only 1 or 2 domains are affected.

Evaluation

If a child presents with developmental delay, a careful physical examination must be performed, in addition to neurologic examination. Specifically, the child should be

Table 71.4 • Developmental Milestones, Age 15 Months to 5 Years

Age	Gross Motor	Fine Motor/Adaptive	Language	Social/Self-help	Emotional
15 mo	Walk backwards, stoop and recover, creep up stairs	Scribble in imitation, immature crayon grasp, stack 2 cubes	4–6 words, mature jargoning, understand familiar ungestured commands	Use spoon and cup, feed doll, begin to undress	Can demonstrate shyness and empathy, begin to share, begin tantrums
18 mo	Run, walk up stairs, kick ball forward, overhand throw	Tower of 4–6 cubes, emerging hand dominance, scribble spontaneously	7–25 words, mature jargoning, point to body parts	Emerging independence, copy household tasks	Demonstrate guilt, begin to understand names of feelings
2 y	Walk up and down stairs alone, jump with 2 feet	Turn pages of book 1 page at a time, tower of 8 cubes, imitates, draws line	2-word phrases, speech 50% understandable, follow 2-step commands	Parallel play, undress except button, unzip, sort objects	Individuation, reaction to events dependent on reactions of others
3 y	Stand on 1 foot 1–2 s, walk up stairs 1 foot per step, pedal tricycle	Copy circle, cut with scissors	3-word phrases, 75% understandable, use pronouns, recognize colors, know name/age/sex, ask questions	Undress completely, partially dress, take turns in games	Fewer emotional outbursts, self-esteem dependent on what others tell him or her
4 y	Hop on 1 foot, alternate feet going down steps	Mature pencil grasp, draw 4-part person (arms and legs coming from head)	Count to 5, speech all understandable, sing songs, tell stories	Dress and undress completely with supervision, creative play, cooperate with others	Not understand reality vs make-believe
5 y	Skip, hop, swing, and climb	Draw person with at least 6 body parts, draw recognizable pictures, copy cross, print 4 letters of first name	Count to 10; speak clearly, although may have articulation errors; follow 3-step commands	Competitive team play, play board games, brush teeth, dress and undress independently	Want to please friends, want to be like friends, can understand difference between reality and make-believe

examined to determine whether head size, ear placement, eye placement, or genitalia are abnormal and if organomegaly is present. Birth defects are considered to be physical abnormalities detected during the neonatal period, or sometimes even before birth. These may include multiple organ systems. Children born with multiple congenital anomalies are at increased risk for neurologic involvement. Of particular importance is the skin examination. Neurocutaneous disorders involve abnormalities of both the skin and the nervous system (see also Chapter 72, "Neurocutaneous Disorders"). Most are thought to arise from abnormal differentiation of the primitive ectoderm. Diagnosis can often be made through simple visual observation. Neurocutaneous disorders include tuberous sclerosis complex, neurofibromatosis, Sturge-Weber syndrome, linear nevus syndrome, hypomelanosis of Ito, incontinentia pigmenti, and ataxia-telangiectasia. Birth defects involving the neurologic system can also be detected through abnormal functioning, such as inability to feed, decreased spontaneous movement, recurrent apneas, or autonomic dysfunction. Seizures are also a common early manifestation of neurologic dysfunction.

The evaluation must also include a thorough history of perinatal or neonatal complications, early head trauma or infections, and seizures or convulsions, and whether there is a family history of neurologic disease. Often, it can be helpful to ask parents about their education history to determine whether they received any special education services and to determine the academic achievements of the parents. A detailed developmental history should be obtained to determine the severity of delay and to determine which domains are affected. Furthermore, developmental delay must be differentiated from developmental plateau and regression. Careful history and examination will be helpful to determine what further testing, if any, is necessary.

Developmental delay occurring across multiple domains is termed global developmental delay, and the child is likely to have intellectual disability. In contrast, delay in an isolated domain may or may not represent intellectual disability, or it may suggest a learning disability. However, language delay must be differentiated from autistic spectrum disorder

and Landau-Kleffner syndrome, the latter being an epileptic encephalopathy with acquired auditory agnosia. Similarly, motor delay due to developmental coordination disorders must be differentiated from cerebral palsy (CP), muscular dystrophies, or disorders of the neuromuscular junction.

Intellectual Disability

Children with global developmental delay are likely to have intellectual disability, previously referred to as mental retardation. Children with mild intellectual disability (IQ, 50–70) are able to understand concepts up to a fourth- to sixth-grade level, are likely to hold a simple job, and enjoy some independence as an adult. Children with moderate intellectual disability (IQ, 35–50) can learn concepts up to a second- to third-grade level, may be able to work in a sheltered workplace, and can communicate well, but they will continue to require support as adults, such as a group home setting. If the intellectual disability is severe (IQ, 20–35), the child may be able to communicate and understand concepts up to a preschool level. These children are unlikely to be able to work, even with maximal supervision, and will require constant supervision. Children with profound disability (IQ <20) likely will not develop meaningful communication and will require extensive nursing care.

Learning Disorders

Global developmental delay should be differentiated from learning disorders. Learning disorders, or learning disabilities, occur when there is significant impairment in one or more domains including reading, language, writing, math, and attention when compared to overall IQ. Learning disorders are diagnosed in school-aged children when they perform below grade level and the disability is felt to significantly impair the child's ability to function in these areas.

Children who have reading disability have dyslexia, which is primarily a disorder in word recognition and phonologic processing. However, for children with speech and language disorders, the difficulties lie with all language, not just written language. Children with developmental language disorders must be differentiated from those with articulation disorders. Whereas children with pure articulation disorders do not have language disabilities and will likely outgrow the articulation disorder with speech therapy, those with language disorders often have difficulties with receptive and expressive language function.

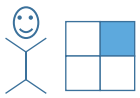
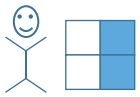
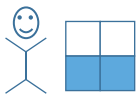
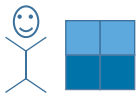
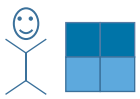
Children with writing difficulties can have symptoms of multiple learning disorders, including dyslexia, language disorder, and attention-deficit disorder. Writing disability can occur because of problems with handwriting, poor visuospatial perception, phonologic processing disorders, and difficulty formulating and organizing ideas in writing. Similarly, calculation and math learning disability, which causes problems with calculation and reasoning, can be due to disorders of reading, writing, language, or attention.

Cerebral Palsy

CP is a permanent, nonprogressive disorder of movement and posture that is due to a neurologic insult that occurs during fetal or infant development. Associated features include abnormal cognition and communication, epilepsy, and musculoskeletal problems. Therefore, children with CP can have intellectual disability, learning disorders, or both. However, the diagnosis of CP does not provide further information on cause. CP is caused by injury to the developing brain, which includes stroke, hypoxia/ischemia, malformations of brain development, early traumatic brain injury, infection, and prematurity.

CP is classified by the type of movement disorder, the distribution of involvement, and the severity (Table 71.5). The movement disorders in CP are most often classified as spastic, dyskinetic, or mixed. Spasticity is a type of hypertonia in which the resistance to passive movement is velocity dependent. It is part of upper motor neuron syndrome, which leads to overactive stretch reflex. Other signs include hyperreflexia, clonus, and extensor plantar response (Babinski sign). By comparison, tone is also increased in dystonic CP. However, the hypertonia is due to involuntary sustained muscle contractions, which lead to abnormal movements and posture. The tone is not velocity

Table 71.5 • Patterns of Involvement in Cerebral Palsy

Cerebral Palsy Classification	Distribution of Involvement
Monoplegia: 1 limb	
Hemiplegia: 1 side	
Paraplegia: lower extremities	
Diplegia: lower > upper extremities	
Double hemiplegia: upper > lower extremities	
Quadriplegia: all 4 extremities equally involved	

Not involved Less involved More involved

dependent. Dystonia is often seen in children with spastic CP. Other signs commonly seen in CP include weakness, poor motor control, persistent primitive reflexes, and ataxia.

If 1 limb, often lower, is involved, the CP is classified as being a monoplegia. Children with hemiplegia have 1 side involved, and the upper extremity is more affected than the lower. If all 4 limbs are involved, but lower more than upper, the child has diplegia. If the converse is true, with upper being more affected than lower, then this is double hemiplegia. In contrast, if only lower limbs are involved, the child has paraplegia, and if all 4 limbs are involved equally, the child has quadriplegia. Involvement of the entire body, including lack of head and neck control, is total-body CP.

Developmental Delay Versus Developmental Plateau and Regression

CP is a static encephalopathy associated with delayed acquisition of milestones. It must be differentiated from developmental plateau and regression. During the first 1 to 2 years of life, a child with CP may demonstrate increasing spasticity and movement disorders. Furthermore, as the child ages, the gap between the child's development and that of other children increases. This does not represent a plateau or loss of milestones, but rather increasing awareness of the child's disabilities.

In contrast, if there is a clear failure to acquire new milestones, even slowly, or a loss of previously acquired milestones, then this is not a static encephalopathy. Developmental plateau and regression are suggestive of progressive neurologic disease that may occur because of metabolic, infectious, autoimmune, or genetic causes. Progressive hydrocephalus is a potentially treatable cause of developmental regression that must be excluded.

- Children with mild intellectual disability (IQ, 50–70) are able to understand concepts up to a fourth- to sixth-grade level, are likely to hold a simple job, and enjoy some independence as an adult.
- Children with profound disability (IQ <20) likely will not develop meaningful communication and will require extensive nursing care.
- Cerebral palsy is a permanent, nonprogressive disorder of movement and posture that is due to a neurologic insult that occurs during fetal or infant development.
- Cerebral palsy is classified by the type of movement disorder, the distribution of involvement, and the severity.
- Developmental plateau and regression are suggestive of progressive neurologic disease that may occur because of metabolic, infectious, autoimmune, or genetic causes. Progressive hydrocephalus is a potentially treatable cause of developmental regression that must be excluded.

72 Neurocutaneous Disorders

GESINA F. KEATING, MD

Introduction

Neurocutaneous disorders, formerly called *phakomatoses*, are characterized by cutaneous and neurologic findings. Many are genetic, but some are sporadic. Often, these disorders affect other organ systems as well and require lifetime surveillance for complications. Table 72.1 gives an overview of neurocutaneous disorders described in this chapter.

Neurofibromatosis Type 1

Epidemiologic Factors and Genetics

Neurofibromatosis type 1 (NF1) is the most common neurocutaneous disorder. Its prevalence is approximately 1 in 3,000 persons, and it is more than 10 times more common than neurofibromatosis type 2 (NF2).

Genetics of NF1 is notable for an autosomal dominant inheritance mode. Approximately one-half of patients with NF1 have a new mutation. The gene is *NF1*, found at chromosome 17q11.20. The gene product is neurofibromin and functions as a tumor suppressor gene. Absence of functional gene product increases RAS activity, thereby increasing cell proliferation and neoplasm development. The penetrance of this disease, even in the same family, is highly variable.

- Genetics of neurofibromatosis type 1 (NF1) is notable for an autosomal dominant inheritance mode.
- The gene *NF1* produces neurofibromin and functions as a tumor suppressor gene.

Clinical Manifestations

The classical presentation of NF1 is that of multiple hyperpigmented macules, referred to as *café au lait spots*. These macules are noted at birth or soon thereafter and their number increases in the first year of life. Other common findings of NF1 early in life include macrocephaly (most commonly megalencephaly and less commonly hydrocephalus), developmental delay (motor and speech), and learning difficulties (50%-75%). The majority of patients with NF have a low average IQ.

Ocular manifestations in NF1 include optic pathway gliomas and Lisch nodules. Optic pathway gliomas may occur in up to one-quarter of patients with NF1. Pathologically, these are pilocytic astrocytomas. They typically present before age 7 years. The vast majority of these tumors are asymptomatic, though optic pathway gliomas may present with visual impairment, proptosis, or precocious puberty. In patients with visual impairment, stability or even spontaneous regression may occur without treatment. Lisch nodules, present on the iris, occur in virtually all NF1 patients by adulthood and have no impact on vision.

Neurofibromas may be dermal or plexiform and are another common manifestation of NF1. They typically are not present until adolescence or adulthood. Neurofibromas are made up of Schwann cells, with a mixture of other cell types. They typically grow along the nerve fibers and are well-circumscribed nodules. They also occur in the dermis and epidermis, with both a purple discoloration at the affected skin and a rubbery quality on palpation. Neurofibromas may increase in number with age and during pregnancy. These may cause pruritus and are only

Abbreviations: CNS, central nervous system; HI, hypomelanosis of Ito; IP, incontinentia pigmenti; LSNS, linear sebaceous nevus syndrome; MAPK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma; SWS, Sturge-Weber syndrome; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau

Table 72.1 • Summary of Neurocutaneous Disorders

Disease	Gene	Chromosome	Gene Product	Inheritance	Skin (Cutaneous) Findings	Neurologic Findings	CNS Tumors	Other Organ System Involvement
NF1	*NF1*	17q11.2	Neurofibromin	AD	Café au lait spots	Macrocephaly, developmental delay	Optic pathway glioma, pilocytic astrocytoma	
NF2	*NF2*	22q12.2	Merlin	AD	NF2 plaques	Deafness, gait instability	Vestibular schwannomas, other schwannomas, meningiomas, ependymomas	Ocular: cataracts
TSC	*TSC1*	9q34.3	Hamartin	AD	Ash-leaf spots, facial angiomas	Epilepsy, intellectual disability	Subependymal giant cell astrocytoma	
	TSC2	16p13.3	Tuberin					
SWS	*GNAQ*	9q21	Guanine nucleotide binding protein	Sporadic	Port wine stain	Epilepsy, leptomeningeal angiomatosis, hemiparesis, intellectual disability		Ocular: glaucoma
AT	*ATM*	11q22-q23	Serine-protein kinase ATM	AR	Telangiectasias	Ataxia and other cerebellar dysfunction	Unlikely, though other cancers occur	Immune system: infections, immunodeficiency; pulmonary: bronchiectasis
VHL disease	*VHL*	3p25.3	pVHL	AD	Retinal hemangioblastoma	Blindness, ataxia, paresis/plegia	Hemangioblastomas of the cerebellum, retina, brainstem, spinal cord	
HI	Mosaicism in 50%			Sporadic	Hypopigmentation along Blaschko lines	Intellectual disability, epilepsy		
IP	*IKBKG*	Xq28	Inhibitor of nuclear factor κ-B kinase subunit γ	X-linked	Stages: bullous, verrucous, hyperpigmentation, atrophic/ hypopigmentation	Intellectual disability, epilepsy		Ocular: retinal detachment
LSNS				Sporadic	Plaques, patches, nodules, or linear lesions	Seizures, intellectual disability		Ocular: coloboma, cataracts, choristoma

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; AT, ataxia telangiectasia; ATM, ataxia telangiectasia mutated; CNS, central nervous system; HI, hypomelanosis of Ito; IP, incontinentia pigmenti; LSNS, linear sebaceous nevus syndrome; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; pVHL, VHL disease protein; SWS, Sturge-Weber syndrome; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau.

rarely painful. Pain may occur with nerve compression or, less commonly, may signal malignant transformation.

Plexiform neurofibromas differ from the dermal neurofibromas in that these may arise in young children. These neurofibromas are soft, poorly defined subcutaneous lesions that can become large, involving a whole limb or other region of the body. The skin over the plexiform neurofibroma frequently has dark pigmentation or hypertrichosis. Plexiform neurofibromas can be deforming, particularly when they occur within the eye orbit. In 3% to 5% of persons with NF1, malignant peripheral nerve sheath tumors arise from a plexiform neurofibroma. Pain or rapid growth may signal malignant transformation.

Central nervous system (CNS) tumors occur frequently in NF1, with optic pathway gliomas the most common CNS tumor. After the development of an optic pathway glioma, other pilocytic astrocytomas or low-grade gliomas may arise in the cerebellum, brainstem, or other sites. As with optic pathway gliomas, many of the CNS tumors in NF1 are asymptomatic and are noted incidentally on imaging obtained for other reasons, with some reports of a 15% to 30% incidence.

Other important findings in NF1 may be skeletal or vascular abnormalities. Skeletal abnormalities include sphenoid wing dysplasia, scoliosis, and pseudarthroses of long bones, which may be prone to fractures. Pectus deformity may occur as well. Vascular abnormalities include renal artery stenosis, presenting with hypertension. Moyamoya syndrome may occur, leading to strokes. Pheochromocytoma is another important cause of hypertension in NF1. However, the main cause of hypertension in NF1 is essential hypertension.

- The classical presentation of NF1 is multiple hyperpigmented macules, called *café au lait spots*.
- Central nervous system (CNS) tumors occur frequently in patients who have NF1, with optic pathway gliomas most common.

Diagnosis

The diagnosis of NF1 is based on clinical findings. The diagnostic criteria are listed in Table 72.2. Café au lait spots are a hallmark of NF1. In prepubertal children, spots should measure at least 5 mm in their largest dimension. In postpubertal patients, spots should measure 15 mm or greater.

Molecular genetic testing can be pursued when the clinical diagnosis is in question. This testing can be helpful in confirming the diagnosis in a patient who does not yet meet the diagnostic criteria for NF1. It can provide essential information with regard to plans for disease surveillance and tumor treatment.

- The diagnosis of NF1 is based on clinical findings.
- Café au lait spots are a hallmark of NF1.

Table 72.2 • NIH Diagnostic Criteria for Neurofibromatosis Type 1

Two or more of the following:

1. ≥6 café au lait spots
2. ≥2 neurofibromas of any type or ≥1 plexiform neurofibroma
3. Freckling (Crowe sign) in axilla or groin
4. Optic glioma
5. ≥2 Lisch nodules (benign pigmented iris hamartomas)
6. Distinctive bony lesion
7. First-degree relative with neurofibromatosis type 1

Abbreviation: NIH, National Institutes of Health.

Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.

Treatment

There is no cure for NF1. Routine clinical evaluation on an annual basis with a physician familiar with NF1 manifestations is the most important treatment of this condition. Recommended screenings are noted in Table 72.3.

Developmental screening should be provided at the diagnosis of children with NF1. In children with developmental delays, early intervention (eg, occupational, physical, speech therapies, neuropsychologic assessments) before kindergarten is recommended.

Magnetic resonance imaging (MRI) of the brain is not considered part of screening in NF1. A consensus statement regarding cranial imaging in NF1 discourages against routine cranial imaging in patients with the diagnosis. MRI should be obtained only when there are abnormal ophthalmologic or neurologic findings or in the case of precocious puberty. Findings of macrocephaly with developmental delay or other learning difficulties are not indications for cranial imaging. Using MRI for screening does not improve the outcome in patients with optic pathway glioma or other asymptomatic tumors that do not require treatment.

Frequently, the management of CNS tumors in NF1 is observation only. In tumors that progress or are symptomatic outside of the optic pathway, treatment with surgical resection is advised when possible. Chemotherapy may be useful if there is residual disease. Radiotherapy should be avoided because of the risk for secondary malignancies.

When an optic pathway glioma is identified in a child with NF1, the tumor and symptoms may be stable or regress. For this reason, the child is frequently best treated with visual examinations at 3-month intervals after the optic pathway glioma is discovered and with repeating the imaging when there are progressive vision difficulties, precocious puberty, or other neurologic signs or symptoms.

Table 72.3 • Recommended Screening in Patients With Neurofibromatosis Type 1

Early developmental screening
Head circumference measurement
Eye examinations (annually for first 10 y, then every 2 y until age 25 y, then as needed)
Blood pressure measurement at least annually
Magnetic resonance imaging of the brain **if** abnormal ophthalmologic or neurologic findings or precocious puberty

Chemotherapy may be used in children with vision decline, though its usefulness may be debated. Radiotherapy should be avoided because of the increased risk of induction of secondary cancers. A similar approach may be taken for pilocytic astrocytomas that arise in other parts of the CNS.

MRI can be helpful in assessing the extent of involvement and subsequent progression in neurofibromas. In particular, plexiform neurofibromas warrant MRI for surveillance, as well as in planning for surgical resection. However, in the absence of pain, the management of plexiform neurofibromas is typically conservative because they are nearly impossible to fully resect and they will regrow.

Genetic counseling for patients with NF1 is recommended as the patient reaches child-bearing age. Screening of family members for NF1 is important as well and can be done with careful clinical examination. By adulthood, more than 90% of patients with NF1 have Lisch nodules, which are essentially pathognomonic for NF1, thus ophthalmologic examination is a useful screen for disease in adult family members.

Mortality Rate

Death due to NF1 is most often related to malignancy or vasculopathy. Malignant peripheral nerve sheath tumor has a lifetime occurrence rate of 8% to 13% in persons with NF1. Vasculopathy, including moyamoya syndrome, renal artery stenosis, and aneurysms, can be important causes of early death. Overall life expectancy is about 8 years less than the general population, with the primary cause of death unrelated to NF1 manifestations.

Neurofibromatosis Type 2

Epidemiologic Factors and Genetics

NF2 is less common than NF1, with a prevalence of 1 in 40,000 persons. NF2 may affect persons of any race/ethnicity. The average age of symptom onset is 18 to 24 years, in early adulthood. The diagnostic criteria are met by age 30 years in most persons with NF2 and in virtually all of them by age 60 years.

NF2 is inherited in an autosomal dominant pattern, and approximately one-half of all patients possess a new mutation. The affected gene, *NF2,* is found at chromosome 22q12.2. The gene product is merlin (moesin-ezrin-radixin-related protein) and functions as a tumor suppressor, impacting cell proliferation. Merlin is also referred to as *neurofibromin 2* and *schwannomin*. The merlin protein is predominantly found in nervous tissue, including Schwann cells, meningeal cells, and nerve cells. Thus, mutations in *NF2* result in tumors of the nervous system, most commonly vestibular schwannomas (previously called *acoustic neuromas*).

- The gene product of *NF2* is merlin (moesin-ezrin-radixin-related protein) and functions as a tumor suppressor.

Clinical Manifestations

The classic presentation of NF2 is bilateral vestibular schwannomas (Figure 72.1). The presence of a vestibular schwannoma is manifested by insidious onset of tinnitus, hearing loss, and vertigo. Other common manifestations are additional nervous system tumors and skin and eye findings.

Nervous system tumors include schwannomas of other cranial nerves, spinal roots, and peripheral nerves. Meningiomas will develop in at least one-half of all patients with NF2. Ependymomas are less frequent, occurring in about 20% of patients, typically arising in the spinal cord. Astrocytomas are rare.

Skin manifestations are NF2 plaques and, far less frequently, café au lait spots. NF2 plaques are seen in about

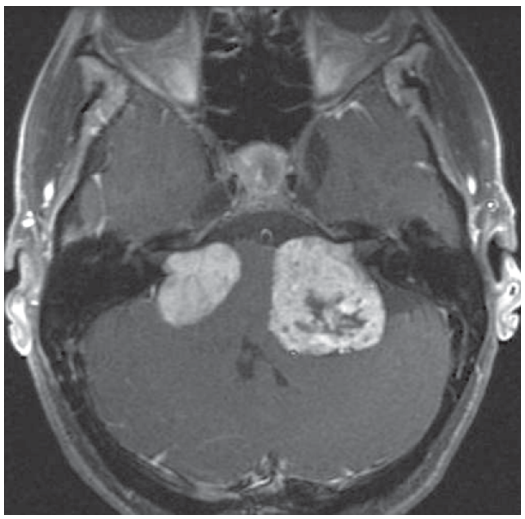


Figure 72.1 *Neurofibromatosis 2 in Magnetic Resonance Imaging.*
T1 with contrast medium shows bilateral cerebellopontine angle extra-axial masses consistent with bilateral acoustic neuromas.

70% of patients, characterized by a raised, hyperpigmented, and sometimes hypertrichotic area of skin, typically smaller than 2 cm in diameter. Histologically, these areas are schwannomas. Café au lait spots are not a diagnostic finding in NF2. Of patients with café au lait spots, less than 1% will have more than 6, with less pigmentation and more irregular margins than seen in NF1.

Ocular manifestations are cataracts, seen in 85% of patients with NF2. Typically, the cataract is a juvenile posterior subcapsular cataract, and it is found in more than one-third of children with NF2. The cataract frequently appears before vestibular schwannomas or other tumors and thus may provide an early diagnostic clue.

- The classic presentation of neurofibromatosis type 2 (NF2) is bilateral vestibular schwannomas.
- Ocular manifestations are cataracts, seen in 85% of patients with NF2.

Diagnosis

The diagnosis of NF2 is based on clinical findings (Table 72.4). The presence of bilateral vestibular schwannoma is pathognomonic for the diagnosis of NF2, even without a family history. In patients with unilateral vestibular schwannoma and no family history of NF2, the presence of 2 or more other neural tumors or cataracts makes the diagnosis of NF2. Even in the absence of unilateral vestibular schwannoma, the diagnosis of NF2 may be made when there are multiple meningiomas and at least 2 of the other tumor types seen in NF2. The possibility of NF2 should receive heightened suspicion for any child with diagnosed meningioma or cataract.

Molecular gene testing is available for NF2. Mutation type relates to the severity and mortality rate of disease. Gene testing detects a mutation in more than 90% of patients with a family history of NF2. In patients without a family history, nearly three-quarters have a mutation identified. However, 25% to 30% of simplex cases are mosaic for an *NF2* mutation, which clinicians must keep in mind.

Table 72.4 • Diagnosis of Neurofibromatosis Type 2

Bilateral vestibular schwannomas
First-degree relative with neurofibromatosis type 2 **and** Unilateral vestibular schwannoma **or** Any 2 of meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular lenticular opacities
Unilateral vestibular schwannoma and any 2 of meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular lenticular opacities
Multiple meningiomas **and** Unilateral vestibular schwannoma **or** Any 2 of schwannoma, glioma, neurofibroma, or cataract

Truncating mutations, which are nonsense or frame-shift mutations, predict more severe disease. The pediatric diagnosis of NF2 is typically associated with truncating mutations and thus more severe disease. Milder phenotypes are typically seen with missense mutations or large or in-frame deletions. Splice mutations can result in either mild or severe disease. Gene testing can be helpful in confirming the diagnosis of NF2 in patients whose clinical manifestations do not yet meet diagnostic criteria or in making presymptomatic diagnosis in those with a positive family history. This finding can be helpful in guiding surveillance and treatment.

- Gene testing can help to confirm the diagnosis of neurofibromatosis type 2 in patients whose clinical manifestations do not yet meet diagnostic criteria or to make a presymptomatic diagnosis in patients with a positive family history.

Treatment

There is no cure for NF2. Treatment consists of surveillance of at-risk persons or patients with early identification of treatable NF2 lesions. Genetic counseling is necessary in the treatment of patients with NF2.

Vestibular schwannomas in NF2 are primarily treated with surgery. Stereotactic radiosurgery, such as Gamma Knife radiosurgery, may be an alternative to surgery or may be used in combination with surgery. Timing is an important consideration, with the goal of preserving natural hearing as long as possible and making use of technology with cochlear or auditory brainstem implant whenever possible.

Despite technology to augment hearing, treatment of hearing loss in NF2 should include instruction in lip reading and sign language. Early referral to an audiologist for hearing evaluation, including brainstem auditory-evoked response testing, is necessary.

Surveillance imaging with MRI is necessary for affected patients, including patients whose findings do not yet meet diagnostic criteria. Surveillance imaging should also be performed around the time of puberty in patients with a family history of NF2. A baseline MRI of the brain and spinal cord should be obtained at diagnosis of NF2 and continue to be obtained annually until at least the fourth decade, when almost all affected persons have received the diagnosis of NF2.

Eye examinations should be undertaken yearly with regard to the likely development of cataracts, seen in more than three-quarters of all patients with NF2.

Cervical spine imaging before surgery is important to identify lesions in that region, to prevent complications from neck extension or manipulation related to anesthesia.

Radiation therapy should be used only with careful consideration of the resultant increased risk of malignancy.

In particular, it should be avoided in children with NF2. Despite this caution, radiation therapy may be unavoidable in treating tumors that are not easily managed surgically.

- In neurofibromatosis type 2, vestibular schwannomas are primarily treated with surgery.
- Radiation therapy should be used only with careful consideration of the resultant increased risk of malignancy.

Mortality Rate

Though typically not malignant, the tumors of NF2 are the chief cause of morbidity and death in these patients. The average age at death is 36 years among persons with NF2. Survival after diagnosis has historically been 15 years. Survival time appears to be increasing because of improved diagnostic imaging that allows earlier interventions for dangerous tumors.

Tuberous Sclerosis Complex

Epidemiologic Factors and Genetics

Tuberous sclerosis complex (TSC) is the second most common neurocutaneous disorder, after NF1, and is 1 of the most common genetic causes of epilepsy.

The genetics in TSC is notable for autosomal dominant inheritance. Two genes are causative for TSC: *TSC1* (on chromosome 9q34.3) and *TSC2* (on chromosome 16p13.3). A mutation in either one of the genes leads to disease. The *TSC1* product is hamartin; the *TSC2* product is tuberin. Hamartin and tuberin join together to form a heterodimer, which functions as a tumor growth suppressor by inhibiting the mammalian target of rapamycin (mTOR). A properly functioning heterodimer affectively "puts the brakes" on mTOR-mediated downstream signaling. Without this protective action, abnormal cell proliferation and differentiation are allowed to occur. In TSC, this process results in hamartia, hamartoma, and even hamartoblastoma formation in multiple organ systems (Table 72.5). Clinical manifestations of TSC are thus related to these affected organ systems.

Hamartias and hamartomas are characterized by their groups of dysplastic cells. In hamartias, the dysplastic cells do not multiply or grow any more rapidly than the normal cells of the affected organ. Subcortical tubers are an example of hamartias (Figure 72.2). Hamartomas also consist of dysplastic cells; however, these cells multiply and grow as benign tumors. Subependymal nodules are an example of hamartomas and, with growth, may become subependymal giant cell astrocytomas (Figure 72.3). Hamartoblastomas are the rare malignant growths in TSC. They are more common in persons with the *TSC2* mutation. Examples of hamartoblastomas include renal cell carcinomas (RCCs), malignant angiomyolipoma, and glioblastoma multiforme.

Table 72.5 • Common Lesions in Patients With Tuberous Sclerosis Complex

Organ	Hamartias	Hamartomas
Brain	Cortical tuber	Subependymal nodule Subependymal giant cell astrocytoma
Retina	Retinal depigmented spots	Astrocytic hamartoma
Skin	Hypomelanotic macules	Facial angiofibroma (adenoma sebaceum) Ungual fibroma Shagreen plaque
Heart		Rhabdomyoma
Kidney	Cysts	Angiomyolipoma
Lung		Lymphangioleiomyomatosis
Liver		Angiomyolipoma
Pancreas		Islet cell adenoma
Colorectal junction		Hamartomatous polyp
Adrenal gland		Angiomyolipoma
Thyroid gland		Papilliform adenoma Fetal thyroid adenoma
Gonads		Testicular angiomyolipoma
Bones	Cysts, osteomatous thickening	
Arteries	Wall defects (aneurysm)	

Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.

New mutations account for TSC in two-thirds to three-quarters of patients. Sporadic cases of TSC are more often caused by mutations in *TSC2* than *TSC1*. Generally, patients with sporadic mutations have more severe disease manifestations.

- Tuberous sclerosis complex (TSC) is 1 of the most common genetic causes of epilepsy.
- The *TSC1* gene product is hamartin, and the *TSC2* product is tuberin.
- In TSC, abnormal cell proliferation and differentiation result in hamartia, hamartoma, and even hamartoblastoma formation in multiple organ systems.

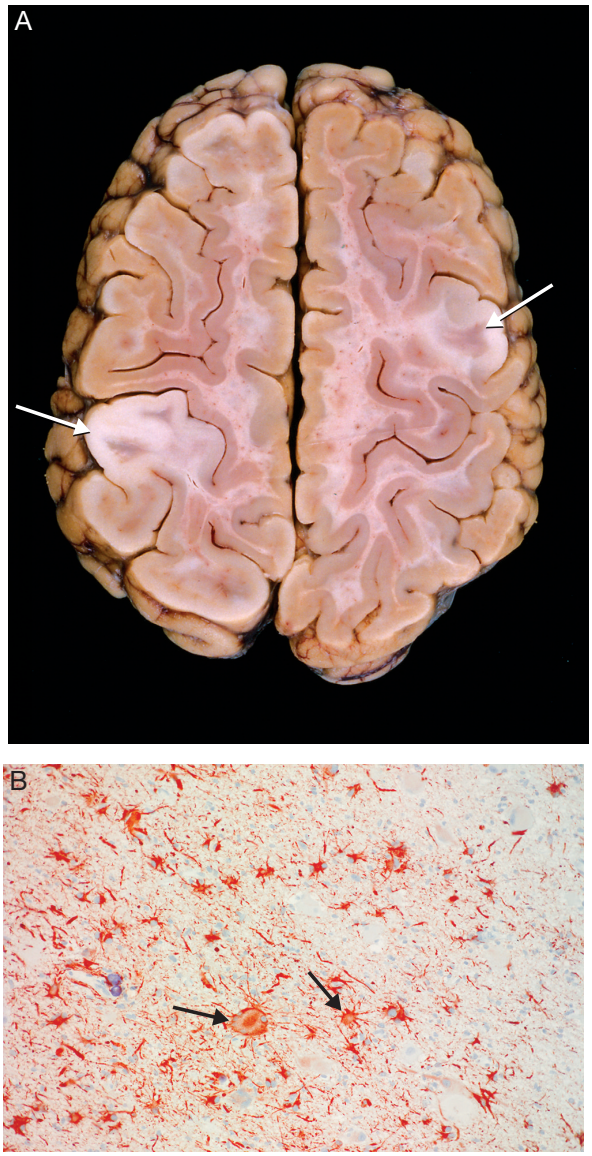


Figure 72.2 *Cortical Tuber in Tuberous Sclerosis Complex. A, Gross specimen, associated with tuberous sclerosis complex. B, Microscopic appearance with atypical astrocytes (arrows).*

Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.

Clinical Manifestations

The combined findings of seizures, mental retardation, and adenoma sebaceum are historically considered the classic triad of TSC manifestations. In reality, this triad is the case for less than one-third of patients with TSC.

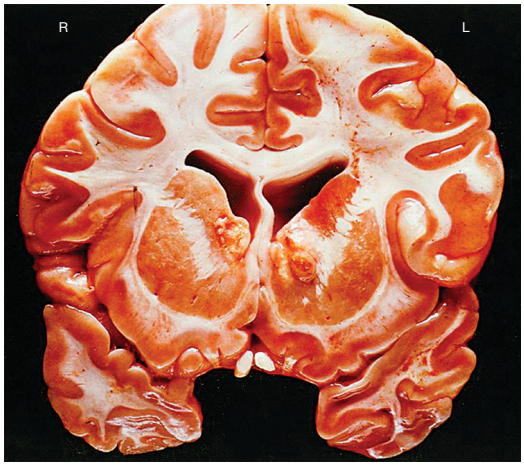


Figure 72.3 *Subependymal Giant Cell Astrocytoma. Gross specimen of subependymal giant cell astrocytoma near foramen of Munro on right in patient with tuberous sclerosis complex.*

(Adapted from Scheithauer BW, Reagan TJ. Neuropathology. In: Gómez MR, Sampson JR, Whittemore VH, editors. Tuberous sclerosis complex. 3rd ed. New York [NY]: Oxford University Press; c1999. p. 101–44. Used with permission.)

Neurologic manifestations are frequently the most disabling problem of the disease and include epilepsy, developmental delay, and autism. Epilepsy affects up to 90% of those with TSC. Most epilepsy is evident by 1 year of age. It may include infantile spasms, said to occur in 30% to 60% of patients with *TSC*. Seizures may be partial or generalized and are often refractory to pharmacotherapy.

Hydrocephalus is another potential neurologic manifestation in TSC. The cerebrospinal fluid obstruction is caused by a subependymal giant cell astrocytoma (SEGA) at the foramen of Monro. SEGAs occur in as many as 14% of patients with TSC.

Further neurologic manifestations are developmental delay and cognitive limitations. These are present in at least one-half of patients and may include autism.

Skin manifestations are present in a majority of patients with TSC. Hypopigmented macules, known as *ash-leaf spots*, are the most commonly found TSC manifestation, with 3 or more occurring in 90% of TSC patients (Figure 72.4). Facial angiofibromas (ie, adenoma sebaceum) are seen in 75% of patients and may be mistaken for early acne (Figure 72.5). Ungual fibromas occur in 21%. Shagreen patches are seen in about 19% of patients and are characterized by an elevated, thickened, "orange peel" area, usually on the lower back. A similar finding can be seen on the forehead, called *forehead fibrous plaque*. Although the skin lesions can be disfiguring, particularly the facial angiofibromas and forehead fibrous plaques, none are related to serious medical problems.

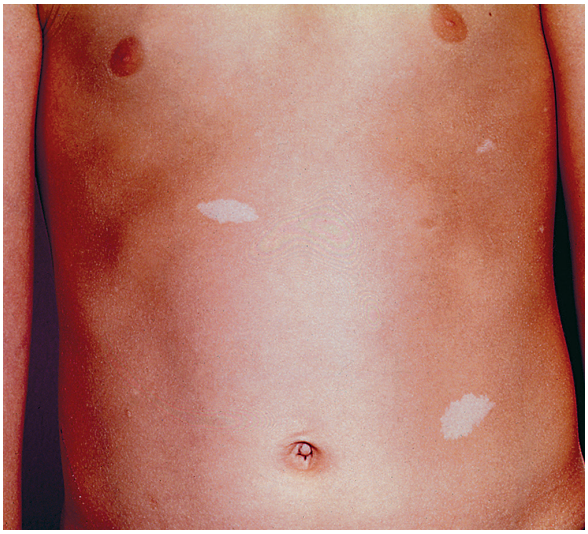


Figure 72.4 *Ash-Leaf Spots in Tuberous Sclerosis Complex. These cutaneous findings may be seen best with a Wood lamp examination.*
(Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.)

Renal lesions are the next most frequent clinical manifestation of TSC, found in up to 80% of patients. These lesions consist of angiomyolipomas in most cases and simple cysts in a few cases, and both lesion types can be bilateral and multiple. The simple cysts may wax and wane, whereas angiomyolipomas increase in size over time. Pain is the most common clinical symptom associated with angiomyolipomas, and hematuria may be observed. Risk of sudden hemorrhage increases with angiomyolipoma size, particularly when greater than 3.5 cm in diameter. Renal failure and hypertension also may result from the kidney lesions. Rarely, RCC or a malignant angiomyolipoma may occur.

Cardiac manifestations are next most common in frequency, with rhabdomyomas found in 50% of patients with TSC. Rhabdomyomas may cause dysrhythmias. The size of the rhabdomyoma may cause outflow obstruction from the left ventricle. However, most lesions are asymptomatic and spontaneously regress with time.

Retinal hamartomas may occur in up to 50% of patients. Less frequently, astrocytomas of the retina develop. Most TSC eye findings do not limit vision.

Lung manifestations include cystic lesions, as well as nodules. The cystic lesions may cause spontaneous pneumothorax. Presence of nodules, termed *lymphangioleiomyomatosis*, affects only girls and women (34%). Interestingly, lymphangioleiomyomatosis is typically seen

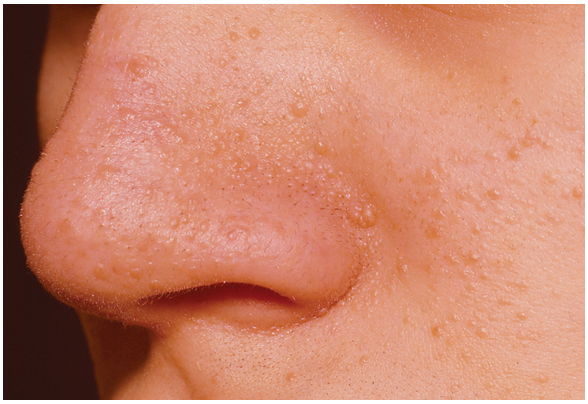


Figure 72.5 *Adenoma Sebaceum Associated With Tuberous Sclerosis Complex.*
(Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.)

in women without mental retardation. The symptoms can be severe in some patients and may include dyspnea with exertion, cough, hemoptysis, pneumothorax, and pleural effusion.

- The combined findings of seizures, mental retardation, and adenoma sebaceum are historically considered the classic triad of TSC manifestations.
- Epilepsy affects up to 90% of patients with TSC. Most epilepsy is evident by 1 year of age and may involve infantile spasms, reported to occur in 30% to 60% of patients with *TSC*.
- Hypopigmented macules, known as *ash-leaf spots*, are the most commonly found TSC manifestation.

Diagnosis

The diagnosis of TSC is based on clinical findings. The diagnostic criteria's major and minor features are listed in Table 72.6. *Definitive* clinical diagnosis is based on the presence of 2 major features or 1 major feature combined with 2 minor features. *Probable* diagnosis of TSC can be made with 1 major feature plus 1 minor feature. *Possible* diagnosis of TSC may be based on finding 1 major or 2 minor features. MRI findings are noted in Figure 72.6.

Molecular genetic testing can be pursued when the clinical diagnosis of TSC is in question. This testing involves sequence analysis of *TSC1* and *TSC2*. In patients with no mutation identified, further testing with deletion and duplication analysis is performed. This information can then be used for testing at-risk family members who are asymptomatic.

Table 72.6 • Diagnostic Criteria for Tuberous Sclerosis Complex

Major Features	Minor Features
Facial angiofibromas or forehead plaque	Multiple randomly distributed pits in dental enamel
Nontraumatic ungual or periungual fibroma	Hamartomatous rectal polyps
Hypomelanotic macules (>3)	Bone cysts
Shagreen patch (connective tissue nevus)	Cerebral white matter migration tracts
Cortical tuber	Gingival fibromas
Subependymal nodule	Nonrenal hamartoma
Subependymal giant cell astrocytoma	Retinal achromic patch
Multiple retinal nodular hamartomas	"Confetti" skin lesions
Cardiac rhabdomyoma, single or multiple	Multiple renal cysts
Lymphangioleiomyomatosis	
Renal angiomyolipoma	

Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.

Treatment

There is no cure for TSC. Treatment consists of surveillance for management of the various organ manifestations (Table 72.7). Genetic counseling is important for persons with TSC, as well as their at-risk family members.

Neurologically, medical care at a comprehensive epilepsy center may be most helpful, where medication, ketogenic diet, and even epilepsy surgery can be offered. Though any cortical tuber may have epileptogenic potential, resection of a considerably active tuber may lead to substantial improvement in epilepsy control. Infantile spasms should be treated with vigabatrin.

Ventricular enlargement caused by a SEGA has need for treatment. Previously, neurosurgical resection was required. More recently, everolimus, an mTOR inhibitor, has been approved for SEGA treatment. This oral medication effectively decreases the size of the SEGA and avoids the need for tumor resection and treatment of hydrocephalus.

- Though any cortical tuber in TSC may have epileptogenic potential, the resection of a considerably active tuber may lead to substantial improvement in epilepsy control.
- Infantile spasms in TSC-related epilepsy should be treated with vigabatrin.

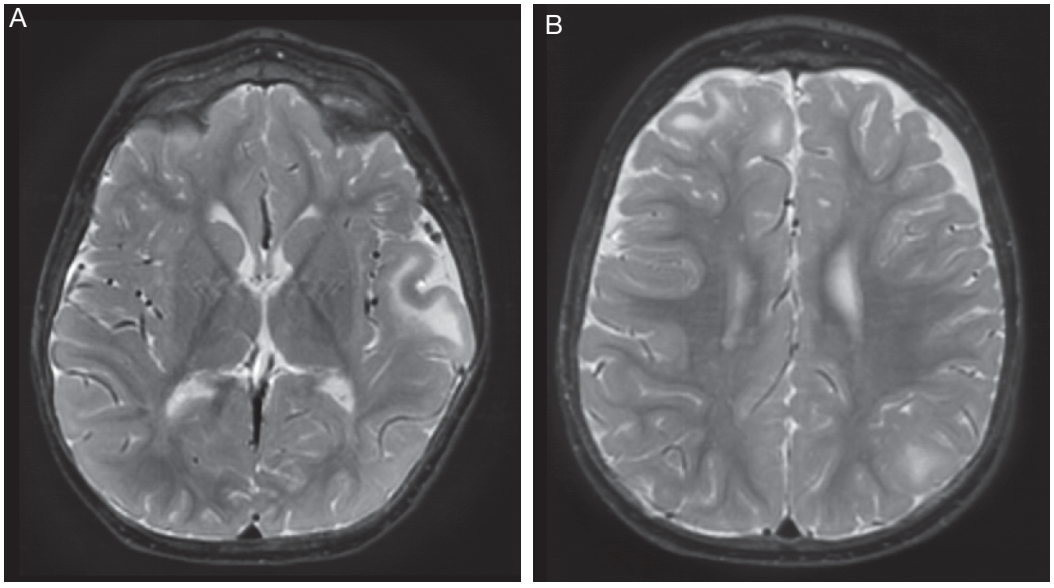


Figure 72.6 *Axial Sections in Tuberous Sclerosis.*
T2-weighted magnetic resonance imaging of brain shows (A) midaxial section and (B) upper axial section from patient with tuberous sclerosis. Multiple cortical tubers involve both cerebral hemispheres. Involvement is prominent in the anterior left temporal lobe, with associated calvarial remodeling.
(Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.)

Table 72.7 • Screening and Surveillance in Tuberous Sclerosis Complex

Screen for developmental delay before age 3 y
Brain imaging at 1- to 2-y intervals until age 20 y, then as needed (surveillance for subependymal giant cell astrocytoma)
Blood pressure at every office visit (for early sign of renal disease)
Renal ultrasonography at diagnosis and then every 1–3 y (if lesion identified, then annual imaging or, if lesion >3.5 cm, semiannual imaging)
High-resolution chest computed tomography after age 18 y

Mortality Rate

Morbidity and mortality rates related to the neurologic manifestations of TSC are notable in TSC. The epilepsy may be refractory to pharmacologic therapy. In patients who have generalized seizures before age 5 years, Lennox-Gastaut syndrome may develop. Poor seizure control is typically accompanied by more serious intellectual disability, with either issue capable of notably limiting the patient's independence. Premature death in TSC is frequently identified as a complication related to neurologic manifestations, such as status epilepticus.

Renal disease such as angiomyolipomas may cause hypertension and renal failure. Cancer, with malignant angiomyolipoma or RCC, is less frequent. Lung manifestations related to lymphangioleiomyomatosis can be severe and can even be fatal in some patients.

von Hippel-Lindau Disease

Epidemiologic Factors and Genetics

von Hippel-Lindau (VHL) disease is a rare disorder, with an incidence of 1 in 36,000 persons. It may manifest at any age, although the average age at diagnosis is 26 years.

VHL has autosomal dominant inheritance. Penetrance of disease is high, though phenotype within 1 family may vary greatly. New mutations account for 20% of cases. The disease gene, *VHL*, is located at chromosome 3p25.3. The gene's product, VHL protein (pVHL), functions as a tumor suppressor gene. Disease occurs when an acquired mutation of *VHL* combines with an inherited *VHL* abnormality, bringing about a 2-hit inactivation of *VHL* and loss of functional pVHL. The effect results in an inability to regulate degradation of hypoxia-inducible factors. In turn, this lack of regulation causes alterations in angiogenesis, cell proliferation, apoptosis, and metabolism, thereby leading to the angiomatosis and tumors characteristic of VHL disease. Thus, VHL disease is a hereditary cancer predisposition syndrome.

Phenotypic variation for pheochromocytoma risk is related to the type of *VHL* mutation present. Families with type 1 mutation have a low risk of pheochromocytoma and typically have deletion or nonsense mutations in *VHL*. Families with type 2 mutations have a high risk of pheochromocytoma, typically have missense mutations in *VHL,* and are further subtyped by their risk of RCC. In type 2A, there is low risk of RCC; in type 2B, there is high risk. Type 2C has risk of pheochromocytoma only. Hemangioblastomas occur in all types of VHL disease.

Clinical Manifestations

Symptoms of VHL disease relate to tumor type and location. Table 72.8 summarizes the various tumor types, along with other clinically relevant information. Initial manifestations of VHL disease are most likely related to retinal, cerebellar, or spinal cord hemangioblastomas.

CNS hemangioblastomas in VHL disease most often present with increased intracranial pressure related to obstructive hydrocephalus caused by a cerebellar lesion. The imaging appearance is generally of a cystic cerebellar tumor with a mural nodule. In 10% of cases, multiple cerebellar lesions exist at presentation. Brainstem and supratentorial hemangioblastomas are less frequent.

Spinal hemangioblastomas typically present with pain, which may be accompanied by motor and sensory symptoms. The location of spinal hemangioblastomas may be intramedullary or extramedullary, or both.

Skin findings are not seen, but nevertheless, VHL disease is designated a neurocutaneous disorder. The retinal hemangioblastomas are considered the cutaneous manifestation of this disease. Retinal angiomas (hemangioblastomas) present with decline in visual field or acuity,

Table 72.8 • von Hippel-Lindau Disease Tumors

Retinal angioma (hemangioblastoma)
CNS hemangioblastomas of combined locations
Cerebellar
Spinal
Brainstem
Renal cell carcinoma
Pheochromocytoma
Pancreatic cysts
Pancreatic tumors
Endolymphatic sac tumor
Epididymal cystadenoma (boys and men)
Broad ligament cystadenoma (girls and women)
Paragangliomas of head and neck

Abbreviation: CNS, central nervous system.

even in the first decade of life. Asymptomatic lesions may also be found on routine funduscopic examination.

Pheochromocytomas present with hypertension, which may be sustained or episodic. Endolymphatic sac tumors should be suspected when abrupt hearing loss occurs. Such hearing loss may be accompanied by aural fullness, vertigo, or tinnitus. Tumors of the kidney, pancreas, liver, and epididymis or broad ligament may be asymptomatic.

- In VHL disease, hemangioblastomas of the CNS most often present with increased intracranial pressure related to obstructive hydrocephalus caused by a cerebellar lesion.
- Skin findings are not seen, but VHL disease nevertheless is designated a neurocutaneous disorder. Retinal hemangioblastomas are considered its cutaneous manifestation.

Diagnosis

The diagnosis of VHL disease is based on clinical findings and confirmed with molecular genetic testing. For patients who have a known family history of VHL disease, clinical diagnosis is made with the presence of a single retinal or CNS hemangioblastoma or RCC. In the absence of a family history of VHL, clinical diagnosis is made when 2 or more retinal or CNS hemangioblastomas are present. Alternatively, the diagnosis is made with 1 retinal or CNS hemangioblastoma and 1 visceral tumor typical for VHL.

Molecular genetic testing is available commercially for confirmation of the VHL disease diagnosis. This testing identifies a mutation in more than 90% of affected persons. Genetic testing for confirmation of disease may be helpful for patients who do not yet fulfill the clinical diagnostic criteria for VHL disease. Even in those who fulfill diagnostic criteria, identifying the mutation facilitates screening of at-risk family members. In patients with negative genetic testing despite fulfilling clinical diagnostic criteria, a mosaic disease status should be suspected.

- The diagnosis of VHL disease is based on clinical findings and confirmed with molecular genetic testing.

Treatment

There is no cure for VHL disease. Treatment consists of early identification of related tumors through screening, then appropriate treatment as indicated. Various guidelines exist for screening and treatment of VHL disease–related tumors, and it is recommended that patient care be coordinated in a center familiar with this disease, when possible.

CNS hemangioblastomas should be screened with baseline MRI of the brain and spine at the time of diagnosis and annually thereafter. Symptomatic lesions should be treated with surgical intervention.

Renal surveillance in VHL disease should be achieved with MRI or ultrasonography of the abdomen performed annually, starting at age 16 years. Pheochromocytoma surveillance should include blood pressure monitoring at any medical visit and at least annually. Urine catecholamine monitoring should occur annually. Pheochromocytoma screening should also take place before any surgery, as well as during pregnancy, because the presence of excess circulating catecholamines may impact perioperative medical management and anesthesia. Pheochromocytoma surveillance should include abdominal ultrasonography at diagnosis and then every 2 years before age 15 years, and annually thereafter. Higher-resolution imaging with MRI or computed tomography is helpful when a suspicious lesion is identified.

Vision screening (assessing for retinal angioma) and hearing screening (assessing for endolymphatic sac tumors) should also be performed.

- CNS hemangioblastomas should be screened with a baseline MRI of the brain and spine at the time of VHL disease diagnosis and annually thereafter.
- Pheochromocytoma screening should also take place before any surgery, as well as during pregnancy, because the presence of excess circulating catecholamines may impact perioperative medical management and anesthesia.

Mortality Rate

Multiple disabilities occur in VHL disease because of multisystem involvement. Death had historically been linked to cerebellar hemangioblastomas in this disease. RCC is now known to be the chief cause of death in patients with VHL disease. Average life expectancy for patients with VHL disease, previously said to be 50 years, is improving with the advances in screening protocols, imaging, and treatment.

Sturge-Weber Syndrome

Epidemiologic Factors and Genetics

Sturge-Weber syndrome (SWS) is a sporadic congenital neurocutaneous disorder. Reported incidence varies from 1 in 20,000 live births to 1 in 50,000 live births.

Recently, the genetics of SWS has been determined. The gene is *GNAQ*, on chromosome 9q21, in which investigators have demonstrated a somatic mosaic mutation only in the affected tissues. The gene product of *GNAQ* is the guanine nucleotide binding protein, G-α(q) protein. This activating mutation leads to increased mitogen-activated protein kinase (MAPK) pathway signaling, ultimately resulting in capillary malformations in the affected tissues of skin, brain, and eye. It is believed that the earlier the *GNAQ* mutation occurs following conception, the more severe the SWS manifestations will be.

- Sturge-Weber syndrome is a sporadic congenital neurocutaneous disorder.

Clinical Manifestations

The classic presenting finding in SWS is facial cutaneous capillary malformation, or port wine stain, typically in the ophthalmic division of the fifth cranial nerve. Other cutaneous regions may be affected as well. Of importance, the port wine stain is typically visible at birth and increases in intensity with time. Presence of a port wine stain generally does not indicate a diagnosis of SWS. However, its presence in the ophthalmic distribution of the fifth cranial nerve increases the likelihood of SWS and should lead to consideration of cranial imaging.

Leptomeningeal angiomatosis, ipsilateral to the port wine stain, leads to the neurologic manifestations of SWS. Poor venous drainage of the affected leptomeninges brings about 1) venous stasis and thrombosis, 2) resultant chronic ischemic damage to the cerebral cortex, and 3) progressive changes over time. The neurologic manifestations of SWS include epilepsy, stroke, intellectual disability (in 33% of cases), hemiparesis (in 25%-60% of cases), and hemianopia. Intellectual disability occurs in nearly all patients with SWS. An increase in intellectual disability typically correlates with an earlier onset of seizure activity.

Ocular manifestations most noted in SWS are glaucoma (30%-70% of cases), buphthalmos (enlargement of affected eye), and choroidal hemangioma of the eye (50% of cases).

- Leptomeningeal angiomatosis, ipsilateral to the port wine stain, leads to the neurologic manifestations of SWS.
- The neurologic manifestations of SWS include epilepsy, stroke, intellectual disability (in 33% of cases), hemiparesis (in 25%-60% of cases), and hemianopia.

Diagnosis

The diagnosis of SWS is based on the cutaneous and neurologic findings. Brain imaging findings serve to further confirm the diagnosis. Neurologic imaging in SWS may show progressive calcifications in the external layers of the cerebral cortex, underlying the areas of angiomatosis, with the characteristic tram-track findings described on skull radiographs (Figure 72.7). Brain MRI nicely shows the pial angiomatosis, as well as late atrophy (Figure 72.8).

SWS has 3 subtypes, with the classic type including facial and leptomeningeal angiomatosis. Glaucoma may or may not accompany any 1 of these 3 types (Table 72.9).

The recent identification of the somatic mosaic mutation *GNAQ* does not currently impact the diagnostic criteria of SWS. The presence of this mutation in affected skin does not indicate whether leptomeningeal involvement is also present. Brain MRI continues to be the most practical evaluation for classical SWS in children who have port wine stain but with no clinical neurologic manifestations yet evident.

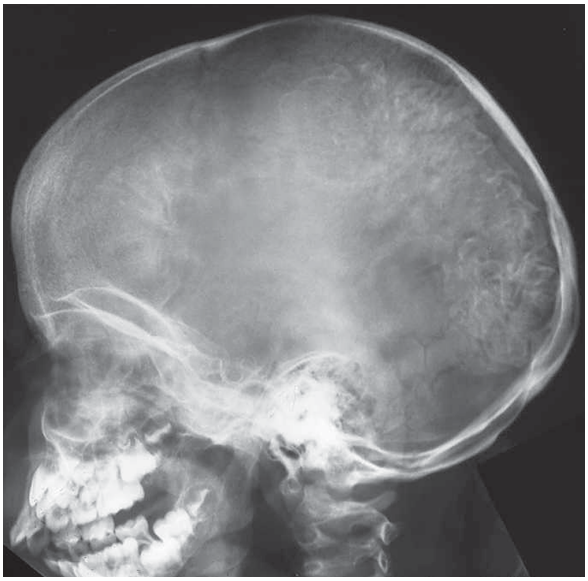


Figure 72.7 *Radiograph Showing Tram-Track Sign. Calcification of leptomeningeal angiomatosis seen in Sturge-Weber syndrome.*

(Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.)

- The diagnosis of SWS is based on the cutaneous and neurologic findings.

Treatment

There is no cure for SWS. Treatment is based on disease manifestations. Neurologic treatment is aimed at seizure management, as well as identification and optimization of any associated neurodevelopmental delays or disabilities and the treatment of migraines. Ophthalmic surveillance for glaucoma should be performed.

In newborns with cutaneous manifestations of SWS, neurologic and ophthalmologic evaluations should take place. Cutaneous findings may occur in isolation (SWS type II).

Genetic counseling is not required for this disease because it is caused by a sporadic somatic mutation. Therefore, even the offspring of persons affected with SWS should not be affected.

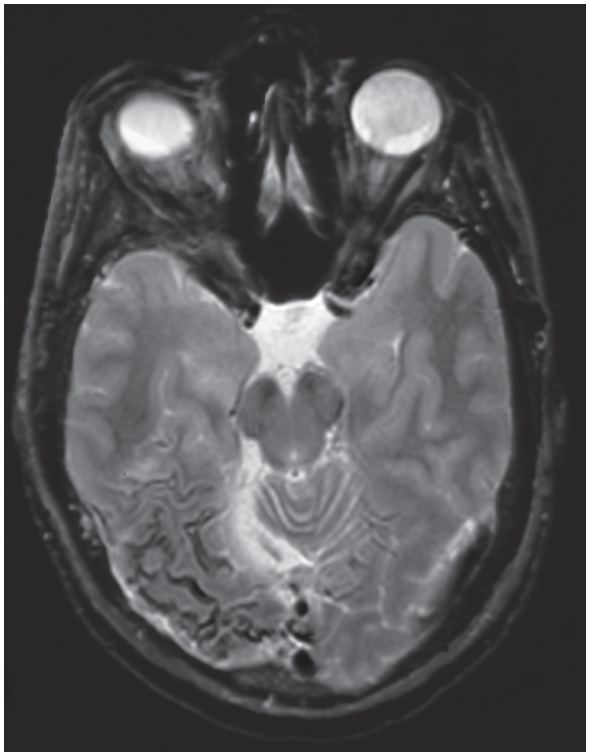


Figure 72.8 *Sturge-Weber Syndrome.*
Magnetic resonance imaging of the head of a 39-year-old woman with Sturge-Weber syndrome shows cortical calcification and atrophy involving the right posterior temporal and occipital lobes. Also present is cerebellar atrophy with prominent vessels superior to the right cerebellar hemisphere.
(Adapted from Lehwald LM, Flemming KD. Neurocutaneous syndromes. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 527–58. Used with permission of Mayo Foundation for Medical Education and Research.)

Linear Sebaceous Nevus Syndrome

Overview

Linear sebaceous nevus syndrome (LSNS) is a subgroup in a more broadly described condition of epidermal nevus syndrome. Epidermal nevi may occur in isolation or as part of a neurocutaneous disorder. These nevi are congenital hamartomas of embryonic ectodermal origin, classified according to their main component. When the main component is sebaceous, then LSNS may result. LSNS is a rare condition that affects skin, CNS, and eyes. Classically, the diagnosis is made from a triad of findings—linear sebaceous nevus, seizures, and mental retardation. The other subtypes of epidermal nevus syndrome are less likely to have neurologic manifestations.

Table 72.9 • Subtypes of Sturge-Weber Syndrome

Type	Facial Angiomatosis[a]	Leptomeningeal Angiomatosis[a]	Glaucoma[a]
I	+	+	+/–
II	+	–	+/–
III	–	+	+/–

[a] + indicates present; –, absent.

Epidemiologic Factors and Genetics

Epidemiologically, occurrence of epidermal nevi is relatively frequent, said to occur in 1 of 1,000 live births. Only a fraction of persons with epidermal nevi have involvement of other organ systems. One-third of the epidermal nevi are estimated to be sebaceous.

The genetic inheritance mode of LSNS is sporadic. Occurrence of this condition comes about through mosaicism due to a somatic mutation. This mutation is believed to be an autosomal dominant lethal mutation that can survive only as a somatic mutation. Somatic mutations in *HRAS* and *KRAS* are found in nevus sebaceous tissues. These RAS system mutations result in constitutive activation of MAPK and phosphatidylinositol-3 kinase/AKT signaling pathways, which have a role in cell growth regulation.

Clinical Manifestations

The classic presentation of LSNS is the triad of linear sebaceous nevi, seizures (including infantile spasm), and cognitive disability. Ocular (eg, coloboma, cataracts) and skeletal manifestations may be present as well.

Skin findings are plaques, patches, or nodules on the face, trunk, or proximal limbs; these findings typically are unilateral. Early in life, they may have a smooth yellow-orange appearance following the Blaschko lines. Involved scalp areas are marked by alopecia. With age, these plaques transition to a more verrucous and darkly pigmented appearance. A small percentage of patients with LSNS may have neoplasms of the skin, which are most often benign.

Diagnosis

The diagnosis of LSNS is based on the presence of a linear sebaceous nevus combined with neurologic manifestations. In children found to have such nevi, awareness of the possibility of other organ system involvement is important and should be evaluated appropriately. Diagnosis may be further supported by brain MRI findings. Cerebral MRI findings may be varied and include atrophy, dilated ventricles, cortical heterotopias, pachygyria, and even hemimegalencephaly.

Treatment

There is no cure for LSNS. Treatment consists of symptomatic care of its neurologic manifestations.

Incontinentia Pigmenti

Epidemiologic Factors and Genetics

Incontinentia pigmenti (IP) is a rare neurocutaneous disorder, so rare that its prevalence is unknown. Its name refers to melanin outside of melanocytes due to scarring in the ectoderm.

Genetics of IP shows an X-linked dominant mode of inheritance. This condition is related to mutations in the *IKBKG* gene, previously known as *NEMO.* The gene is located at Xq28. The gene protein functions in regulation of apoptosis. This X-linked dominant condition presents in girls and is lethal in most boys. The mechanism of lethality is unknown. When IP is seen in boys, disease can be related to mosaicism or XXY genotypes.

Clinical Manifestations

Cutaneous findings dominate the manifestations of IP, with variable other neurologic, ophthalmologic (retinal detachment), hair (alopecia or wooly and coarse traits), teeth (peglike), and nail findings. Skeletal abnormalities may also occur.

Skin findings evolve in stages. They manifest in early infancy and continue on into adulthood. In the first 8 weeks of life, they are blisterlike or bullous eruptions. These evolve to a wartlike hypertrophic rash and later into a "marble cake" appearance.

Neurologic manifestations are present in some patients with IP. Findings may include developmental delay, seizures, and intellectual disability; however, most patients with IP are intellectually normal.

Diagnosis

The diagnosis of IP is based primarily on the skin findings as the major criteria. Retinal, dental, hair, and skin findings serve as minor diagnostic criteria, the lack of which casts some doubt on the diagnosis in patients without a family history for IP.

MRI findings are detected in association with seizures, including polymicrogyria and neuronal heterotopia. Other reported CNS findings include dysgenesis of the corpus callosum, diffuse atrophy, hydrocephalus, and ischemic or hemorrhagic cerebrovascular changes.

Molecular genetic testing is available to confirm the diagnosis. Alternatively, skin biopsy showing characteristic findings of melanin deposits outside of melanocytes may assist in confirming the diagnosis.

Treatment

There is no cure for IP. Treatment is provided as needed for its various manifestations. Ongoing follow-up for ophthalmologic, neurologic, and dental findings is required. Genetic counseling for affected girls is indicated. In families with a history of IP, female infants should be screened for skin and retinal findings.

Hypomelanosis of Ito

Epidemiologic Factors and Genetics

Hypomelanosis of Ito (HI) is a relatively common neurocutaneous disorder. The presence of any vesicular or verrucous skin changes preceding hyperpigmentation in infancy is characteristic of IP, not HI. Genetic inheritance is sporadic and heterogeneous, with no 1 specific gene or chromosomal abnormality found that links to the diagnosis of HI. Mosaicism is found in about one-half of the affected patients and may involve any of the chromosomes, thus leading to varied phenotypes.

Clinical Manifestations

The classic presentation of HI is hypopigmentation of the skin along Blaschko lines. These macular regions may consist of a coalescence of smaller spots or streaks or whorls, typically running in narrow bands along the trunk. Buttocks and limbs may be affected as well. Palms, soles, and mucous membranes are generally spared. Other dermatologic manifestations can involve the hair. Scalp hair may show abnormalities of growth, color, and texture. Hypertrichosis may be seen on the face or even the genital area, without precocious puberty. In many patients, the skin changes alone may be seen. Nondermatologic manifestations are variable in HI.

Neurologic manifestations include cognitive and behavioral problems and seizures.

Diagnosis

The diagnosis of HI is based solely on the cutaneous findings of the pigmentary abnormalities along Blaschko lines. Diagnosis does not hinge on the presence of any extracutaneous manifestations.

Treatment

Treatment is aimed at symptoms. If familial occurrence of HI is noted in a patient, referral to a geneticist for further evaluation and genetic counseling is indicated.

Ataxia Telangiectasia

Ataxia telangiectasia is an autosomal recessive condition presenting with progressive ataxia and evidence of telangiectasias of the conjunctiva and pinna of the ear. Patients with ataxia telangiectasia may have other movement disorders, including choreoathetosis, dystonia, oculomotor apraxia, myoclonus, and tremor. Accompanying features include recurrent sinopulmonary infections and immunodeficiency. Patients also may be prone to ionizing radiation, with an increased risk of malignancy.

This condition is further discussed in Chapter 26, "Cerebellar Disorders and Ataxias."

73 Neurometabolic Disorders Associated With Disturbances of Small Molecule Metabolism[a]

DEBORAH L. RENAUD, MD

Introduction

Inborn errors of metabolism affect approximately 1 in 1,000 to 1 in 3,000 live births. Most of these inherited conditions are autosomal recessive, although a few are autosomal dominant or X-linked. Mitochondrial DNA disorders may be maternally inherited.

The clinical symptoms associated with inborn errors of metabolism are a reflection of the effects of a disruption of normal biochemical processes required for synthesis, breakdown, or transport of metabolites. This impairment leads to accumulation of metabolites that cause toxic effects, inadequate metabolite required for normal cellular activity, or secondary disruption of essential metabolic pathways. In general, small molecule disorders, involving the metabolism of amino acids, organic acids, carbohydrates, fatty acids, and other biochemical pathways, may present with acute exacerbations superimposed on long-term neurologic symptoms. The presence of acute biochemical disturbances, such as hypoglycemia, lactic acidosis (Figure 73.1), or hyperammonemia (Figure 73.2), is suggestive of an inborn error of metabolism in this clinical setting. Expanded newborn screening, which currently includes fatty acid oxidation defects and specific amino acid and organic acid disorders, has led to early diagnosis and treatment of these disorders.

Large molecule and organelle disorders, including lysosomal storage disorders, peroxisomal disorders, and mitochondrial disorders are covered in, Chapter 74 and Chapter 75.

- In general, small molecule disorders, involving the metabolism of amino acids, organic acids, carbohydrates, fatty acids, and other biochemical pathways, may present with acute exacerbations superimposed on long-term neurologic symptoms.

Disorders of Carbohydrate Metabolism

Selected disorders of carbohydrate metabolism are discussed herein and summarized in Table 73.1.

Pyruvate Dehydrogenase Complex Deficiency

Overview

Pyruvate dehydrogenase is a multienzyme complex. Deficiency of pyruvate dehydrogenase complex (PDHC) may be due to a defect in the E1 pyruvate decarboxylase α and β subunits, E2 transacetylase, E3 dihydrolipoamide

[a] Portions previously published in Renaud DL. Leukoencephalopathies associated with macrocephaly. Semin Neurol. 2012 Feb;32(1):34–41. Used with permission.

Abbreviations: AL, argininosuccinic acid lyase; ASL, argininosuccinate lyase; ASS, argininosuccinate synthetase; BCAA, branched chain amino acid; BCKA, branched chain α-ketoacid; BCKAD, branched α-ketoacid dehydrogenase; CBS, cystathionine β-synthase; CoA, coenzyme A; CPS, carbamoylphosphate synthase; CSF, cerebrospinal fluid; ETF, electron transfer flavoprotein; GAI, glutaric acidemia type I; GLUT1, glucose transporter 1; MMA, methylmalonyl–coenzyme A mutase; MRI, magnetic resonance imaging; MSUD, maple syrup urine disease; NMDA, *N*-methyl-D-aspartate; OTC, ornithine transcarbamylase; PDHC, pyruvate dehydrogenase complex; PKU, phenylketonuria

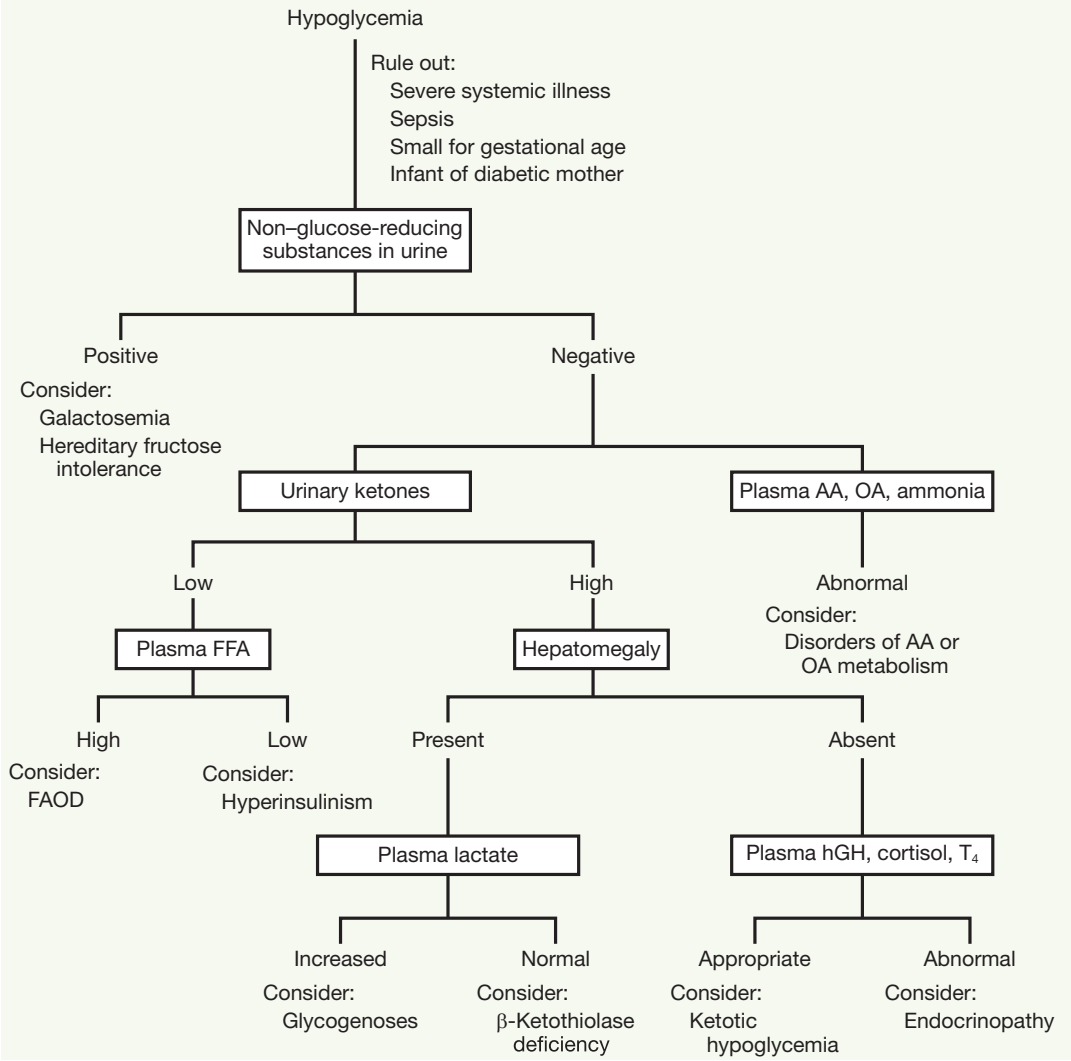


Figure 73.1 *Approach to Differential Diagnosis of Hypoglycemia.*
AA indicates amino acid; FAOD, fatty acid oxidation defect; FFA, free fatty acid; hGH, human growth hormone; OA, organic acid; T_4, thyroxine.
(Adapted from Clarke JTR. A clinical guide to inherited metabolic diseases. 3rd ed. Cambridge [United Kingdom]: Cambridge University Press; c2006. Chapter 4, Hepatic syndrome. p. 116–42. Used with permission.)

dehydrogenase, E3 binding protein (protein X), or the pyruvate dehydrogenase phosphatase component of the PDHC. E1 defects, the most common, are X-linked dominant; the other defects are autosomal recessive.

PDHC activity is a rate-limiting step in the aerobic oxidation of glucose by the brain. The degree of lactic acidemia correlates with the severity of the disease.

Clinical Presentation and Diagnosis

Severe lactic acidosis at birth is the hallmark of the fatal infantile lactic acidosis form. Less severe forms may present with Leigh disease or developmental delay associated with ataxia, muscular weakness, or retinal degeneration, or a combination.

Increased lactic acid, pyruvic acid, and alanine levels, with a lactate to pyruvate ratio less than 25, suggest a defect in the pyruvate dehydrogenase pathway or in one of the gluconeogenic enzymes. A consistently increased lactate to pyruvate ratio greater than 30 is suggestive of pyruvate carboxylase deficiency, a mitochondrial respiratory chain defect, or a Krebs cycle defect. Patients with E3 deficiency also have biochemical features of maple syrup urine disease (MSUD). Decreased PDHC enzyme activity in cultured skin fibroblasts is confirmatory.

Treatment

Treatment includes thiamine supplementation and ketogenic diet, as well as carnitine supplementation. Neurologic

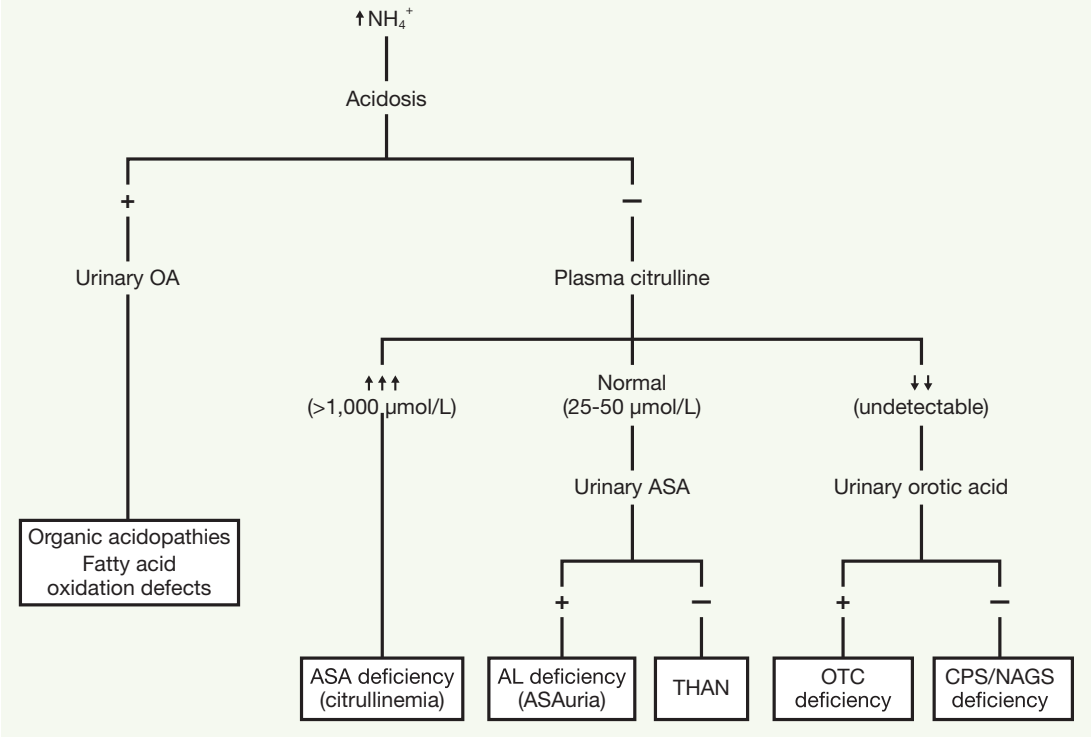


Figure 73.2 *Differential Diagnosis of Urea Cycle Defects in the Newborn.*
AL indicates argininosuccinic acid lyase; ASA, argininosuccinic acid synthetase; CPS, carbamoylphosphate synthetase I; NAGS, N*-acetylgutamate synthetase; OA, organic acid; OTC, ornithine transcarbamoylase; THAN, transient hyperammonemia of the newborn.*
(Adapted from Clarke JTR. A clinical guide to inherited metabolic diseases. 3rd ed. Cambridge [United Kingdom]: Cambridge University Press; c2006. Chapter 7, Acute metabolic illness in the newborn. p. 198–227. Used with permission.)

deficits are common despite early treatment. Differentiation of PDHC deficiency from pyruvate carboxylase deficiency is important because treatment with the ketogenic diet makes pyruvate carboxylase deficiency worse.

- Severe lactic acidosis at birth is the hallmark of the fatal infantile lactic acidosis form of pyruvate dehydrogenase complex deficiency.

GLUT1 Deficiency

Overview

Glucose transporter deficiency results from a defect in glucose transport across the blood-brain barrier due to decreased activity of glucose transporter 1 (GLUT1). Inheritance is autosomal dominant, with homozygous mutations producing a severe phenotype that is presumed to be embryonic lethal.

Table 73.1 • Comparison of Selected Disorders of Carbohydrate Metabolism

Disorder	Genetics and Pathophysiologic Factors	Clinical Presentation	Other Comments
Pyruvate dehydrogenase complex deficiency	X-linked dominant or AR Pyruvate dehydrogenase as the rate-limiting step in aerobic oxidation of glucose	Severe infantile form and childhood form Lactic acidosis Developmental delay Weakness +/− ataxia	Thiamine supplementation Ketogenic diet Carnitine supplementation
GLUT1 deficiency	AD Decreased GLUT1 glucose transport across blood-brain barrier	Seizure Encephalopathy Developmental delay Microcephaly Abnormal movements	Ketogenic diet Diagnosis: low glucose level in CSF

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CSF, cerebrospinal fluid; GLUT1, glucose transporter 1.

Clinical Presentation and Diagnosis

Severe forms present with infantile onset seizures and epileptic encephalopathy, developmental delay, deceleration of head growth with acquired microcephaly, abnormal involuntary movements, and spasticity. Milder forms have been described with exercise-induced movement disorders or absence epilepsy. A low glucose level (<40 mg/dL or <2.7 mmol/L) in cerebrospinal fluid (CSF) with a low CSF to blood glucose ratio (<0.45) and normal to low CSF lactate level in the presence of normal blood glucose is suggestive of GLUT1 deficiency. Molecular analysis is confirmatory.

Treatment

Treatment with the ketogenic diet improves seizures and other paroxysmal events but is less effective for improving the cognitive deficits.

- Glucose transporter deficiency results from a defect in glucose transport across the blood-brain barrier due to decreased activity of glucose transporter 1 (GLUT1).
- Signs suggestive of GLUT1 deficiency are a low glucose level (<40 mg/dL or <2.7 mmol/L) in cerebrospinal fluid (CSF) with a low CSF to blood glucose ratio (<0.45) and normal to low levels of CSF lactate, in the presence of normal blood glucose level.

Congenital Disorders of Glycosylation

Overview

Congenital disorders of glycosylation are characterized by a disturbance of various steps in glycoprotein biosynthesis in the cytoplasm, endoplasmic reticulum, and Golgi body. As a result of abnormal glycosylation, various proteins may be misfolded or mislocalized within the cell, including enzymes, transporters, membrane proteins, and hormones.

Clinical Presentation

Congenital disorders of glycosylation may present with a wide range of clinical symptoms involving virtually any organ system and with complex patient presentation. The analysis of glycosylation pattern through transferrin isoelectric focusing is used initially, followed with molecular analysis to determine the specific defect.

Disorders of Creatine Metabolism

Overview

Interconversion of creatine and phosphocreatine is catalyzed by creatine kinase, supplying phosphate for the conversion of adenosine diphosphatase to adenosine triphosphatase. Phosphocreatine and creatine, lost in creatinine formation, are replenished from the diet and de novo synthesis (approximately 50%). Creatine is actively transported across the blood-brain barrier by the X-linked sodium-dependent creatine transporter located on chromosome Xq28.

Three disorders of creatine metabolism have been described. The 2 synthesis enzyme defects—guanidinoacetate methyltransferase deficiency and arginine-to-glycine amidinotransferase deficiency—are autosomal recessive conditions. Creatine transporter defect is X-linked and affects boys more severely than girls. Low creatine levels are present in the brain in all forms. Blood and urine analyses of creatine and guanidinoacetate and molecular studies distinguish between the synthesis and transport defects.

Clinical Presentation and Diagnosis

Clinical symptoms of creatine disorders include hypotonia, developmental delay, autism, movement disorder, and seizures. Magnetic resonance imaging (MRI) may show abnormalities of the globus pallidi. Magnetic resonance spectroscopy shows absent or markedly decreased creatine peak.

Treatment

Treatment with oral creatine monohydrate can improve the magnetic resonance spectroscopy creatine peak in synthesis defects but does not significantly change the size of the creatine peak in patients with X-linked creatine transporter deficiency. Patients with synthesis defects treated with creatine monohydrate show improvement in development, extrapyramidal symptoms, and seizures, although the response may be incomplete in patients with guanidinoacetate methyltransferase deficiency due to an increased guanidinoacetate level. Treatment of X-linked creatine transporter defect is more challenging because of limited or absent transport of creatine across the blood-brain barrier.

- Clinical symptoms of creatine disorders include hypotonia, developmental delay, autism, movement disorder, and seizures.

Aminoacidurias

Overview

Amino acids are the building blocks of proteins, hormones, and enzymes. Amino acid disorders are caused by a defect in the metabolic pathway of amino acids. These disorders often present in infants. They also may present with seizures and developmental delay. Amino acid disorders may be associated with metabolic acidosis, hyperammonemia, and hypoglycemia. Newborns receive screening for many of these disorders to prevent serious sequelae. Quantitative plasma amino acids and urine organic acids also may aid

Table 73.2 • Comparison of Selected Aminoacidurias

Disorder	Genetics and Pathophysiologic Factors	Clinical Presentation	Other Comments
Phenylketonuria	AR	If untreated: developmental delay, seizures, hypopigmentation, microcephaly	Newborn screening
Homocystinuria	AR Cystathionine β-synthase deficiency	Developmental delay Seizures May have lens dislocation May have stroke or thrombosis	Increased homocysteine level in plasma and urine
Maple syrup urine disease	AR Branched α-ketoacid dehydrogenase complex deficiency	5 phenotypes Neonatal classic form: seizures, ketoacidosis, lethargy, reduced tone and feeding Intermediate form: developmental delay, seizures Intermittent form: episodic ataxia	Newborn screening
Nonketotic hyperglycinemia (glycine encephalopathy)	AR	Newborn: lethargy, hypotonia, apnea, seizures	Increased CSF glycine value

Abbreviations: AR, autosomal recessive; CSF, cerebrospinal fluid; GLUT1, glucose transporter 1.

the diagnosis. Selected aminoacidurias are described herein and summarized in Table 73.2.

Phenylketonuria

Overview

Classic phenylketonuria (PKU) is an autosomal recessive condition due to phenylalanine hydroxylase deficiency that occurs in 1 of 10,000 live births. This enzyme catalyzes the conversion of phenylalanine to tyrosine and requires tetrahydrobiopterin as a cofactor. Dihydrobiopterin reductase deficiency is a defect of tetrahydrobiopterin recycling, which results in variant PKU associated with impaired synthesis of L-dopa and 5-hydroxytryptophan (precursors of dopamine and serotonin synthesis).

Screening and Treatment

Newborn screening for PKU is widespread and has greatly improved outcome. All newborns with PKU identified through screening should be tested for disorders of tetrahydrobiopterin metabolism. Children treated from the neonatal period with a phenylalanine-restricted diet can have normal intelligence. Dietary treatment should be lifelong. Tetrahydrobiopterin-deficient forms of PKU are treated with a phenylalanine-restricted diet, L-dopa, 5-hydroxytryptophan, and folinic acid. If untreated, PKU results in developmental delay, seizures, hypopigmentation, and microcephaly. Inadequately treated maternal PKU during pregnancy can cause microcephaly and developmental delay in the newborn.

- If untreated, phenylketonuria results in developmental delay, seizures, hypopigmentation, and microcephaly.

Homocystinuria

Overview

Classic homocystinuria is associated with cystathionine β-synthase (CBS) deficiency. Increased methylation of homocysteine to methionine leads to the increased plasma and CSF levels of methionine in classic homocystinuria. Pyridoxine is a cofactor for CBS, and therefore patients with residual enzyme activity may respond to pyridoxine. Remethylation cycle defects, resulting in impaired conversion of homocysteine to methionine, include 5-methylene tetrahydrofolate reductase deficiency and disorders of cobalamin metabolism. Disorders of cobalamin E and cobalamin G result in isolated homocystinuria, whereas disorders of cobalamin C, cobalamin D, and cobalamin F result in combined homocystinuria and methylmalonic acidemia. Low methionine level is present in the remethylation disorders because of impaired conversion of homocysteine to methionine. All forms of homocystinuria are autosomal recessive and have increased plasma homocysteine and urine homocysteine levels (Figure 73.3).

Clinical Presentation

Clinical features of homocystinuria include developmental delay and seizures. Late-onset forms may present primarily with psychiatric manifestations. Ectopia lentis with downward dislocation of the lens is a common finding. Many patients have a marfanoid habitus, and early osteoporosis may result in fractures. Thromboembolism and stroke may occur at any age in someone with homocystinuria and are the most common cause of death.

Treatment

CBS deficiency is treated with pyridoxine for patients who respond to pyridoxine therapy and a

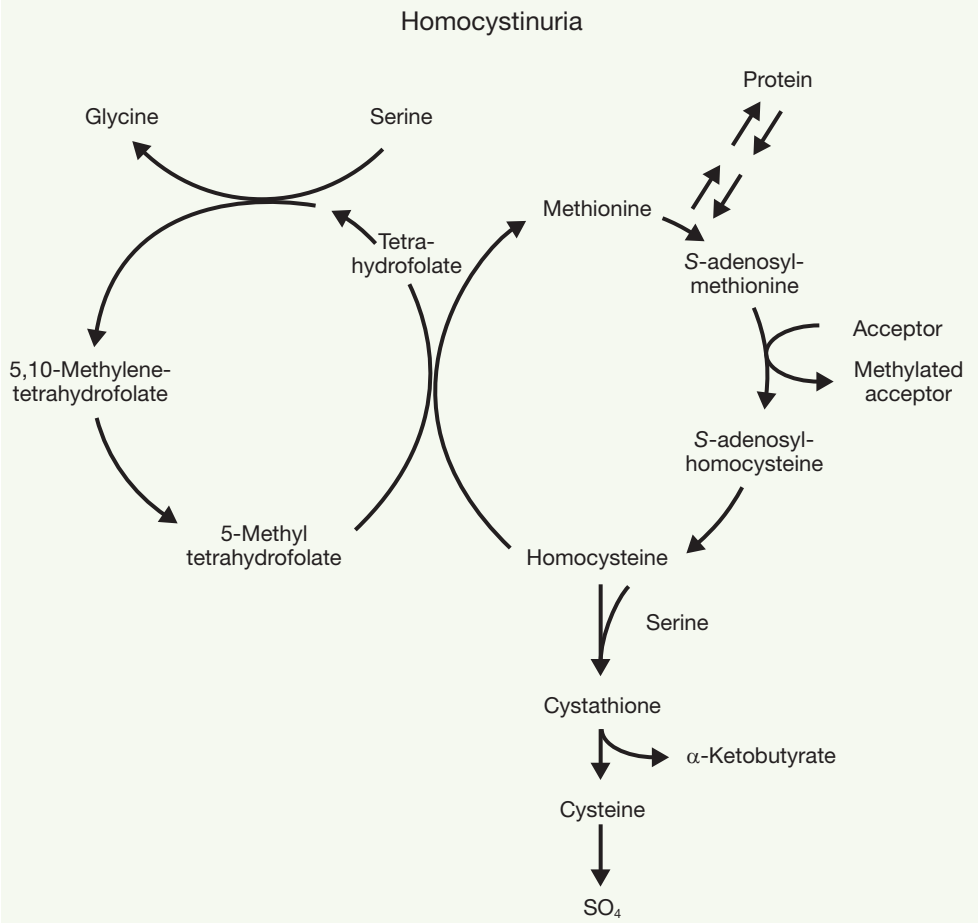


Figure 73.3 *Metabolic Pathways Indicated in Homocystinuria.*
(Adapted from Murali HR, Renaud DL. Inborn errors of metabolism. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 933–80. Used with permission of Mayo Foundation for Medical Education and Research.)

low-methionine, cysteine-supplemented diet. Remethylation defects are treated with hydroxycobalamin (vitamin B_{12}) and folinic acid in large doses. Betaine, which decreases total plasma homocysteine through conversion to methionine, is used in all forms. Clinical outcome is improved by aggressive treatment to decrease total plasma homocysteine.

- Clinical features of homocystinuria include developmental delay and seizures.
- Thromboembolism and stroke may occur at any age in a person with homocystinuria and are the most common cause of death.

Maple Syrup Urine Disease

Overview

MSUD is an autosomal recessive condition due to deficient activity of the branched chain α-ketoacid dehydrogenase (BCKAD) complex. This metabolic defect results in the accumulation of the branched chain amino acids (BCAAs) leucine, isoleucine, and valine and their corresponding branched chain α-ketoacids (BCKAs). The presence of alloisoleucine is diagnostic. Enzymatic and molecular confirmation is available; newborn screening for MSUD is available as well. The E3 form (dihydrolipoyl dehydrogenase deficiency) is a severe condition with combined deficiencies of BCKAD, pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase.

Clinical Presentation and Phenotypes

Five phenotypes have been described on the basis of clinical and biochemical features.

1. *Classic MSUD* is the most common and most severe form. Neonatal onset of lethargy, poor feeding, increased or decreased muscle tone, seizures, and ketoacidosis (with maple syrup odor) is typical.

Untreated classic MSUD results in progressive decerebrate posturing as a manifestation of dystonia, coma, and death. Prognosis is generally poor in this group, even with early treatment, because of recurrent metabolic decompensations.

2. *Intermediate MSUD* presents in late infancy or early childhood with developmental delay, seizures, and failure to thrive. Persistently increased levels of BCAAs, BCKAs, and alloisoleucine are present, but acute metabolic decompensations are unusual.
3. Children with *intermittent MSUD* have normal early development. Episodic ataxia and lethargy associated with ketoacidosis occur at the time of infection or stress. The biochemical profile is normal when asymptomatic but is typical of MSUD during acute episodes of metabolic decompensation.
4. Patients who have *thiamine-responsive MSUD* have a clinical course similar to the intermediate form of MSUD. Biochemically, BCAA and BCKA decrease in response to thiamine supplementation.
5. *Dihydrolipoyl dehydrogenase deficiency in MSUD* presents with lactic acidosis, failure to thrive, hypotonia, developmental delay, and movement disorder with progressive neurologic deterioration.

Treatment

Lifelong dietary treatment includes restriction of BCAA to normalize plasma levels of BCAA and provision of adequate calories and essential amino acids to promote normal growth. A trial of thiamine supplementation should be used to determine thiamine responsiveness. Aggressive treatment during metabolic crises and infections is important.

- Classic MSUD is the most common and most severe form. Neonatal onset of lethargy, poor feeding, increased or decreased tone, seizures, and ketoacidosis (with maple syrup odor) is typical.
- Lifelong dietary treatment includes restriction of branched chain amino acids (BCAAs) to normalize plasma levels of BCAAs and to provide adequate calories and essential amino acids to promote normal growth.

Nonketotic Hyperglycinemia (Glycine Encephalopathy)

Overview

The glycine cleavage system is a multienzyme complex with 4 protein components known as *P protein* (pyridoxal phosphate-dependent glycine decarboxylase), *H protein* (lipoic acid–containing protein), *T protein* (aminomethyltransferase), and *L protein* (lipoamide dehydrogenase). The most common enzyme to be defective is P protein. Glycine level is increased in the CSF and the ratio of cerebrospinal glycine to plasma is increased (>0.08 [normal, <0.02]). Glycine is an excitatory neurotransmitter acting through *N*-methyl-D-aspartate (NMDA) receptors in the brain.

All forms of nonketotic hyperglycemia are autosomal recessive. Variant forms have been described that have more variable clinical phenotypes and have CSF to plasma ratios of glycine between 0.02 and 0.08. Transient nonketotic hyperglycinemia of the newborn also has been described, presenting in a similar manner to classic nonketotic hyperglycinemia but with an improved outcome.

Clinical Presentation

The classic phenotype presents in the early newborn period, with progressive lethargy, hypotonia, and apnea leading to coma with ventilator dependence. Intractable seizures are common, and hiccups in utero may be described. Most children with this phenotype die in the neonatal period or survive with severe developmental delay and hypotonia that evolves to hypertonia. A burst suppression pattern is present in the neonatal period and can evolve to hypsarrhythmia later in infancy. Milder forms of nonketotic hyperglycinemia may present later in infancy or in early childhood with infantile spasms and developmental delay, as well as other neurologic symptoms.

Treatment

Treatment with sodium benzoate (which conjugates with glycine to form hippurate) and dextromethorphan (an NMDA receptor antagonist) may improve seizure control but does not improve development substantially. Treatment with benzoate should be accompanied with carnitine supplementation. Valproic acid, which inhibits the glycine cleavage system, should be avoided.

Urea Cycle Disorders

Overview

Hyperammonemia is a hallmark of disorders of urea cycle metabolism but also may be seen in organic acidopathies and fatty acid oxidation defects due to secondary inhibition of the urea cycle. Respiratory alkalosis in the presence of hyperammonemia is suggestive of a urea cycle defect. A presumptive diagnosis can be determined through quantitative analysis of amino acids in plasma and urine and measurement of orotic acid with confirmation through enzymatic or molecular analysis (Figure 73.2). X-linked ornithine transcarbamylase (OTC) deficiency is the most

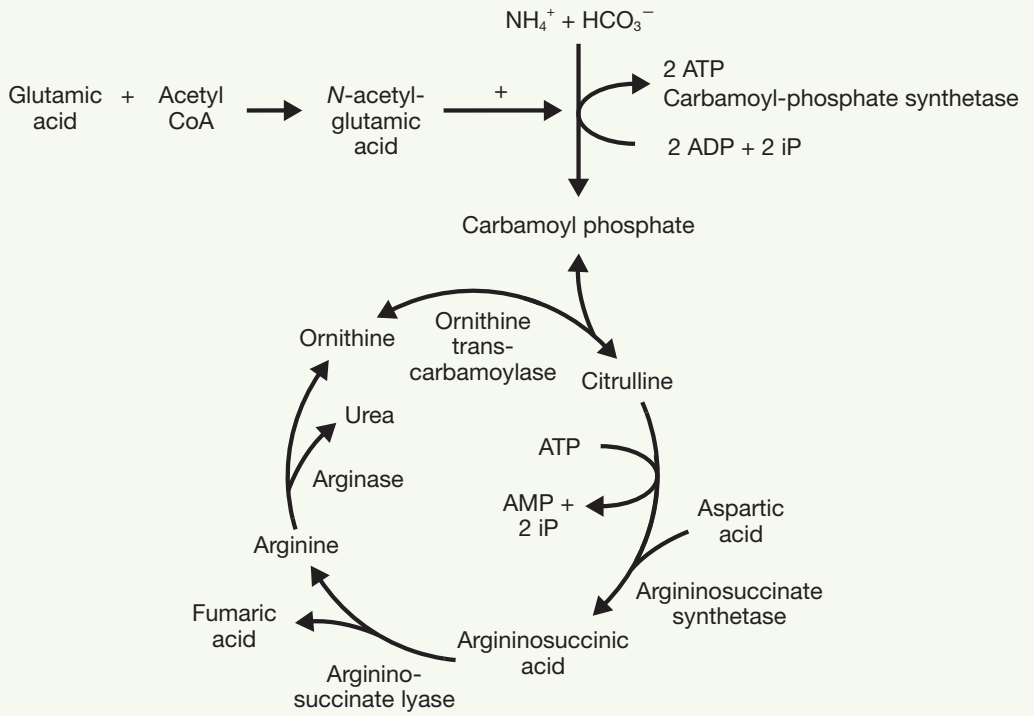


Figure 73.4 *Urea Cycle.*
ADP indicates adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; CoA, coenzyme A; iP, inorganic phosphorus.
(Adapted from Murali HR, Renaud DL. Inborn errors of metabolism. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 933–80. Used with permission of Mayo Foundation for Medical Education and Research.)

common urea cycle disorder and accounts for almost two-thirds of all patients with these disorders. All other conditions—including carbamoylphosphate synthase (CPS) deficiency, argininosuccinate synthetase (ASS) deficiency (also known as *citrullinemia*), arginosuccinate lyase (ASL) deficiency, and arginase deficiency—are autosomal recessive (Figure 73.4).

Clinical Presentation

Neonatal onset of OTC (usually in male infants), CPS, ASS, and AL deficiencies present with hyperammonemia, anorexia, encephalopathy, and respiratory alkalosis and evolve to coma and seizures. Symptoms typically occur between 24 and 72 hours of life. Unless treated early and aggressively, this form is frequently fatal because cerebral edema is present. Late-onset OTC, CPS, ASS, and AL deficiencies can present anytime in life. Children may have long-term symptoms of developmental delay, growth delay, and seizures. Episodes of acute decompensation associated with infections and high-protein meals present with hyperammonemia, vomiting, altered mental status, and ataxia. Female carriers of OTC deficiency may present postpartum with hyperammonemic encephalopathy or present with symptoms following consumption of high-protein meals. AL deficiency is distinguished by hepatomegaly and trichorrhexis nodosa in the late-onset form. Unlike the other urea cycle disorders, arginase deficiency does not cause symptoms in the newborn but rather presents with progressive spastic quadriplegia, seizures, and developmental delay. Hyperammonemia is less severe and is infrequent in arginase deficiency. Episodic encephalopathy can occur in newborns with partial deficiency of CPS and in female carriers of OTC deficiency.

Treatment

Prompt and aggressive treatment of acute hyperammonemia is critical. All dietary and parenteral sources of nitrogen intake must be discontinued, and intravenous fluids, consisting of 10% dextrose at 1.5 times the maintenance dose, should be started to provide 8 to 10 mg/kg/min of glucose. Intravenous administration of sodium benzoate, sodium phenylacetate, and arginine hydrochloride should be started as soon as possible to eliminate ammonia. Hemodialysis or peritoneal dialysis is indicated in the acute phase when hyperammonemia persists with these intravenous measures. Long-term treatment of urea cycle disorders consists of a low-protein diet with adequate calories for growth and an essential amino acid mixture. Citrulline supplementation is

needed for CPS and OTC deficiencies; arginine supplementation is needed for ASS and AL deficiencies. Long-term treatment with oral sodium benzoate and sodium phenylacetate is usually needed to prevent hyperammonemia. Liver transplantation may be an option for some patients who have neonatal onset OTC deficiency and CPS deficiency.

- Hyperammonemia is a hallmark of disorders of urea cycle metabolism but also may be seen in organic acidopathies and fatty acid oxidation defects because of secondary inhibition of the urea cycle.
- Neonatal onset of ornithine transcarbamylase deficiencies (usually in male infants) and carbamoylphosphate synthase, argininosuccinate synthetase, and arginosuccinate lyase deficiencies present with hyperammonemia, anorexia, encephalopathy, and respiratory alkalosis and evolve to coma and seizures.
- Episodes of acute decompensation associated with infections and high-protein meals present with hyperammonemia, vomiting, altered mental status, and ataxia.
- Prompt and aggressive treatment of acute hyperammonemia is critical.

Organic Acidurias

Overview

Organic aciduria results from accumulation of organic acid metabolites due to disorders in the metabolic pathways. Patients often present in infancy with poor feeding and lethargy, as well as developmental delay and, sometimes, seizures. Patients may have detectable metabolic acidosis, mild hyperammonemia, and ketosis. Episodic symptoms may be triggered by intercurrent illness or dehydration. Diagnosis is confirmed with quantitative analysis of plasma amino acids and qualitative assessment of urine organic acids. Table 73.3 summarizes selected disorders of organic acids.

- Patients with organic acidurias often present in infancy with poor feeding and lethargy, as well as developmental delay and, sometimes, seizures.
- Patients may have detectable metabolic acidosis, mild hyperammonemia, and ketosis.

Propionic Acidemia

Overview

Propionic acidemia is an autosomal recessive condition due to propionyl coenzyme A (CoA) carboxylase deficiency. Propionyl CoA carboxylase has α and β subunits and is biotin dependent. The enzyme converts propionyl CoA to methylmalonyl CoA. Deficiency results in the accumulation of propionyl CoA and its metabolites; ketosis; and hyperglycinemia. Hyperammonemia results from secondary inhibition of the urea cycle. Newborn screening has improved the early detection of propionic acidemia in infants.

Table 73.3 • Overview of Selected Organic Acidurias

Disorder	Genetics	Clinical Features	Other Comments
Propionic acidemia	AR Propionyl CoA carboxylase deficiency	Acute: lethargy, vomiting, hypotonia and seizures with metabolic acidosis Chronic, intermittent: episodic encephalopathy, vomiting, acidosis Chronic: developmental delay	Newborn screening
Methylmalonic acidemia	AR	Acute: lethargy, hypotonia, vomiting, seizures with metabolic acidosis Intermittent form: encephalopathy, vomiting, acidosis often triggered by infection or protein ingestion	May have immune defects May have hepatomegaly
Biotinidase deficiency	AR	Seizure, hypotonia, ataxia, developmental delay	Newborn screening
Glutaric acidemia type I	AR Glutaryl-CoA dehydrogenase	Microcephaly Encephalopathy (3–24 mo) precipitated by concurrent illness May have seizures	Striatal necrosis on MRI
Glutaric acidemia type II	AR Multiple acyl-CoA dehydrogenase deficiency	Congenital abnormalities Myopathy, vomiting, hypoglycemia, hepatomegaly	Hypoketotic hypoglycemia Metabolic acidosis

Abbreviations: AR, autosomal recessive; CoA, coenzyme A; MRI, magnetic resonance imaging.

Clinical Presentation

Acute presentation in the neonatal period consists of severe metabolic acidosis with vomiting, progressive lethargy, hypotonia, and seizures. Neutropenia is common at diagnosis. The chronic intermittent form presents with episodes of encephalopathy, vomiting, ketoacidosis, and dehydration, particularly in the setting of infection or protein ingestion. Long-term neurologic features include developmental delay, hypotonia, and failure to thrive. Long-term sequelae include cardiomyopathy, osteoporosis, and pancreatitis. MRI may show bilateral basal ganglia involvement associated with dystonia clinically.

Treatment

A low-protein diet with restricted amounts of valine, isoleucine, methionine, and threonine is the cornerstone of long-term treatment. Episodes of ketoacidosis should be treated with protein restriction, sodium bicarbonate, carnitine, and glucose. Carnitine supplementation should be provided to help with excretion of carnitine esters and to prevent carnitine depletion. Metronidazole or neomycin may be used to decrease propionate and ammonia production by gut bacteria.

Methylmalonic Acidemia

Overview

Methylmalonyl-CoA mutase (MMA) converts L-methylmalonyl-CoA to succinyl-CoA, which enters the tricarboxylic acid cycle. Vitamin-B_{12} (adenosylcobalamin) is required as the cofactor. MMA deficiency can be complete (mut^0) or partial (mut^-). Defects in the synthesis of adenosylcobalamin (eg, cobalamin A, cobalamin B) result in methylmalonic acidemia alone. Defects in the synthesis of adenosylcobalamin and methylcobalamin (cobalamin C and cobalamin D) and defective lysosomal transport of cobalamin (cobalamin F) result in MMA deficiency with homocystinuria. Increased urine homocystine with low serum methionine and normal cobalamin levels occur in cobalamin C, cobalamin D, and cobalamin F defects. All forms are autosomal recessive. Newborns of mothers with B_{12} deficiency may have mildly increased methylmalonic acid levels detected through newborn screening. Severe mutase deficiency (mut^0), cobalamin A, and cobalamin B present in a similar manner.

Clinical Presentation and Diagnosis

Acute presentation in the neonatal period consists of severe metabolic acidosis with vomiting, progressive lethargy, hypotonia, and seizures. Pancytopenia and immune dysfunction are common at the time of diagnosis. The chronic intermittent form presents with episodes of encephalopathy, vomiting, ketoacidosis, and dehydration, particularly in the setting of infection or protein ingestion. Long-term neurologic features include developmental delay, hypotonia, and failure to thrive. Long-term sequelae include hepatomegaly, nephropathy, and pancreatitis. MRI may show bilateral basal ganglia involvement associated with dystonia clinically.

Treatment

Episodes of metabolic acidosis should be treated with protein restriction and with sodium bicarbonate, carnitine, and glucose. Hydroxocobalamin supplementation is important for all forms of MMA deficiency. Low-protein diet with restricted amounts of valine, isoleucine, methionine, and threonine is used for patients who have insufficient response to B_{12}, but it is not indicated for patients who have a response to B_{12} treatment, especially those with combined MMA deficiency and homocystinuria. Carnitine supplementation should be provided to help with excretion of carnitine esters and to prevent carnitine depletion. Betaine is used for treatment of homocystinuria. Metronidazole or neomycin may be used to decrease methylmalonate and propionate metabolite production by gut bacteria.

Disorders of Biotin Metabolism

Multiple Carboxylase Deficiency

Multiple carboxylase deficiency is a rare autosomal recessive condition due to holocarboxylase synthetase deficiency. Defective function of several biotin-dependent enzymes, including acetyl CoA carboxylase, propionyl CoA carboxylase, 3-methyl crotonyl CoA carboxylase, and pyruvate carboxylase, leads to an accumulation of BCAAs and organic acidemia. These enzymes have important roles in gluconeogenesis, fatty acid synthesis, and amino acid catabolism. Children often present in the neonatal period with metabolic acidosis, lethargy, hypotonia, and seizures. Prognosis improves with high-dose biotin supplementation.

Biotinidase Deficiency

Biotinidase deficiency (prevalence rate of 1 in 60,000–100,000 persons) is an autosomal recessive disorder of biotin recycling. Clinical and biochemical findings are similar to those in multiple carboxylase deficiency but may be milder and have later onset. Newborn screening for biotinidase deficiency has been instituted in most US states. Characteristic organic acids are associated with decreased levels of biotinidase in the serum and leukocytes. Children whose biotinidase deficiency is not detected in the newborn period present with seizures, hypotonia, ataxia, and developmental delay. Common signs are alopecia and an eczemalike rash that is difficult to treat. Treatment with biotin replacement improves clinical symptoms. Untreated biotinidase deficiency leads to chronic cerebellar degeneration.

Glutaric Acidemia Type I

Overview

Glutaric acidemia type I (GAI) is an autosomal recessive disorder (prevalence rate of 1 in 30,000 persons) due to a

deficiency of glutaryl-CoA dehydrogenase. Deficiency of this mitochondrial enzyme results in accumulation of glutaric acid and 3-hydroxyglutaric acid in the blood, urine, and CSF.

Clinical Presentation

Macrocephaly is present at birth or within the first few weeks of life. Most children with GAI present with an acute encephalopathic crisis between 3 and 24 months of age in the setting of an infection or illness with dehydration. Behavioral arrest is accompanied by either severe hypotonia or diffuse rigidity. Associated symptoms include decreased level of consciousness, seizures, and dystonia. After the acute event, most children have residual dystonia of variable severity, which is difficult to treat. Intelligence is relatively preserved.

Children who do not experience an acute encephalopathic crisis may present with a slowly progressive neurologic disorder with seizures, physical disability, and fasting hypoglycemia.

Diagnosis

Newborn screening with tandem mass spectrometry to measure glutarylcarnitine (C5DC) from dried blood spots is available. The screening can identify newborns with GAI who are at risk for acute striatal necrosis, and implementation of prospective treatment has improved neurologic outcome. DNA-based newborn screening is used for populations known to excrete small amounts of glutaric acid.

Characteristic MRI findings of GAI include widening of the Sylvian fissure, decreased opercularization of the insula, mild ventriculomegaly, and expansion of CSF spaces anterior to the temporal lobes. Patients may be prone to acute subdural hematomas, which may be accompanied by retinal hemorrhages, raising suspicion of nonaccidental trauma. Acute striatal necrosis presents with swelling and necrosis in the putamen initially and with spreading to the adjacent caudate nuclei and globus pallidus. White matter changes in GAI involve the periventricular white matter primarily.

Increased levels of glutaric acid and 3-hydroxyglutaric acid in the urine organic acids is suggestive of biochemical diagnosis of GAI, although patients who excrete small amounts of glutaric acid may have normal or intermittent abnormalities in the urine. The finding of C5DC on acylcarnitine analysis may be hampered by carnitine deficiency, which is commonly present in children with GAI. Analysis of glutaryl-CoA dehydrogenase activity in fibroblasts or leukocytes is diagnostic and may be followed with molecular DNA analysis.

Treatment

Treatment of GAI consists of both emergency therapy for episodes of acute encephalopathy and maintenance therapy. The first principle of emergency treatment is avoidance of delay in initiation of outpatient disease management during illnesses or in association with immunizations or surgical procedure. High-energy fluids should be initiated to prevent catabolism and maintain hydration. Protein intake should be stopped or decreased to limit the production of potentially toxic glutaric acid and 3-hydroxyglutaric acid. Carnitine supplementation should be doubled to augment physiological detoxification and prevent secondary carnitine deficiency. If neurologic signs such as lethargy develop or oral treatment is not feasible, then emergency department treatment with intravenous fluids, glucose, and carnitine should be initiated without delay.

Maintenance treatment for GAI consists of dietary and pharmacologic therapies. Dietary protein is restricted to age-appropriate daily requirements using natural protein, specialized lysine-free low-tryptophan formula, and essential amino acid formula. Carnitine supplementation of 50 to 100 mg/kg/day should be lifelong. Currently, no evidence indicates that supplementation with riboflavin, creatine, or antioxidants is beneficial. Treatment of neurologic complications includes use of benzodiazepines, baclofen, anticholinergics, or botulinum toxin for dystonia and anticonvulsants for seizures. Valproic acid, which can deplete carnitine, should be avoided.

Outcome is more severe when the striatal injury is acquired at an earlier age. Basal ganglia injury occurs in 85% to 94% of children who did not have a diagnosis before the acute crisis but is decreased to 35% in children prospectively treated because of early diagnosis.

- Most children with glutaric acidemia type I present with an acute encephalopathic crisis between 3 and 24 months of age in the setting of an infection or illness with dehydration.

Glutaric Acidemia Type II

Glutaric acidemia type II, also called *multiple acyl-CoA dehydrogenase deficiency*, is a rare autosomal recessive condition due to a defect in electron transfer from flavoprotein dehydrogenases to the respiratory chain, resulting in functional deficiency of multiple enzymes. Electron transfer flavoprotein (ETF) and ETF–ubiquinone oxidoreductase are nuclear encoded proteins through which electrons are transferred to ubiquinone in the respiratory chain.

Inherited defects of either protein cause glutaric acidemia type II, which presents with hypoketotic hypoglycemia and metabolic acidosis. Severe forms may be associated with multiple congenital anomalies. Milder forms may present at any age with episodic vomiting, hypoglycemia, hepatomegaly, and proximal myopathy.

Increased organic acid levels in a characteristic pattern in the clinical setting of hypoketotic hypoglycemia and metabolic acidosis are suggestive of this disorder. Specific diagnosis is through fibroblast analysis of ETF and ETF–ubiquinone oxidoreductase activity.

No effective treatment is available for patients who present in early infancy. A diet restricted in fat and protein, in conjunction with treatment with riboflavin and L-carnitine, may be helpful in patients who are less severely affected.

L-2-Hydroxyglutaric Aciduria

Overview

L-2-hydroxyglutaric aciduria is a rare autosomal recessive disorder caused by mutations in both alleles of the *L2HDGH* gene, resulting in deficiency of L-2-hydroxyglutarate dehydrogenase activity. L-2-hydroxyglutarate dehydrogenase is a flavin adenine nucleotide–linked mitochondrial enzyme that converts L-2-hydroxyglutarate to α-ketoglutarate.

Clinical Presentation

Clinically, L-2-hydroxyglutaric aciduria presents with variable degrees of psychomotor and speech delay, followed by a slowly progressive neurodegenerative disorder with cognitive decline. Slowly progressive ataxia presents with ataxic gait, intention tremor, and dysarthria. Mild pyramidal signs with increased deep tendon reflexes and spasticity eventually develop, with mild extrapyramidal signs that include dystonia. Macrocephaly and seizures are frequently described. An increased risk of brain tumors has been associated with L-2-hydroxyglutaric aciduria.

Diagnosis

MRI findings are characteristic and consist of abnormal signal intensity, with low signal on T1-weighted images and increased signal on T2-weighted images, in the subcortical white matter bilaterally and with frontal predominance. Involvement of the globus pallidus, caudate, and putamen bilaterally, as well as the dentate nucleus, is characteristic at all stages. Cerebellar and brainstem white matter is not involved.

Biochemically, L-2-hydroxyglutaric aciduria presents with notably increased levels of L-2-hydroxyglutaric acid in the urine and CSF. Plasma amino acid analysis shows increased lysine values.

Fatty Acid Oxidation Disorders

Overview

Triglycerides (glycerols with 3 fatty acids) provide a more efficient energy store than glycogen. Free fatty acids can be metabolized in muscle through fatty acid oxidation as a source of energy. Free fatty acids bound to albumin cannot pass through the blood-brain barrier and are converted to ketones in the liver for use by the brain. Fatty acid oxidation disorders can be divided into plasma membrane carnitine transporter deficiency, carnitine cycle disorders, and defects of fatty acid oxidation (Table 73.4).

Clinical Presentation

Clinical presentations suggestive of a fatty acid oxidation disorder include acute decompensation associated with febrile illness or fasting, hypoketotic hypoglycemia, Reye syndrome, chronic proximal myopathy, hypotonia, recurrent myoglobinuria (associated with prolonged exercise or febrile illness), hepatomegaly with steatosis, and cardiomyopathy. Sudden death and sudden infant death syndrome have been described, and a family history of these conditions should prompt investigation for fatty acid oxidation disorders.

Treatment

Treatment of acute decompensation with hypoketotic hypoglycemia consists of intravenous glucose or dextrose at 8 to 10 mg/kg/min (ie, 10% dextrose at 1.5 times the maintenance fluids). Long-term treatment includes exercise management with avoidance of prolonged exercise and cornstarch drinks before exercise and the prevention of prolonged fasting. Fasting at the time of anesthesia should be avoided and continuous glucose provided whenever fasting. Rhabdomyolysis-precipitating drugs, such as aspirin and valproic acid, should be avoided.

- Clinical presentations suggestive of a fatty acid oxidation disorder include acute decompensation associated with febrile illness or fasting, hypoketotic hypoglycemia, Reye syndrome, chronic proximal myopathy, hypotonia, recurrent myoglobinuria (associated with prolonged exercise or febrile illness), hepatomegaly with steatosis, and cardiomyopathy.
- Rhabdomyolysis-precipitating drugs, such as aspirin and valproic acid, should be avoided in treatment of fatty acid oxidation disorder.

Disorders of Nucleic Acid Metabolism (Purines and Pyrimidines)

Lesch-Nyhan Syndrome

Boys are primarily affected by this rare X-linked disorder, which results from a deficiency of hypoxanthine-guanine phosphoribosyltransferase, the rate-limiting step in the salvage pathway of purine degradation. Most boys who have Lesch-Nyhan syndrome present in infancy with variable developmental delay leading to debilitating neurologic disability, dystonia, choreoathetosis, dysphagia, dysarthria,

Table 73.4 • Classification of Disorders of Fatty Acid Oxidation

Disorder	Enzyme Defect	Clinical Features
Carnitine cycle disorders		
Plasma membrane carnitine transporter deficiency	Sodium ion-dependent carnitine transporter	Myopathy, rhabdomyolysis, cardiomyopathy, hypoglycemia, hepatomegaly, sudden death
CPT I deficiency	Carnitine palmitoyltransferase I	Hepatomegaly, hypoglycemia, encephalopathy but **no** myopathy or cardiomyopathy
CPT II deficiency	Carnitine palmitoyltransferase II	Myopathy, exercise intolerance, rhabdomyolysis (cardiomyopathy or arrhythmias)
Carnitine-acylcarnitine translocase deficiency	Carnitine-acylcarnitine translocase	Hyperammonemia, hypoglycemia, cardiac arrhythmias, hypotonia
Fatty acid oxidation disorders		
VLCAD deficiency	Very long-chain acyl-CoA dehydrogenase	Myopathy, rhabdomyolysis, cardiomyopathy, hepatomegaly, hypoglycemia
LCAD deficiency	Long-chain acyl-CoA dehydrogenase	Myopathy, rhabdomyolysis, cardiomyopathy, hypoglycemia
MCAD deficiency	Medium-chain acyl-CoA dehydrogenase	Hypoketotic hypoglycemia, Reye syndrome–like episodes, sudden death, **no** myopathy
SCAD deficiency	Short-chain acyl-CoA dehydrogenase	Myopathy, failure to thrive, acidosis, progressive developmental delay
Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II)	ETF or ETF-Qo	Myopathy, hepatomegaly, hypoglycemia, acidosis, facial dysmorphism, multiple congenital abnormalities, cardiomyopathy
Trifunctional protein or LCHAD deficiency	Trifunctional protein/long-chain hydroxyacyl-CoA dehydrogenase	Myopathy, rhabdomyolysis, cardiomyopathy, hepatic dysfunction, hypoglycemia, neuropathy, pigmentary retinopathy
SCHAD deficiency	Short-chain hydroxyacyl-CoA dehydrogenase	Myopathy, cardiomyopathy, sudden death ketotic hypoglycemia, hepatic dysfunction

Abbreviations: CoA, coenzyme A; CPT I, carnitine palmitoyltransferase I; CPT II, carnitine palmitoyltransferase II; ETF, electron transfer flavoprotein; ETF-Qo, electron transfer flavoprotein–coenzyme Q oxidoreductase; LCAD, long-chain acyl–coenzyme A dehydrogenase; LCHAD, long-chain hydroxyacyl–CoA dehydrogenase; MCAD, medium-chain acyl–coenzyme A dehydrogenase; SCAD, short-chain acyl–coenzyme A dehydrogenase; SCHAD, short-chain hydroxyacyl–coenzyme A dehydrogenase; VLCAD, very long-chain acyl–coenzyme A dehydrogenase.

spasticity, and seizures. Severe self-mutilation behavior is characteristic.

Hyperuricemia is suggestive of diagnosis in the appropriate clinical setting. Hypoxanthine-guanine phosphoribosyltransferase activity is confirmatory in peripheral lymphocytes or cultured fibroblasts.

Management includes a purine-restricted diet, maintenance of adequate hydration to prevent uric acid stones, and allopurinol therapy to block overproduction of uric acid. Supportive care includes measures to prevent self-harm.

- Boys are primarily affected by Lesch-Nyhan syndrome, a rare X-linked disorder.
- Severe self-mutilation behavior is characteristic in Lesch-Nyhan syndrome.

Dihydropyrimidine Dehydrogenase Deficiency

This autosomal recessive condition results from a deficiency of dihydropyrimidine dehydrogenase, the rate-limiting step in the degradation of the pyrimidines uracil and thymidine. Accumulation of these metabolites results in a variable degree of developmental delay, seizures, and hypotonia. Milder cases and disease carriers may have toxicity associated through treatment with 5-fluorouracil.

Porphyria

Overview

Acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria are autosomal dominant conditions, whereas 5-aminolevulinic acid dehydratase–deficient porphyria is autosomal recessive. The prevalence of acute intermittent porphyria is approximately 1 in 20,000 persons. These 4 acute hepatic porphyrias cause neurologic disease and have similar clinical features.

Clinical Features

Acute attacks usually occur after puberty, generally in the third or fourth decade, and present with severe abdominal

Table 73.5 • Porphyrias

Disease	Deficient Enzyme	Inheritance	Clinical Features	Diagnosis
5-Aminolevulinic acid dehydratase-deficient porphyria (ADP)	5-Aminolevulinic acid dehydratase	Autosomal recessive	Abdominal pain, peripheral neuropathy, increased susceptibility to lead poisoning	Normal urinary PBG in the presence of increased urinary ALA and coproporphyrin Markedly decreased erythrocyte ALAD activity
AIP	Porphobilinogen deaminase partial deficiency	Autosomal dominant	Abdominal pain, acute neuropathy, seizures, autonomic dysfunction	Marked increase in PBG Markedly increased urinary excretion of ALA and PBG
Hereditary coproporphyria	Coproporphyrinogen oxidase partial deficiency	Autosomal dominant	Same as for AIP	Marked increase in urinary and fecal coproporphyrin III
Variegate porphyria	Protoporphyrinogen oxidase deficiency	Autosomal dominant	Same as for AIP	Fecal protoporphyrin, coproporphyrin III, and urinary coproporphyrin III are markedly increased during active disease Increased urinary ALA and PBG

Abbreviations: AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALAD, 5-aminolevulinic acid dehydrase; PBG, porphobilinogen.

Adapted from Murali HR, Renaud DL. Inborn errors of metabolism. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester (MN): Mayo Clinic Scientific Press and Florence (KY): Informa Healthcare USA; c2007. p. 933–80. Used with permission of Mayo Foundation for Medical Education and Research.

pain and other gastrointestinal problems, urinary retention, and urine that is dark red or the color of port wine. Seizures are common, particularly in association with hyponatremia. Features of sympathetic overactivity or autonomic instability may be present. Severe anxiety, insomnia, depression, disorientation, hallucinations, and paranoia can occur during acute attacks. Precipitating factors that incite acute attacks are most often drugs: barbiturates, sulfonamides, analgesics, nonbarbiturate hypnotics, anticonvulsants, and female sex hormones. Fasting or malnutrition, stress, infection, smoking, and alcohol consumption also may precipitate an acute attack.

Long-term neurologic characteristics include primarily motor axonal peripheral neuropathy, symmetrical proximal muscle weakness, and neuropathy of the tenth and seventh cranial nerves. Photosensitivity and skin manifestations are the main clinical features of the other types of porphyria (Table 73.5).

Treatment

Management includes prompt treatment of intercurrent illnesses; adequate nutritional intake and avoidance of precipitating drugs may help prevent porphyria attacks. Heme therapy (ie, hematin, heme albumin, or heme arginate) and carbohydrate loading repress hepatic 5-aminolevulinic acid synthase and reduce urinary 5-aminolevulinic acid and porphobilinigen. These are considered specific therapies for acute porphyrias. Protection from sunlight is necessary for photosensitivity.

- Acute attacks of porphyria usually occur after puberty, generally in the third or fourth decade, and present with severe abdominal pain and other gastrointestinal problems, urinary retention, and urine that is dark red or the color of port wine.
- Long-term neurologic characteristics of porphyria include primarily motor axonal peripheral neuropathy, symmetrical proximal muscle weakness, and neuropathy at the tenth and seventh cranial nerves.
- Management of porphyria includes prompt treatment of intercurrent illnesses; adequate nutritional intake, and avoidance of precipitating drugs may help prevent porphyria attacks.

74 Lysosomal Storage Disorders

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Introduction

Lysosomes degrade macromolecules such as glycosphingolipids, glycoproteins, and glycosaminoglycans. Lysosomal storage diseases are a heterogeneous group of disorders resulting from intracellular accumulation of substrates. Mechanisms of lysosomal storage disorders include primary deficiency of specific hydrolases, defects in activator protein required for enzyme-substrate interaction in posttranslational modification of enzymes or in transport of the substrate from lysosomes, or abnormalities of fusion between autophagic vacuoles and lysosomes. Substrate accumulation is slowly progressive, leading to significant morbidity and mortality.

Lysosomal storage disorders are clinically, enzymatically, and genetically heterogeneous and affect 1 in 6,000 live births. Classification according to the nature of the stored substances (sphingolipidoses, mucopolysaccharidoses (MPS), mucolipidoses, oligosaccharidoses, glycogen storage diseases, and lipid storage disorders) offers a biochemical organization. Categorizing by age of onset and according to phenotypic expression offers a practical means for directing the evaluation of patients with a suspected lysosomal storage disorder.

Treatment is symptomatic and supportive. Enzyme replacement therapy is available commercially for Gaucher disease, Fabry disease, and MPS I, II, and VI. Genetic testing and prenatal diagnosis are possible for most sphingolipidoses, which allow for genetic counseling. Lysosomal storage disorders are autosomal recessive in inheritance except for Fabry, Hunter (MPS II), and Danon diseases, which are X-linked recessive.

- Lysosomes degrade macromolecules such as glycosphingolipids, glycoproteins, and glycosaminoglycans.
- Classification according to the nature of the stored substances (sphingolipidoses, mucopolysaccharidoses, mucolipidoses, oligosaccharidoses, glycogen storage diseases, and lipid storage disorders) offers a biochemical organization.
- Enzyme replacement therapy is available commercially for Gaucher disease, Fabry disease, and mucopolysaccharidoses I, II, and VI.
- Lysosomal storage disorders are autosomal recessive in inheritance except for Fabry, Hunter, and Danon diseases, which are X-linked recessive.

Sphingolipidoses

Sphingolipids are essential components of myelin and include gangliosides, glucocerebroside, sphingomyelin, galactocerebroside, sulfatide, and trihexoside. Sphingolipidoses present with symptoms of central or peripheral nervous system degeneration and systemic features such as hepatosplenomegaly and skeletal deformities.

Gangliosidoses

Gangliosidoses are caused by enzyme deficiencies leading to accumulation of gangliosides (glycosphingolipids containing varying amounts of monosaccharides and sialic acid) in multiple organs, especially the brain.

GM1 Gangliosidosis

GM1 gangliosidosis is caused by deficiency of the enzyme β-galactosidase. Periodic acid-Schiff (PAS)–positive lipid material accumulates in the neurons and visceral cells. Loss of neurons, gliosis, arrest of myelination, and cerebral atrophy occur with disease progression.

The classic infantile form manifests in healthy infants between 3 and 6 months of age, who then present with

Abbreviations: MPS, mucopolysaccharidosis; PAS, periodic acid-Schiff

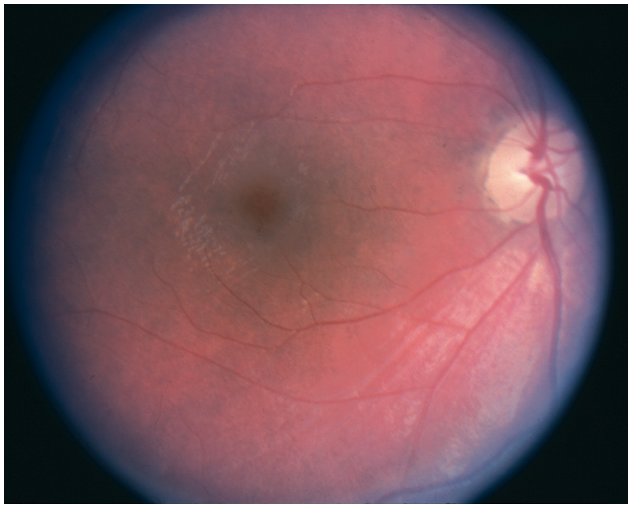

Figure 74.1 *Cherry-Red Spot.*
This spot was observed on ophthalmoscopic examination of a patient with Tay-Sachs disease.
(Courtesy of Brian R. Younge, MD, Mayo Clinic, Rochester, Minnesota. Used with permission.)

developmental regression. Typical features include progressive neurodegeneration with seizures, movement disorder, initial hypotonia that rapidly progresses to spasticity, cherry-red spot on funduscopy (Figure 74.1), hepatosplenomegaly, and early death. Coarse facies and dysostosis multiplex can be seen.

Neuroimaging shows diffuse cerebral atrophy and delayed myelination. The late infantile or juvenile forms have variable age of onset, progressive neurodegeneration, and early dementia. Cherry-red spot is usually absent. Skeletal dysplasia has been described. In the adult-onset form, progressive gait disorder and spasticity occur. Confirmatory diagnosis is based on a deficiency of β-galactosidase in leukocytes or cultured fibroblasts and/or detection of mutation in the *GLB1* gene; there is relative deficiency of the enzyme in juvenile and adult forms. Treatment is supportive.

GM2 Gangliosidosis

GM2 gangliosidoses are a group of inherited disorders caused by excessive accumulation of GM2 ganglioside in the central nervous system. Hydrolysis of GM2 ganglioside requires 2 isoenzymes of hexosaminidase (hexosaminidase A and B) and GM2 activator of hexosaminidase A, giving rise to different forms of GM2 gangliosidoses (Table 74.1).

Tay-Sachs disease is caused by mutation of the α subunit of hexosaminidase A. (Hexosaminidase A is composed of 1 α and 1 β subunit.) PAS-positive lipid-soluble material accumulates in the cortical neurons (ballooned neurons) and to a lesser degree in cerebellar Purkinje cells. Electron microscopy shows characteristic inclusion bodies called membranous cytoplasmic bodies. Disease progression results in neuronal loss, gliosis, arrest of myelination, and ectopic dendritogenesis. The classic infantile form was the most common phenotype prior to the institution of screening in the Ashkenazi population. Infants are healthy until about 2 to 6 months of age, after which regression is seen.

Table 74.1 • GM2 Ganglioside Storage Disease Phenotypes

Disorder	Age at Onset	Enzyme Defect
Tay-Sachs disease	3–6 mo	Hexosaminidase A
Sandhoff disease	3–6 mo	Hexosaminidase A and B
AB variant	3–6 mo	Activator
Juvenile GM2 gangliosidosis	2–6 y	Hexosaminidase A
Adult gangliosidosis	>6 y	Hexosaminidase A

Typical features include motor regression, progressive blindness, seizures, exaggerated startle reflex, and spasticity. Cherry-red spot and macrocephaly are present. Organomegaly is absent in Tay-Sachs disease. In the late infantile or juvenile forms, psychiatric presentation and early-onset dementia are common but cherry-red spot is absent. Adult-onset forms have slowly progressive motor neuron disease similar to spinocerebellar ataxia.

Sandhoff disease is caused by the deficiency of hexosaminidase A and B enzymes due to mutation in the β subunit. (Hexosaminidase A is composed of 1 α and 1 β subunit, and hexosaminidase B is composed of 2 β subunits.) Clinical presentation is similar to that of Tay-Sachs disease, but organomegaly is also present. Hexosaminidase A and B are normal in deficiency of activator AB. Neuroimaging in GM2 gangliosidoses shows severe diffuse cerebral atrophy. Confirmatory diagnosis is based on a deficiency of hexosaminidase A or both A and B in leukocytes or cultured fibroblasts. In juvenile and adult GM2 gangliosidoses, there is relative enzyme deficiency. Treatment is supportive.

Gaucher Disease

Gaucher disease is due to deficiency of β-glucocerebrosidase, resulting in accumulation of glucocerebrosides. It is most common in the Ashkenazi population. Three main disease variants exist (Table 74.2). Pathologic examination of bone marrow or central nervous system shows the presence of Gaucher cells (modified macrophages with striated cytoplasm). Definite diagnosis is based on reduced activity of β-glucocerebrosidase in lymphocytes (preferably) or leukocytes and/or detection of mutation in the gene that codes for β-glucocerebrosidase, *GBA*.

In addition to supportive therapy, enzyme replacement therapy with imiglucerase and substrate reduction therapy

Table 74.2 • Gaucher Disease Phenotypes

	Type 1 (95%)	Type 2 (1%)	Type 3 (4%)
Onset	Infancy/childhood/ adulthood	3–6 mo; can have neonatal presentation with hydrops fetalis	Childhood
Neurodegeneration with seizures	–	++++	+++
Hepatosplenomegaly	++++	+	+
Fractures/bone involvement	++++	–	+
Ethnicity	Ashkenazi	Panethnic	Norrbottnian Swedish

Abbreviations: ++++, commonly present; +, sometimes present; –, absent.

with miglustat are available for systemic diseases but do not affect the neurologic symptoms.

Niemann-Pick Disease (Types A and B)

Niemann-Pick disease (types A and B) results from deficiency of sphingomyelinase with progressive deposition of sphingomyelin, forming large foam cells mainly in the reticuloendothelial tissue. Ballooned ganglion cells in cerebellum, brainstem, and spinal cord are also seen.

Niemann-Pick disease type A (NPD-A) is a neurodegenerative disorder characterized by infantile onset (usually within the first 3 months of life), marked hepatosplenomegaly, failure to thrive, interstitial lung disease, cherry-red spot, and a rapid course to death, typically in the second year of life.

Niemann-Pick disease type B (NPD-B) was originally thought to have no neurologic manifestations and is characterized by hepatosplenomegaly, pulmonary infiltrates, and skeletal dysostosis. Disease course is one of slow progression. More recent studies have demonstrated neurologic involvement with cerebellar signs, intellectual disability, and macular cherry-red spots in patients with NPD-B. A spectrum of phenotypes between types A and B is now known. Treatment is supportive. Enzyme replacement therapy is undergoing clinical trials for NPD-B.

Fabry Disease

Fabry disease is an X-linked recessive disorder of glycosphingolipid catabolism resulting from deficiency of the enzyme α-galactosidase. Storage of ceramide trihexoside occurs within vascular endothelium. Foam cells with vacuolated cytoplasm are found in smooth, striated, and cardiac muscle; bone marrow; reticuloendothelial cells; and renal glomeruli.

Clinical manifestations include a multisystemic disorder starting in childhood (Table 74.3). Cognition is unaffected. Acroparesthesia, angiokeratomas, whorled corneal deposits, and posterior capsular cataracts are seen in young patients. In older patients, cerebral infarctions and hemorrhage are seen.

The disease is progressive if untreated, and death is usually due to renal failure or hypertrophic cardiomyopathy. Heterozygote female patients can be asymptomatic, have an attenuated form, or be affected the same as typical male patients. Diagnosis can be made by demonstration of α-galactosidase deficiency in leukocytes or by detection of mutation in the *GLA* gene. Urinary excretion of ceramide trihexoside can be used as a screening test. Symptomatic treatment of painful crises is with anticonvulsants. Enzyme replacement therapy is approved by the US Food and Drug Administration. It reverses systemic manifestations of the disease, stabilizes renal function, and decreases episodes of acroparesthesias.

Farber Disease

Farber disease, also called Farber lipogranulomatosis, results from deficiency of acid ceramidase. Presentation is in infancy, although later-onset forms also exist. Manifestations include mild to severe psychomotor retardation, periarticular nodules and joint swelling, and hoarseness due to upper airway involvement. Cherry-red spot can be seen. Ceramidase activity can be studied in cultured fibroblasts after loading with a precursor. Confirmation can be made by detection of mutation in the *ASAH1* gene. Treatment is supportive.

Table 74.3 • Fabry Disease Phenotype at Different Ages

Age	Signs and Symptoms
Childhood	Pain in extremities leading to "Fabry crisis"
Adolescence	Angiokeratomas, whorled corneal deposits, posterior capsular cataracts
Adulthood	Recurrent cerebral infarctions and hemorrhage, cardiomyopathy, arrhythmias
Middle age	Renal failure

Clinically distinct lysosomal leukodystrophies are metachromatic leukodystrophy and Krabbe disease (see Chapter 75, "Inherited Leukoencephalopathies").

- Tay-Sachs disease is caused by mutation of the α subunit of hexosaminidase A.
- Typical features of Tay-Sachs disease include motor regression, progressive blindness, seizures, exaggerated startle reflex, and spasticity. Cherry-red spot and macrocephaly are present.
- Fabry disease is an X-linked recessive disorder of glycosphingolipid catabolism resulting from deficiency of the enzyme α-galactosidase.
- In young patients, clinical features of Fabry disease include acroparesthesia, angiokeratomas, whorled corneal deposits, and posterior capsular cataracts. In older patients, cerebral infarctions and hemorrhage are seen.
- Enzyme replacement therapy is approved by the US Food and Drug Administration for Fabry disease. It reverses systemic manifestations, stabilizes renal function, and decreases episodes of acroparesthesias.

Mucopolysaccharidoses

MPS are a group of disorders due to defects in the breakdown of glycosaminoglycans including heparan sulfate, dermatan sulfate, keratan sulfate, chondroitin sulfate, and hyaluronan (Table 74.4).

MPS share many clinical features in variable degrees. These include a chronic and progressive course, multisystemic involvement, organomegaly, dysostosis multiplex, and coarse facies. Hearing, vision, joint mobility, respiratory, and cardiovascular systems are also affected to different extents. Profound intellectual disability is characteristic of MPS I (Hurler syndrome), severe MPS II (Hunter syndrome), and all subtypes of MPS III (Sanfilippo syndrome). Distinct bony abnormalities are seen in MPS IV A (Morquio syndrome type A).

Supportive management is important, with particular attention to neurologic complications such as communicating hydrocephalus and cord compression, cardiac valvular complications, and respiratory complications. Enzyme replacement therapy is commercially available for MPS I, II, and VI.

- Clinical features of mucopolysaccharidoses include a chronic and progressive course, multisystemic involvement, organomegaly, dysostosis multiplex, and coarse facies.

Mucolipidoses

Mucolipidosis types II and III are due to defective post-translational modification of lysosomal enzymes in the Golgi apparatus. The enzymes do not reach their target lysosomes and are secreted into the extracellular medium.

Mucolipidosis type II, or I-cell disease, resembles Hurler syndrome with earlier onset and more severe course but without mucopolysaccharidoses, whereas type III, or pseudo-Hurler polydystrophy, is milder and later in onset than Hurler syndrome. Survival into adulthood is possible in type III.

Mucolipidosis type IV is relatively common among the Ashkenazi population. It results from mutation in mucolipidin 1, a calcium channel protein, and presents without specific dysmorphism, but psychomotor delay and corneal clouding are present.

Diagnosis of mucolipidosis types II and III can be made biochemically by estimation of the serum lysosomal enzyme levels; diagnosis of type IV is based on detection of mutations in the gene that codes for mucolipidin 1, *MCOLN1*.

Oligosaccharidoses

Overview

Oligosaccharidoses are disorders in the breakdown of complex carbohydrate side chains of glycoproteins. Progressive accumulation of partially degraded oligosaccharides in brain and visceral tissue produces the clinical features.

Clinical features resemble those of MPS. They include skeletal deformities and coarse facies, with progressive neurologic symptoms and seizures. There are 4 distinct forms, and diagnosis is based on deficiency of specific enzymes in fibroblasts or leukocytes and abnormal urine oligosaccharides. Treatment of oligosaccharidoses is supportive.

Fucosidosis

Fucosidosis results from deficiency of α-fucosidase. Vacuolated lymphocytes in peripheral blood and foam cells in bone marrow are seen. Infants are normal at birth but then develop progressive coarsening of facial features, impaired growth and development, and organomegaly. Dysostosis multiplex is commonly seen. Angiokeratomas are present in the more indolent forms.

Mannosidosis

α-Mannosidosis results from deficiency of α-mannosidase. Vacuolated lymphocytes in peripheral blood and foamy vacuolated hepatocytes are seen. Clinical manifestations resemble those of severe MPS. Coarse facial features, hernias, hepatosplenomegaly, macrocephaly, and severe impairment in mental development are typical features. Magnetic resonance imaging of the brain shows evidence of atrophy and abnormal signal in white matter. Dysostosis multiplex is extreme.

Table 74.4 • Mucopolysaccharidoses

MPS	Type	Inheritance	Enzyme	Intellectual Disability	Corneal Clouding	Hepato-splenomegaly	Other Features
Hurler	I	AR	α-L-iduronidase	+	+	+	Coarse facies, cardiac disease, hernias
Hunter	II	X-recessive	Iduronate sulfatase	+	–	+	Coarse facies, aggressive behavior
Sanfilippo type A	III A	AR	Heparan *N*-sulfatase	+	–	–/+	Mild facial features, severe cerebral disease
Sanfilippo type B	III B	AR	α-*N*-acetylglucosaminidase	+	–	–/+	Mild facial features, severe cerebral disease
Sanfilippo type C	III C	AR	Acetyl-CoA:α-glucosaminide acetyltransferase	+	–	–/+	Mild facial features, severe cerebral disease
Sanfilippo type D	III D	AR	*N*-acetyl glucosamine 6-sulfatase	+	–	–/+	Mild facial features, severe cerebral disease
Morquio type A	IV A	AR	*N*-acetylgalactosamine 6-sulfatase	+	+	–	Distinct bony abnormalities
Morquio type B	IV B	AR	β-galactosidase	+	+	+	Mild bony abnormalities
Maroteaux-Lamy	VI	AR	*N*-acetylgalactosamine 4-sulfatase (arylsulfatase B)	–	+	+	Bony abnormalities, cardiac valvular disease
Sly	VII	AR	β-glucuronidase	+	+	+	Coarse features
	IX	AR	Hyaluronidase	+	–	–	Short stature, periarticular soft-tissue masses

Abbreviations: AR, autosomal recessive; MPS, mucopolysaccharidosis; +, present; –, absent; +/–, present or absent.

β-Mannosidosis results from deficiency of β-mannosidase. Typically, dysmorphism, organomegaly, and dysostosis multiplex are absent. Age of onset is variable. Seizures, quadriplegia, and behavioral abnormalities are present at the severe end of the spectrum and angiokeratomas at the mild end. Sensorineural hearing loss is prominent.

Sialidosis

Sialidosis has been classified as mucolipidosis type I but is an oligosaccharidosis due to neuraminidase deficiency. Type I sialidosis has adult onset with a classic presentation of cherry-red spot–myoclonus syndrome. Type II clinical features are variable, resembling those of MPS phenotypes with congenital and infantile onset.

Infantile Sialic Acid Storage Disease

Infantile sialic acid storage disease and Salla disease are transport disorders due to mutation in *SLC17A5*, the gene coding for sialin, a lysosomal membrane protein that transports sialic acid out of lysosomes. Infantile sialic acid storage disease has a severe phenotype with infantile-onset visceral involvement, cardiomyopathy, neurologic regression, and skeletal dysplasia. Salla disease has a mild phenotype, with late onset and survival into adulthood.

- Clinical features of oligosaccharidoses include skeletal deformities and coarse facies, with progressive neurologic symptoms and seizures.

Lipid Storage Disorders

Niemann-Pick Disease Type C

Niemann-Pick disease type C is a disorder of endosomal-lysosomal trafficking that results from mutations in either the *NPC1* gene (95%) or the *NPC2* gene. Polymorphic cytoplasmic bodies or zebra bodies are classically seen on pathologic examination. Central nervous system has ectopic dendritogenesis, axonal spheroids, neurofibrillary tangles, and ballooned neurons.

The most severe forms present in the perinatal period, either as fetal ascites with organomegaly or at birth with marked hepatosplenomegaly, ascites, pulmonary infiltrates, and jaundice accompanied by hepatic failure. There is a high mortality rate in affected neonates. Infantile and juvenile presentations include developmental delay, seizures, gelastic cataplexy, ataxia, spasticity, dystonia, vertical supranuclear gaze palsy, and sleep disturbances. Adults present with an insidiously progressive dementia.

Treatment with bone marrow and liver transplant has been tried without any effect on the neurologic outcome. Miglustat, a disease-modifying therapy, has been approved for treating the neurologic manifestations of Niemann-Pick disease type C.

Neuronal Ceroid-Lipofuscinoses

Neuronal ceroid-lipofuscinoses are a heterogeneous group of inherited progressive neurodegenerative disorders with accumulation of ceroidlike and lipofuscinlike autofluorescent storage material in the neurons (Figure 74.2). They are classified by age of onset and clinical features into infantile (Santavuori-Haltia disease, CLN1), late infantile (Jansky-Bielschowsky disease, CLN2), juvenile (Batten-Spielmeyer-Vogt disease, CLN3), and adult (Kufs disease, CLN4) forms. Mutation analysis has shown that these clinical categories are genetically heterogeneous. Cerebral gray matter involvement leads to progressive cognitive and motor deterioration, intractable myoclonic seizures, and early death. Visual loss due to atrophy of the retinal pigment epithelium is a feature of most forms. There are no abnormalities outside the nervous system.

Pathologic examination shows diffuse cortical atrophy with a thin cortical ribbon. Intraneuronal lipopigments are autofluorescent and PAS-positive. Electron microscopy shows granular osmiophilic deposits in infantile forms, curvilinear bodies in late infantile forms, and fingerprint bodies in juvenile forms. Treatment is symptomatic.

- Niemann-Pick disease type C is a disorder of endosomal-lysosomal trafficking that results from mutations in either the *NPC1* gene (95%) or the *NPC2* gene.
- Infantile and juvenile presentations of Niemann-Pick disease type C include developmental delay, seizures, gelastic cataplexy, ataxia, spasticity, dystonia, vertical supranuclear gaze palsy, and sleep disturbances.
- Miglustat, a disease-modifying therapy, has been approved for treating the neurologic manifestations of Niemann-Pick disease type C.
- In neuronal ceroid-lipofuscinoses, cerebral gray matter involvement leads to progressive cognitive and motor deterioration, intractable myoclonic seizures, and early death.

Glycogen Storage Diseases

Pompe Disease

Pompe disease, glycogen storage disease type IIa, results from lysosomal acid maltase (α-glucosidase) deficiency. Age of onset is variable, but myopathy is common to all forms.

The classic infantile-onset form manifests with prominent cardiomegaly, hypotonia, hepatomegaly, and death due to cardiorespiratory failure usually before age 2 years.

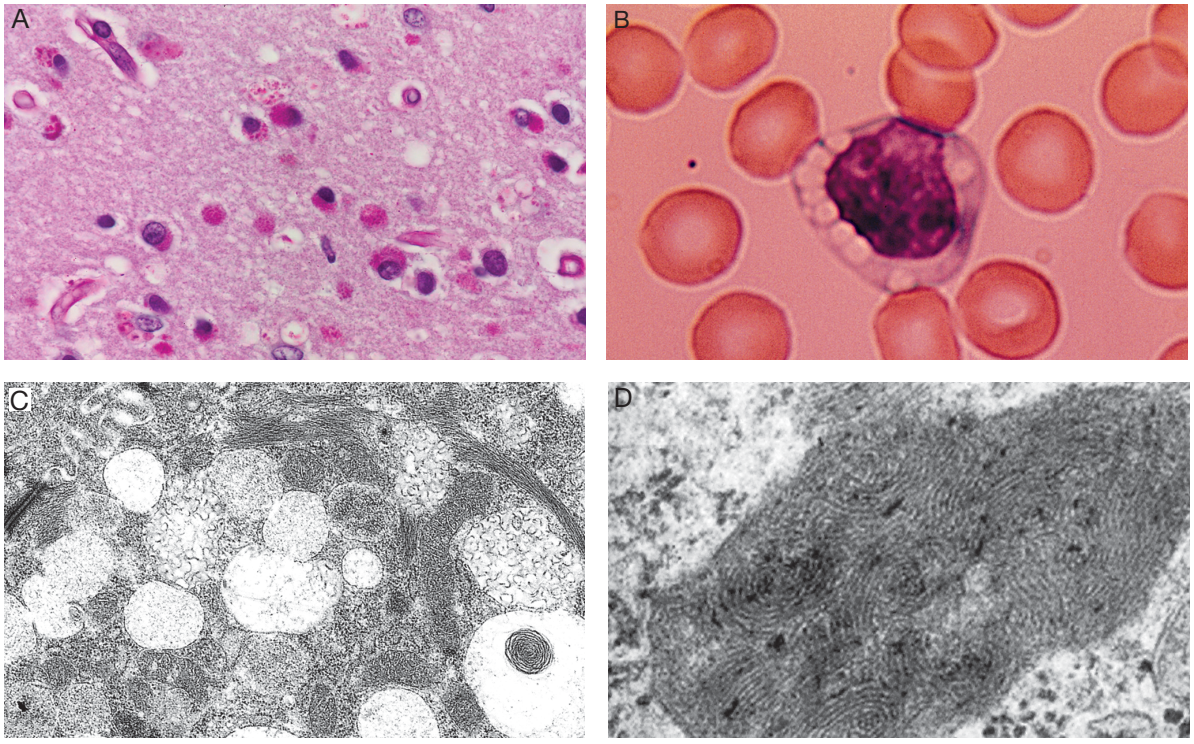

Figure 74.2 *Neuronal Ceroid-Lipofuscinosis.*
A, Neuronal storage material reacting strongly with periodic acid-Schiff stain. B, The blood smear of an affected patient shows a vacuolated lymphocyte. Electron microscopy demonstrates curvilinear bodies within a sweat gland epithelial cell in a patient with late-infantile disease (C) and fingerprint bodies in a patient with the juvenile form (D).
(A and B, Adapted from Murali HR, Renaud DL. Inborn errors of metabolism. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 933–80. Used with permission of Mayo Foundation for Medical Education and Research. C, Adapted from Ellison D, Love S, Chimelli L, Harding BN, Lowe JS, Vinters HV, et al. Neuropathology: a reference text of CNS pathology. 3rd ed. Edinburgh [United Kingdom]: Mosby/Elsevier; c2013. Chapter 23, Lysosomal and peroxisomal disorders. p. 479–98. Used with permission. D, Adapted from Sedel F, Goebel HH, Anthony DC. Hereditary metabolic diseases. In: Gray F, Duyckaerts C, De Girolami U, editors. Escourolle and Poirier's manual of basic neuropathology. 5th ed. Oxford [UK]: Oxford University Press; c2014. p. 227–56. Used with permission.)

The adult-onset form is slowly progressive with proximal myopathy. Late infantile and juvenile forms have skeletal muscle involvement.

Diagnosis is confirmed by either absence (infantile-onset form) or reduced activity (late-onset form) of α-glucosidase in white blood cells. See also Chapter 43, "Inherited Muscle Disorders."

Danon Disease

Danon disease, sometimes referred to as glycogen storage disease type IIb, is an X-linked condition caused by mutations in the *LAMP2* gene. The *LAMP2* gene codes for a protein called lysosomal-associated membrane protein 2 (LAMP-2), which is involved in the fusion between autophagic vacuoles and lysosomes. Mutations in this gene lead to the accumulation of autophagic vacuoles. Microscopic characteristics of LAMP-2 deficiency include small autophagic vacuoles in muscle fibers and excessive glycogen accumulation similar to that observed with acid maltase deficiency.

Clinical features include hypertrophic cardiomyopathy, skeletal myopathy, and intellectual disability. Male patients typically present in their teens and rarely survive beyond their 20s. Age of onset in females is less well defined.

- In Pompe disease, age of onset is variable but myopathy is common to all forms.
- Clinical features of Danon disease include hypertrophic cardiomyopathy, skeletal myopathy, and intellectual disability.

75 Inherited Leukoencephalopathies[a]

DEBORAH L. RENAUD, MD

Introduction

Leukoencephalopathies are disorders that selectively involve the white matter of the brain. Acquired causes of leukoencephalopathy include inflammatory, infectious, vascular, neoplastic, and toxic disorders. Hereditary leukoencephalopathies encompass those conditions that demonstrate progressive destruction or loss of previously acquired central myelin (leukodystrophies) as well as those conditions associated with impaired formation of myelin (dysmyelination or hypomyelination) (Table 75.1). The study of clinical features, neuroimaging patterns, and biochemical and neuropathologic features of leukoencephalopathies has led to the discovery of the genetic defects responsible for many of these conditions. Variations in phenotype-genotype correlation can make prediction of the underlying condition challenging. Despite recent advances in molecular studies, approximately 50% of patients with hereditary leukoencephalopathies remain without a diagnosis. A systematic approach to guide investigations is important to lead to a diagnosis. An overview of select inherited leukoencephalopathies is presented in Table 75.2, and details are reviewed in this chapter.

Table 75.1 • Leukoencephalopathies Associated With Hypomyelination

Pelizaeus-Merzbacher disease
Pelizaeus-Merzbacher–like disease
Allan-Herndon-Dudley disease
Childhood ataxia with central hypomyelination/vanishing white matter disease
Cockayne syndrome
Fucosidosis
Hypomyelination with congenital cataracts
Hypomyelination with hypogonadotropic hypogonadism and hypodentia
Tremor-ataxia with central hypomyelination
Hypomyelination with atrophy of basal ganglia and cerebellum
Oculodentodigital syndrome
Salla disease
Serine synthesis defects
Tay syndrome (trichothiodystrophy with hypersensitivity to sunlight)
Waardenburg-Hirschsprung syndrome with peripheral neuropathy and central hypomyelination
18q deletion syndrome

Aicardi-Goutieres Syndrome

At least 5 different genes (*TREX1, RNASEH2B, RNASEH2C, RNASEH2A,* and *SAMHD1*) have been associated with this autosomal recessive condition. Aicardi-Goutieres syndrome usually presents with an early encephalopathy followed by stabilization of neurologic symptoms.

Neuroimaging reveals leukoencephalopathy with calcifications and cerebral atrophy. Cerebrospinal fluid analysis reveals chronic lymphocytosis and elevated interferon-α and neopterin levels. Treatment is symptomatic.

[a] Portions previously published in Renaud DL. Leukoencephalopathies associated with macrocephaly. Semin Neurol. 2012 Feb;32(1):34–41. Epub 2012 Mar 15; Renaud DL. Lysosomal disorders associated with leukoencephalopathy. Semin Neurol. 2012 Feb;32(1):51–4. Epub 2012 Mar 15; and Renaud DL. Clinical approach to leukoencephalopathies. Semin Neurol. 2012 Feb;32(1):29–33. Used with permission.

Abbreviations: AMN, adrenomyeloneuropathy; GALC, galactocerebrosidase; MLC, megalencephalic leukoencephalopathy with subcortical cysts; MRI, magnetic resonance imaging; NAA, N-acetylaspartic acid; PMD, Pelizaeus-Merzbacher disease; RCDP, rhizomelic chondrodysplasia punctata

Table 75.2 • A Review of Select Inherited Leukodystrophies

Disorder	Genetics	Clinical Features	Other
Alexander disease	AD *GFAP* gene	Infantile (<2 y) form: Macrocephaly, developmental delay, seizures Juvenile (2–13 y) form: Developmental delay Adult form: Ataxia, spasticity, myoclonus	MRI: Leukoencephalopathy Pathology: Rosenthal fibers
Krabbe disease	AR Galactocerebrosidase deficiency	Infantile (2–5 mo) form: Poor feeding, developmental arrest, poor head control Later: Opisthotonic posturing, myoclonus, regression, visual loss, seizures Late-onset form: Dementia, visual problems, neuropathy	MRI: Diffuse leukoencephalopathy
Metachromatic leukodystrophy	AR Arylsulfatase A deficiency	Late-infantile form (1–2 y): Weakness, decreased reflexes, hypotonia Later: Cognitive and motor regression Late: Optic atrophy, seizures Juvenile and adult forms: Behavioral/cognitive symptoms, neuropathy	MRI: T2 hyperintensity in periventricular white matter sparing U fibers; tigroid stripes Pathology: Metachromatic granules
Pelizaeus-Merzbacher disease	X linked Proteolipid protein (deficiency)	Rotatory eye movements, hypotonia, involuntary movements, spasticity	MRI: Severe reduction or absence of central myelin EMG: Peripheral neuropathy (demyelinating)
X-linked adrenoleukodystrophy	X linked *ABCD1* gene Peroxisomal disorder	Childhood (2–10 y) form: Behavioral changes, neurologic dysfunction, visual loss, adrenal insufficiency Adolescent/adult (20–40 y) form: Spastic paraparesis, peripheral neuropathy	MRI: Symmetrical parietooccipital white matter changes; may involve splenium of corpus callosum

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EMG, electromyography; MRI, magnetic resonance imaging.

Alexander Disease

Overview and Epidemiology

Alexander disease is a primary disorder of astrocytes due to a toxic gain-of-function mutation in the gene that encodes glial fibrillary acidic protein, *GFAP*. An autosomal dominant de novo mutation accounts for the majority of cases, although autosomal dominant familial adult-onset cases have been described.

Clinical Presentation

The classic infantile form of Alexander disease is the most widely recognized. Children present before 2 years of age with macrocephaly, developmental delay, and seizures. Progressive spasticity, ataxia, and bulbar signs follow, and hydrocephalus may develop. The mean survival is approximately 4 years.

The juvenile form presents between 2 and 13 years of age with developmental delay and seizures followed by gradual deterioration or with a presentation similar to that of the adult form. Mean survival is approximately 8 years after onset of deterioration, although the clinical symptoms are much more variable than in the infantile form.

Adults with Alexander disease present with bulbar and pseudobulbar signs, ataxia, and spasticity as well as a variety of other neurologic symptoms, including palatal myoclonus, nystagmus, autonomic dysfunction, sleep apnea, and scoliosis. Because of the variable presentation, a high index of suspicion is needed to identify adults with Alexander disease.

Diagnosis and Treatment

Magnetic resonance imaging (MRI) findings suggestive of Alexander disease include extensive cerebral white matter changes with frontal predominance, a periventricular rim with high signal on T1-weighted images and low signal on T2-weighted images, abnormalities of the basal ganglia and thalami, brainstem abnormalities, and contrast enhancement of particular gray and white matter structures. MRI findings in juvenile and adult-onset cases are more variable and therefore may not meet these criteria. White matter changes may be minimal and may be stable over many years despite disease progression. Scalloped garlandlike signal enhancement lining the outer rim of the lateral ventricles may be present on T2 and FLAIR images. Clinical symptoms suggestive of Alexander disease in conjunction with MRI findings fulfilling any of these criteria should

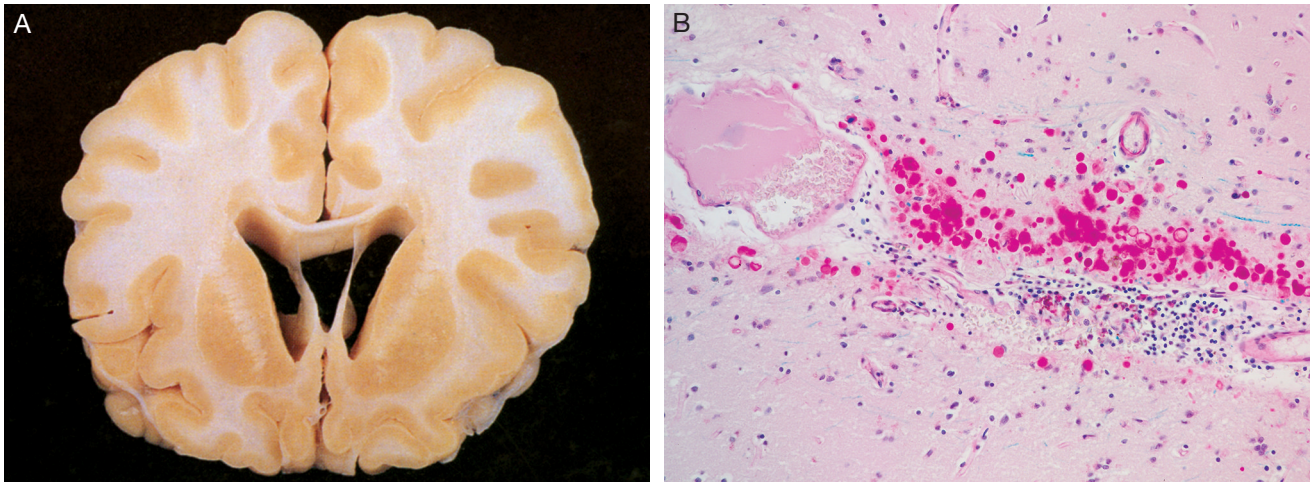

Figure 75.1 *Alexander Disease.*
A, Gross brain specimen shows diffuse discoloration of the white matter. B, A characteristic microscopic feature is Rosenthal fibers, which are often deposited around blood vessels, as shown here.
(Adapted from Murali HR, Renaud DL. Inborn errors of metabolism. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 933–80. Used with permission of Mayo Foundation for Medical Education and Research.)

prompt molecular analysis of the *GFAP* gene, particularly in adult patients.

The classic pathologic feature of Alexander disease is the presence of Rosenthal fibers (Figure 75.1) in the astrocytic processes around small blood vessels and astrocytic cell bodies in the subpial, periventricular, and subependymal regions in particular. Rosenthal fibers are eosinophilic (in light microscopy) and osmophilic (in electron microscopy) inclusions consisting of intermediate filaments and irregular deposition of dense material.

Treatment of Alexander disease currently is symptomatic, consisting of anticonvulsants for seizures, orthopedic and pharmacologic management of spasticity, and nutritional support.

- Alexander disease is a primary disorder of astrocytes due to a toxic gain-of-function mutation in the gene that encodes glial fibrillary acidic protein, *GFAP*.
- Children with Alexander disease present before 2 years of age with macrocephaly, developmental delay, and seizures.
- MRI findings suggestive of Alexander disease include extensive cerebral white matter changes with frontal predominance.
- The classic pathologic feature of Alexander disease is the presence of Rosenthal fibers.

Canavan Disease

Overview and Epidemiology

Canavan disease is an autosomal recessive condition due to the deficiency of aspartoacylase. Defective hydrolysis of N-acetylaspartic acid (NAA) results in increased levels of NAA in blood, urine, cerebrospinal fluid, and brain.

Clinical Presentation

Children with Canavan disease usually show no abnormalities for the first few months of life. Developmental delay may start to be manifest between 3 and 6 months. After 6 months of age, the head circumference starts to increase, and macrocephaly is evident by 1 year of age. Development becomes delayed, followed by regression of previously attained skills. Poor head control is accompanied by hypotonia early in the course, which then evolves into spasticity. In the second year, seizures, sleep disturbance, irritability, and optic atrophy complicate the neurologic presentation. Gastroesophageal reflux, failure to thrive, and feeding problems are common, necessitating placement of a feeding tube. Survival time is variable. Death may occur early in the course in less than 1 year, or a prolonged course with survival into adulthood may be seen. A milder, later-onset variant has been described in association with milder mutations.

Diagnosis and Treatment

MRI scans may be normal initially, followed by diffuse white matter degeneration and eventual brain atrophy. Spongy degeneration affects the white matter of the cerebral hemispheres primarily, but also the white matter of the cerebellum, brainstem, internal and external capsules, subcortical U fibers, and spinal cord. MR spectroscopy reveals an elevated NAA peak. The diagnosis is suggested by increased NAA levels on urinary organic acid analysis

and is confirmed by measurement of aspartoacylase activity in skin fibroblasts and DNA mutation analysis.

There currently is no specific treatment for Canavan disease. Symptomatic treatment of neurologic complications includes physical therapy and pharmacologic treatment of spasticity, antiepileptic medications for seizures, sleep management, and tube feeding.

Childhood Ataxia With Central Hypomyelination/Vanishing White Matter Disease

Overview and Epidemiology

Leukoencephalopathy with vanishing white matter is an autosomal recessive condition due to mutations in the genes encoding each of the 5 subunits of eukaryotic translation initiation factor eIF2B. This key regulator of translation initiation is responsible for regulation of protein synthesis in response to mild stressors. Diagnosis is confirmed by mutation analysis.

Clinical Features

Children with vanishing white matter disease present with prominent ataxia with mild spasticity and relatively spared cognition initially. (See also Chapter 26, "Cerebellar Disorders and Ataxias.") The course is chronic and progressive with episodes of deterioration initiated by minor infections, minor head trauma, or acute fright. Episodes present with hypotonia, irritability, vomiting, and seizures evolving to decreased level of consciousness or unexplained coma. Recovery from each episode is slow and incomplete. Seizures and optic atrophy may develop.

Adolescents and adults tend to have a milder and more protracted course. Neurologic symptoms may include ataxia, gait abnormality with mild spasticity, seizures, complicated migraine, and cognitive or psychiatric problems. In female patients, ovarian failure may precede or coexist with neurologic symptoms (also known as ovarioleukodystrophy). Stress-induced episodes of deterioration are less common than in young children.

Diagnosis and Treatment

MRI findings are diagnostic in the childhood form but are more variable in later-onset forms. Diffuse symmetrical cerebral white matter changes are present early and spare the subcortical U fibers, outer corpus callosum, internal capsules, and anterior commissure. Progressive cystic degeneration results in replacement of the white matter by cerebrospinal fluid. Within the cystic regions, radial stripes extend from the ventricular wall to the subcortical region. Cerebellar atrophy of varying degrees develops later in the course in all forms.

There currently is no specific treatment for leukoencephalopathy with vanishing white matter. Treatment is supportive and symptomatic.

Krabbe Disease

Overview and Epidemiology

Krabbe disease, also known as globoid cell leukodystrophy, is an autosomal recessive disorder due to a deficiency of galactocerebrosidase (GALC) that affects both central and peripheral nervous system white matter. Extensive demyelination and gliosis with globoid cells result from the accumulation of galactosylceramide and psychosine, the 2 main substrates for GALC. Saposin A deficiency is a very rare cause of Krabbe disease.

The incidence of Krabbe disease has been estimated at 1 in 100,000, with approximately 85% to 90% of patients having the early infantile form, although newborn screening results suggest that a higher proportion of patients may have later-onset forms.

Clinical Features

The infantile form has an onset at 2 to 5 months of age with irritability, stiffness, poor feeding, developmental arrest, poor head control, and episodes of increased temperature without fever. Stage II of the infantile form consists of opisthotonic posturing, myoclonus, developmental regression, vision loss, and seizures. In stage III, infants develop lack of spontaneous movement and hypotonia and generally die of respiratory infections before age 2 years.

Late-onset Krabbe disease presents with vision problems, burning paresthesia, peripheral neuropathy, and dementia with slow, progressive neurologic decline.

Diagnosis

MRI scans may be normal in up to 25% of symptomatic infants. Otherwise, MRI scans reveal diffusely increased T2 signal in the periventricular, deep, or cerebellar white matter. Pathologic features are shown in Figure 75.2.

The diagnosis is confirmed by measurement of GALC activity in leukocytes or skin fibroblasts.

Treatment

Treatment of Krabbe disease is primarily supportive and symptomatic. Umbilical cord blood transplantation in symptomatic patients with infantile-onset disease results in minimal neurologic benefit. Transplantation in asymptomatic infants within the first 3 years of life results in prolonged survival with progressive motor and neurologic deficits. Therefore, early hematopoetic stem cell transplantation attenuates the clinical course of infantile Krabbe disease and prolongs survival but is not curative.

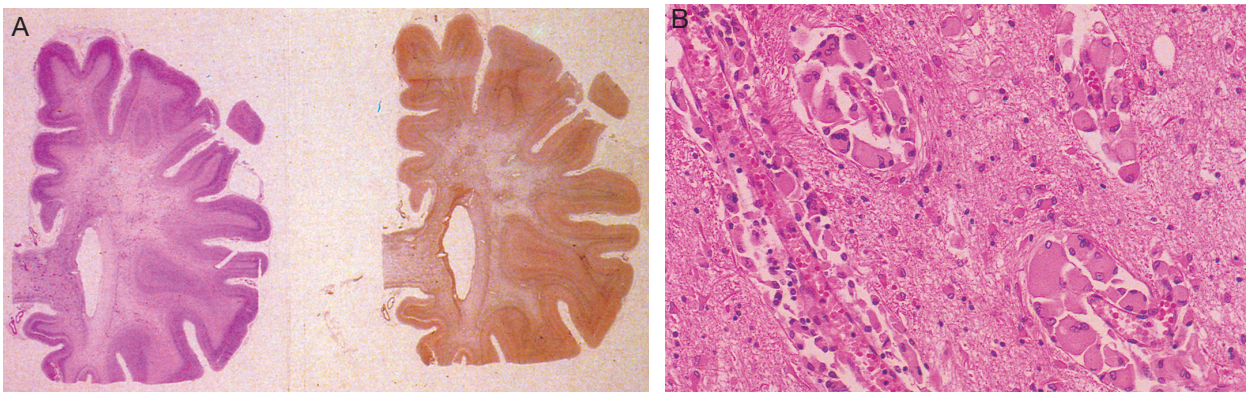

Figure 75.2 *Krabbe Globoid Cell Leukodystrophy.*
A, Diffuse pallor of white matter with sparing of the U fibers (left, Luxol fast blue stain; right, Bodian stain). B, Perivascular clusters of multinucleated globoid macrophages. (Hematoxylin-eosin stain.)
(Adapted from Okazaki H, Scheithauer BS. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 245. Used with permission of Mayo Foundation for Medical Education and Research.)

- Krabbe disease, also known as globoid cell leukodystrophy, is an autosomal recessive disorder due to a deficiency of galactocerebrosidase that affects both central and peripheral nervous system white matter.
- Stage II of the infantile form of Krabbe disease consists of opisthotonic posturing, myoclonus, developmental regression, vision loss, and seizures.

Megalencephalic Leukoencephalopathy With Subcortical Cysts

Overview and Epidemiology

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an autosomal recessive leukoencephalopathy. Approximately 80% of patients with MLC have 2 mutations in the *MLC1* gene. Recently, a second gene, *HEPACAM*, was found to be associated with MLC. *HEPACAM* encodes a membrane protein called GlialCAM, which is an MLC1-interacting protein in junctions between astrocytes.

Clinical Features

Macrocephaly is present in the first year of life. There is a mild delay in the acquisition of gross motor skills with a gradual onset of motor deterioration with ataxia and spasticity. Cognitive abilities are relatively spared. Seizures are common. This classic presentation is present in patients with autosomal recessive mutations in *MLC1* and *HEPACAM*. A second, improving clinical phenotype has been described in patients with an autosomal dominant (de novo or inherited from 1 parent) mutation in *HEPACAM*. Patients with this clinical phenotype also have macrocephaly in the first year of life but demonstrate an improvement, rather than deterioration, in motor function over time. Intelligence may be normal in some of these patients, but other patients have developmental delay, some with features of pervasive developmental disorder. The majority of parents carrying the affected allele have a history of macrocephaly.

Diagnosis and Treatment

MRI findings are characteristic and should lead to molecular analysis of the *MLC1* and *HEPACAM* genes. Diffuse subcortical and periventricular white matter abnormalities are associated with mild swelling of the cerebral white matter and subcortical cysts located in the bilateral anterior temporal regions and sometimes also the frontal or parietooccipital regions. MRI findings in patients with 1 mutation in the *HEPACAM* gene are initially milder and improve over time.

There currently is no specific treatment for MLC. Supportive treatment of seizures and spasticity is indicated.

Metachromatic Leukodystrophy

Overview and Epidemiology

Metachromatic leukodystrophy (incidence, 1 in 40,000) is an autosomal recessive disorder associated with deficiency of arylsulfatase A and accumulation of 3-O- sulfogalactosylceramide (sulfatide) in oligodendrocytes, Schwann cells, and some neurons. Arylsulfatase A pseudodeficiency due to polymorphisms in the gene encoding arylsulfatase A, *ARSA*, is present in 0.2% to 0.5% of whites, resulting in decreased activity in vitro but no clinical symptoms. Deficiency of the activator protein, saposin B, is a rare variant of metachromatic leukodystrophy. Arylsulfatase A deficiency can also

be seen as a component of multiple sulfatase deficiency, a complex condition with symptoms of metachromatic leukodystrophy, mucopolysaccharidoses, and ichthyosis.

Clinical Features

The most common clinical phenotype is the late-infantile form. Children present between 1 and 2 years of age, following a period of apparently normal early development, with hypotonia, weakness, and decreased deep tendon reflexes affecting gait. Spasticity then evolves, followed by cognitive regression and decline in fine motor skills due to a combination of spasticity and peripheral neuropathy. Optic atrophy and seizures occur late in the disease course. Death usually results from a respiratory tract or other infection.

Patients with the juvenile form present with decreased school performance, change in behavior, and psychiatric symptoms between 3 and 16 years of age. Gross motor impairment and signs of peripheral neuropathy precede progressive spasticity and neurologic decline.

Patients with adult-onset disease usually show a slow decline in intellectual abilities over years accompanied by behavioral or psychiatric changes, memory difficulties, and signs of gait disturbance due to spasticity and peripheral neuropathy. Patients with all forms may have demyelination of the central nervous system, peripheral nervous system, or both at the time of presentation. Cholecystitis can be seen as a nonneurologic complication of metachromatic leukodystrophy.

Diagnosis and Treatment

MRI scans reveal confluent, symmetrical T2 hyperintensity in the periventricular white matter with sparing of the subcortical U fibers. The white matter changes tend to progress from the parietooccipital to frontal regions in late-infantile cases and are frontal dominant in juvenile and adult-onset cases. Tigroid stripes, consisting of spared perivascular white matter, extend radially. In severe disease, projection fibers, corpus callosum, and cerebellum may show white matter changes. Atrophy is present late in the course due to white matter volume loss. Figure 75.3 shows typical pathologic findings in metachromatic leukodystrophy.

Diagnosis of metachromatic leukodystrophy is confirmed by the presence of low arylsulfatase A activity in leukocytes or skin fibroblasts in conjunction with increased sulfatide excretion in the urine. Patients with saposin B deficiency have normal arylsulfatase A activity (in vitro) but have increased sulfatide excretion in the urine. Patients with pseudodeficiency have decreased arylsulfatase A activity but no excretion of sulfatide in the urine; the diagnosis can be confirmed by molecular analysis.

Treatment of metachromatic leukodystrophy is primarily symptomatic and supportive. Hematopoietic cell transplantation can stabilize the central nervous system demyelination in patients with juvenile and adult-onset forms of metachromatic leukodystrophy when performed early in the disease course.

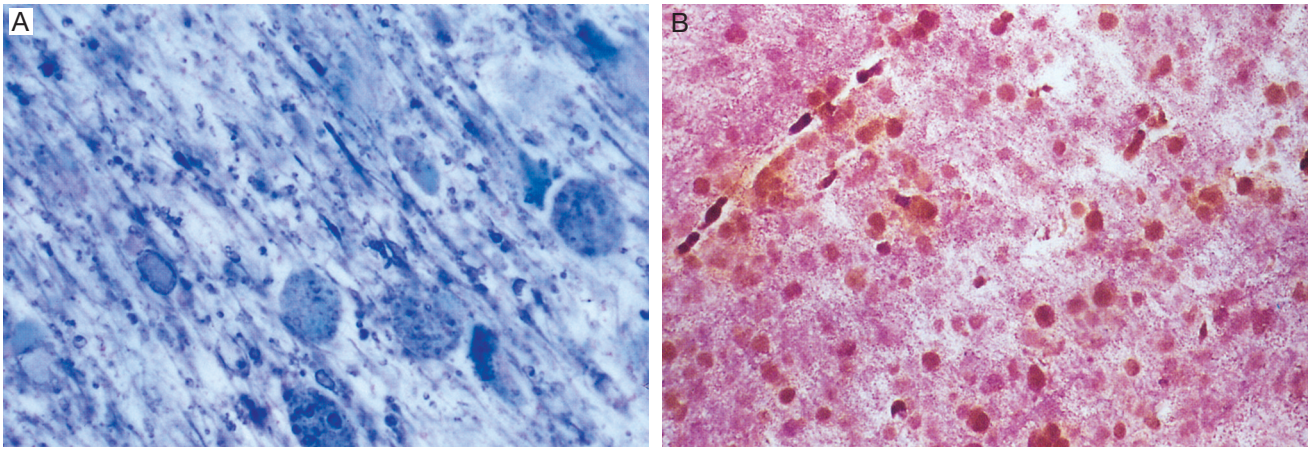

Figure 75.3 *Metachromatic Leukodystrophy.*
A, Subcortical white matter with severe loss of myelin and ballooned macrophages interspersed among the remaining myelinated fibers. B, Frozen section stained with acidified cresyl violet demonstrates the metachromatic brown-purple appearance of macrophages containing stored sulfatide.
(Adapted from Ellison D, Love S, Chimelli L, Harding BN, Lowe JS, Vinters HV, et al. Neuropathology: a reference text of CNS pathology. 3rd ed. Edinburgh [UK]: Mosby/Elsevier; c2013. Chapter 23, Lysosomal and peroxisomal disorders. p. 23.13. Used with permission.)

- Metachromatic leukodystrophy (incidence, 1 in 40,000) is an autosomal recessive disorder associated with deficiency of arylsulfatase A and accumulation of 3-O-sulfogalactosylceramide (sulfatide) in oligodendrocytes, Schwann cells, and some neurons.
- Children with metachromatic leukodystrophy present between 1 and 2 years of age, following a period of apparently normal early development, with hypotonia, weakness, and decreased deep tendon reflexes affecting gait.
- In metachromatic leukodystrophy, MRI scans reveal confluent, symmetrical T2 hyperintensity in the periventricular white matter with sparing of the subcortical U fibers.
- Diagnosis of metachromatic leukodystrophy is confirmed by the presence of low arylsulfatase A activity in leukocytes or skin fibroblasts.

Pelizaeus-Merzbacher and Pelizaeus-Merzbacher–Like Disease

Overview and Epidemiology

Pelizaeus-Merzbacher disease (PMD) (incidence, 1 in 100,000) is an X-linked disorder due to deficient formation of proteolipid protein (PLP) in the central nervous system associated with mutations or duplication of the *PLP* gene. PMD-like disease, associated with autosomal recessive mutations in the gene encoding gap junction A12 protein, resembles PMD clinically but affects both males and females.

Clinical Features

Classic PMD presents with rotatory eye movements and hypotonia, followed by slowly progressive involuntary movements and spasticity. The connatal form has onset at birth with severe features and more rapid progression including intractable seizures. Some patients present with a late-onset X-linked spastic paraparesis.

Diagnosis

MRI reveals a severe reduction or absence of central myelin (Figure 75.4). Nerve conduction studies may show evidence of a demyelinating peripheral neuropathy.

- Pelizaeus-Merzbacher disease (PMD) (incidence, 1 in 100,000) is an X-linked disorder due to deficient formation of proteolipid protein in the central nervous system associated with mutations or duplication of the *PLP* gene.
- Classic PMD presents with rotatory eye movements and hypotonia, followed by slowly progressive involuntary movements and spasticity.

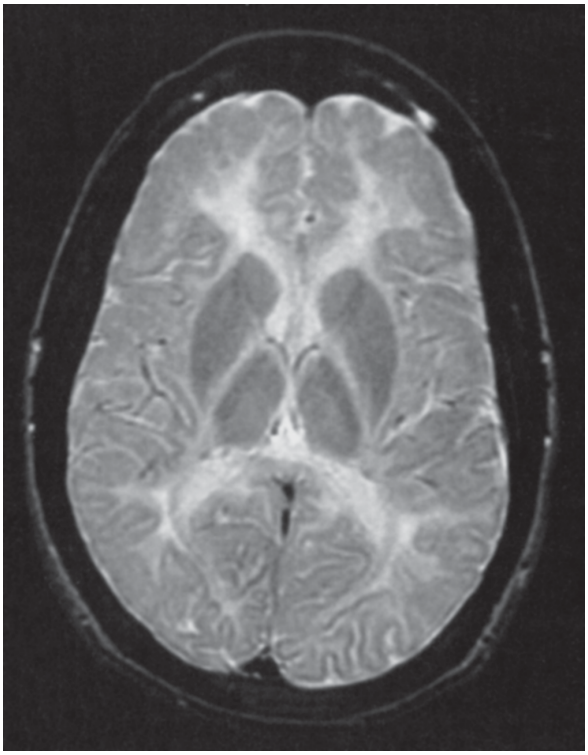

Figure 75.4 *Pelizaeus-Merzbacher Disease. T2-weighted magnetic resonance image of the brain in a 20-year-old patient shows diffuse high signal in white matter with sparing of subcortical U fibers.*
(Adapted from Koeppen AH, Robitaille Y. Pelizaeus-Merzbacher disease. J Neuropathol Exp Neurol. 2002 Sept; 61[9]:747–59. Used with permission.)

- In PMD, MRI reveals a severe reduction or absence of central myelin. Nerve conduction studies may show evidence of a demyelinating peripheral neuropathy.

Peroxisomal Disorders

Zellweger Syndrome, Neonatal Adrenoleukodystrophy, Infantile Refsum Disease, and Pipecolic Acidemia

Overview and Epidemiology

Defects of peroxisomal biogenesis result from defective import of PTS1 and PTS2 matrix enzymes, associated with mutations in *PEX* genes, which encode peroxins. Peroxisomal enzymes are mislocalized to the cytosolic compartment, leading to severe impairment of cholesterol synthesis, bile acid metabolism, oxidation of very long-chain and branched-chain fats, ether phospholipid synthesis, and phytanic acid and pipecolic acid metabolism. Apparent absence of or significant reduction in the number of peroxisomes has been demonstrated in 4

disorders historically considered to be distinct: Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease, and pipecolic acidemia. It is now clear that these are related disorders that form a spectrum of clinical severity from the early lethal phenotype seen in Zellweger syndrome to the later-onset symptoms of infantile Refsum disease and pipecolic acidemia.

Clinical Features

Classic findings of Zellweger syndrome include characteristic dysmorphic facial features and other malformations, accompanied by severe neurologic dysfunction with hypotonia, seizures, and ultimate deterioration. Liver function is abnormal, as is that of the gastrointestinal tract, leading to failure to thrive. Neuronal heterotopia and renal cortical cysts are seen pathologically. Proximal limb shortening may be present. Death usually occurs within the first year of life.

Neonatal adrenoleukodystrophy and infantile Refsum disease may present in the first 6 months of life similarly to Zellweger syndrome, but with slightly later onset of symptoms. These disorders, along with pipecolic acidemia, can also appear in early childhood (before 3 years of age) with milder symptoms including developmental delay, hypotonia, hearing impairment, retinopathy, and nystagmus. Biochemical findings in patients with neonatal adrenoleukodystrophy, infantile Refsum disease, and pipecolic acidemia are similar to those in Zellweger syndrome but may be more subtle.

Rhizomelic chondrodysplasia punctata (RCDP) type 1, characterized by abnormal facies, developmental delay, cataracts, abnormal calcifications of epiphyses, and severe proximal limb shortening, results from failure to import PTS2-associated enzymes due to mutations in the *PEX7* gene. RCDP type 2 (dihydroxyacetone phosphate acetyltransferase deficiency) and RCDP type 3 (alkyldihydroxyacetone phosphate synthase deficiency) have similar clinical features but are isolated disorders of ether phospholipid biosynthesis resulting in plasmalogen deficiency with normal phytanic acid levels.

X-Linked Adrenoleukodystrophy

Overview and Epidemiology

X-linked adrenoleukodystrophy is the most common peroxisomal disorder, affecting approximately 1 in 20,000 males, in all ethnic groups. X-linked adrenoleukodystrophy is caused by mutations in the *ABCD1* gene, which encodes adrenoleukodystrophy protein, an adenosine triphosphate–binding transporter located in the peroxisomal membrane.

Different clinical phenotypes can occur within the same family. The lack of genotype-phenotype correlation suggests that multiple genetic and environmental factors contribute to the development of individual phenotypes in patients with similar genotypes.

Clinical Features

Several clinical phenotypes have been associated with defects in the *ABCD1* gene. Classic cerebral childhood adrenoleukodystrophy accounts for 35% of cases. The childhood cerebral form presents initially with behavioral changes and school difficulties at 2 to 10 years of age, followed by progressive neurologic dysfunction, visual loss, and adrenal insufficiency.

The adolescent and adult-onset cerebral phenotypes have similar features to the childhood cerebral disease, but a latter age of onset. Approximately 40% to 45% of males develop adrenomyeloneuropathy (AMN) in the second to fourth decade, presenting with progressive spastic paraparesis and peripheral neuropathy. Up to half may develop cerebral symptoms.

Addison disease alone may be present in 10% to 20% of patients with adrenoleukodystrophy, and these patients have a high risk of later developing neurologic symptoms. Adrenal insufficiency occurs independently of neurologic symptoms. Patients may remain asymptomatic for decades. At least 50% of female carriers develop symptoms of AMN after age 40 years.

Diagnosis

MRI scans in cerebral forms show symmetrical involvement of the parietooccipital white matter or splenium of the corpus callosum in 80% of boys (Figure 75.5). Symmetrical involvement of frontal white matter or genu of the corpus callosum is present in 10% to 15% of boys. Less common patterns include corticospinal tract or frontopontine projection fibers, cerebellar white matter, and concomitant parietooccipital and frontal white matter involvement.

Treatment

Lorenzo's oil has been given to patients with X-linked adrenoleukodystrophy for more than 2 decades since it was initially shown to normalize plasma very long-chain fatty acids. Recent studies, however, have demonstrated no beneficial effects of Lorenzo's oil on the natural course of the neurologic disease. Significant adverse effects, including elevated liver enzyme levels and thrombocytopenia, are often observed. Bone marrow transplant may result in long-term stabilization and sometimes improvement in clinical symptoms when performed early in cerebral X-linked adrenoleukodystrophy. Once neurologic symptoms have progressed beyond the early stages, bone marrow transplant has not been shown to alter the natural course of these diseases.

Presymptomatic boys with X-linked adrenoleukodystrophy should be monitored with serial MRI and neuropsychological assessments to detect early indications of cerebral disease and need for bone marrow transplant. Genetic counseling should be provided to patients and their families. Patients with adrenoleukodystrophy and AMN should be treated for adrenal insufficiency as required.

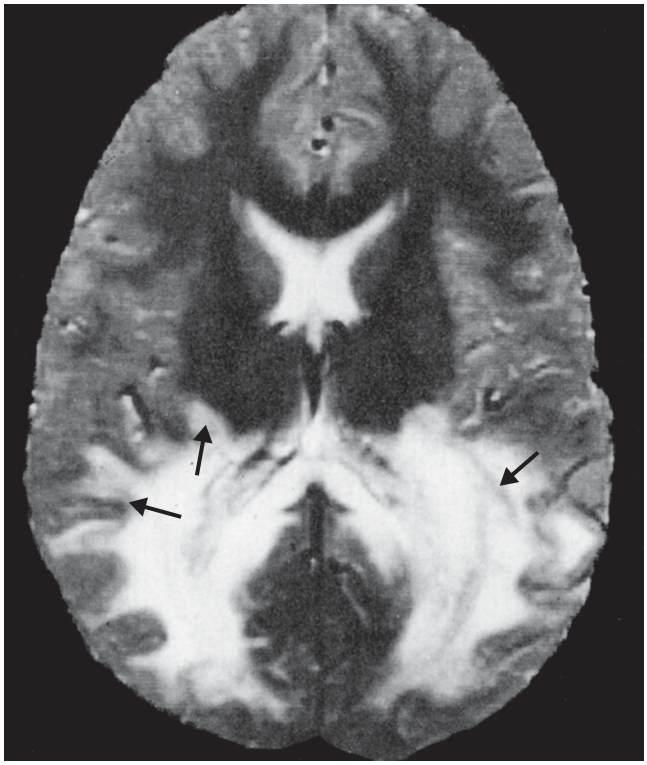

Figure 75.5 *X-Linked Adrenoleukodystrophy.*
T2-weighted magnetic resonance image of the brain shows symmetrical, confluent demyelination bilaterally of occipital white matter and splenium of corpus callosum. Arrows indicate intermediate zones of active demyelination. (Adapted from Osborn AG. Diagnostic neuroradiology. St. Louis [MO]: Mosby-Year Book; c1994. Chapter 17, Inherited metabolic, white matter, and degenerative diseases. p. 716–47. Used with permission.)

Refsum Disease

Classic Refsum disease is an autosomal recessive condition due to deficiency of phytanic acid oxidase. Clinical findings include retinitis pigmentosa, cerebellar ataxia, and peripheral neuropathy, with onset of symptoms varying from childhood to the fifth decade of life. There is no cognitive impairment. This disorder is characterized by accumulation of phytanic acid in blood and tissues; other peroxisomal enzyme functions are normal.

Adult-Onset Autosomal Dominant Leukodystrophy

Adult-onset autosomal dominant leukodystrophy is a slowly progressive leukoencephalopathy associated with a duplication of the gene that encodes lamin B1, *LMNB1*.

Symptoms usually present in the fourth or fifth decade with early autonomic abnormalities followed by pyramidal motor dysfunction and cerebellar ataxia. A slowly progressive dementia is commonly described.

MRI findings consist of symmetrical, often extensive, white matter T2 signal hyperintensities in the frontal lobe; the next most common locations for change are the parietal lobe and middle cerebellar peduncle. Atrophy of the brainstem, corpus callosum, and spinal cord may also be seen.

- X-linked adrenoleukodystrophy is the most common peroxisomal disorder.
- X-linked adrenoleukodystrophy is caused by mutations in the *ABCD1* gene, which encodes adrenoleukodystrophy protein, an adenosine triphosphate–binding transporter located in the peroxisomal membrane.
- The childhood cerebral form of adrenoleukodystrophy presents initially with behavioral changes and school difficulties at 2 to 10 years of age, followed by progressive neurologic dysfunction, visual loss, and adrenal insufficiency.
- MRI scans in cerebral forms of adrenoleukodystrophy show symmetrical involvement of the parietooccipital white matter or splenium of the corpus callosum in 80% of boys.
- Recent studies have demonstrated no beneficial effects of Lorenzo's oil on the natural course of X-linked adrenoleukodystrophy.
- Clinical findings in Refsum disease include retinitis pigmentosa, cerebellar ataxia, and peripheral neuropathy, with onset of symptoms varying from childhood to the fifth decade of life.

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (commonly referred to as CADASIL) is the most common hereditary multi-infarct leukoencephalopathy. This condition results from autosomal dominant mutations in the *NOTCH3* gene. See Chapter 11, "Ischemic Stroke: Uncommon and Special Situations," for further details.

Cerebrotendinous Xanthomatosis

Overview

Cerebrotendinous xanthomatosis is an autosomal recessive disease due to a deficiency in the mitochondrial enzyme sterol 27-hydroxylase. Abnormal conversion of cholesterol

into cholic and chenodeoxycholic acids leads to elevated cholestanol levels in plasma and bile. Cholestanol accumulation occurs in the brain, tendons, eyes, and other tissues. Lipoprotein levels are normal.

Clinical Features

Initial presentation may consist of juvenile-onset cataracts. Children may have unexplained chronic diarrhea. In adulthood, neurologic manifestations gradually develop, including spastic paraparesis, pyramidal tract signs, cerebellar ataxia, peripheral neuropathy, and bulbar symptoms. A spinal variant with myelopathic features has been described. The majority of untreated patients eventually develop a progressive dementia. Seizures, myopathy, and extrapyramidal and psychiatric symptoms may be present.

Diagnosis and Treatment

Xanthomas, typically of the Achilles tendon, are suggestive of this diagnosis. Other extracerebral manifestations include atherosclerosis, osteoporosis, and respiratory, endocrine, and liver abnormalities. MRI findings include T2 signal hyperintensity of the dentate nucleus and the supratentorial white matter. Treatment with chenodeoxycholic acid, which inhibits the synthesis of abnormal bile acids, reduces the cholestanol levels.

76 Mitochondrial Disease

RADHIKA DHAMIJA, MBBS; RALITZA H. GAVRILOVA, MD

Introduction

Primary mitochondrial diseases are a heterogeneous group of disorders that result from defects of the oxidative phosphorylation system of the mitochondria. Mitochondrial diseases are relatively common, though often underrecognized, with an estimated incidence of 1 in 10,000 live births.

Mitochondria are double-membrane–bound cytoplasmic organelles whose primary function is to provide energy (ie, adenosine triphosphate) from the breakdown of carbohydrates, protein, and lipids by means of the electron transport chain and the oxidative phosphorylation system.

The respiratory chain of the mitochondria is located in the inner mitochondrial membrane. It consists of 5 multimeric protein complexes (complexes I-IV and ATP synthase [ie, complex V]). The structural proteins of these complexes are encoded by 13 mitochondrial and more than 70 nuclear genes (Table 76.1). Therefore, primary mitochondrial disorders can result from mutations of either mitochondrial or nuclear genes. Subsequently, mitochondrial disorders may follow a maternal or mendelian inheritance pattern.

Mitochondria are ubiquitous. As a result, in the case of mitochondrial dysfunction, all systems may be affected, but the tissues with the highest energy demands, such as the central nervous system, skeletal and cardiac muscle, or liver, are affected most often. Therefore, multisystem presentation and a positive family history may suggest a mitochondrial disorder. See Volume 1, Chapter 29, "Patterns of Inheritance in Neurogenetic Disease," for details on mitochondrial inheritance.

The most common mitochondrial syndromes due to mutations in mitochondrial DNA (mtDNA) and nuclear genes are discussed in this chapter and divided by molecular mechanism. Tables 76.2 and 76.3 provide a general overview of select mitochondrial disorders due to point mutations of mtDNA and those due to large-scale rearrangements of mtDNA, respectively.

Table 76.1 • Genes Involved in Electron Transport Chain Complexes

Complex	Mitochondrial Genes	Nuclear Genes
Complex I (nicotinamide adenine dinucleotide dehydrogenase)	7	>44
Complex II (succinate coenzyme Q reductase)	0	4
Complex III (ubiquinol:cytochrome c oxidoreductase)	1	>10
Complex IV (cytochrome c oxidase)	3	10
Complex V (adenosine triphosphate synthase)	2	14
Total	13	>70

- Primary mitochondrial disorders can result from mutations of either mitochondrial or nuclear genes.

Point Mutations of mtDNA

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Strokelike Episodes

Overview and Genetics

The syndrome of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) is a

Abbreviations: CPEO, chronic progressive external ophthalmoplegia; CSF, cerebrospinal fluid; KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonic epilepsy with ragged red fibers; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NARP, neurogenic weakness, ataxia, and retinitis pigmentosa

Table 76.2 • General Features of Select Mitochondrial Disorders Due to Point Mutations in Mitochondrial DNA

Disease	Genetics	Clinical Features	Other
Myoclonic epilepsy with ragged red fibers (MERRF)	Point mutations of mitochondrial DNA	Onset: adolescence to early adulthood Proximal muscle weakness Associated features (not present in all cases): seizure (myoclonic or generalized tonic-clonic), ataxia, dementia, hearing loss, short stature, optic atrophy, pigmentary retinopathy	CK: normal or mildly elevated Serum or CSF lactate: elevated Muscle biopsy: ragged red fibers on Gomori trichrome staining
Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS)	Point mutations of mitochondrial DNA	Onset: childhood to adulthood Proximal muscle weakness; fatigability Associated features: headaches, encephalopathy, seizures, stroke, short stature, hearing loss, optic atrophy, cardiomyopathy, diabetes	Serum or CSF lactate: elevated Neuroimaging: basal ganglia calcification, atrophy; stroke may be present Muscle biopsy: ragged red fibers on Gomori trichrome staining
Neurogenic weakness, ataxia, and retinitis pigmentosa (NARP)	Point mutations of mitochondrial DNA	Onset: childhood to adulthood Peripheral neuropathy, ataxia, and retinitis pigmentosa	Brain MRI: T2 changes in basal ganglia; atrophy EMG: sensorimotor peripheral neuropathy CSF lactate: elevated
Leber hereditary optic neuropathy (LHON)	Point mutations of mitochondrial DNA	Onset: 2nd decade Painless visual loss; may affect both eyes simultaneously or in succession over weeks to months	Funduscopy: disc edema evolving to atrophy

Abbreviations: CK, creatine kinase; CSF, cerebrospinal fluid; EMG, electromyography; MRI, magnetic resonance imaging.

maternally inherited multisystem disorder caused by point mutations of mtDNA.

Clinical Features

MELAS has a variable age of onset but most commonly presents before the age of 30 years. Initial symptoms depend on the age of onset and include developmental delay (before 6 years of age), myopathy presenting as exercise intolerance (between 6 and 10 years of age), or sensorineural hearing loss (after the age of 10 years). However, because of the nonspecific nature of these initial symptoms, the diagnosis may remain unrecognized until the

Table 76.3 • General Features of Select Mitochondrial Disorders Due to Large-Scale Rearrangements of Mitochondrial DNA

Disease	Genetics	Clinical Features	Other
Kearns-Sayre syndrome	Single large mitochondrial DNA mutation of varying size; usually sporadic	Onset: <20 y Progressive external ophthalmoplegia Proximal muscle weakness Associated features: retinitis pigmentosa, heart block/arrhythmia, short stature, hearing loss, dementia, ataxia, endocrine disorders (eg, diabetes mellitus)	Potential for respiratory difficulties with CNS depressants, surgery, and infection Prognosis: poor
Chronic progressive external ophthalmoplegia	Autosomal dominant and maternally inherited forms	Onset: childhood/adolescence Progressive external ophthalmoplegia and ptosis	Potential for respiratory insufficiency and decreased ventilatory drive with CNS depressants, surgery, infection
Pearson syndrome	Mitochondrial DNA deletions	Onset: <5 y Hypotonia, developmental delay, ataxia, tremor Anemia Pancreatic insufficiency	Often fatal in children <4 y

Abbreviation: CNS, central nervous system.

patient develops the characteristic strokelike episode or progressive encephalopathy.

Strokelike episodes are defined as recurrent neurologic deteriorations resembling stroke, often combined with seizures or encephalopathy but with distinct neuroimaging findings (lesions that most commonly affect the parieto-occipital cortex and are not confined to a single vascular territory). Disease course is often relapsing-remitting. Recurrent strokelike episodes lead to progressive neurologic deterioration including hemiparesis, hemianopia, gait imbalance, and cognitive impairment.

Other associated features are short stature, migraine headaches, type 2 diabetes mellitus, and gastrointestinal dysmotility with recurrent vomiting or intestinal pseudo-obstruction. Cardiomyopathy and cardiac conduction abnormalities (Wolff-Parkinson-White syndrome) are less common. Ophthalmoplegia is rare but has been seen in some patients.

Diagnosis

Diagnosis is based on the combination of clinical, radiologic, biochemical, histologic, and genetic/molecular abnormalities. Neuroimaging findings are characteristic and demonstrate the presence of a metabolic stroke with cortical (and/or subcortical) involvement that is not confined to a single vascular territory (Figure 76.1). The lesions evolve over days to weeks to cortical atrophy. Symmetrical calcification of the basal ganglia may also be seen in some cases.

Histologic examination of affected muscle may show the presence of ragged red fibers representing subsarcolemmal proliferation of mitochondria on modified Gomori trichrome staining. Electron microscopy may reveal an increased number or abnormal structure of the mitochondria. Electrocardiogram can be abnormal, with evidence of cardiomyopathy, Wolff-Parkinson-White syndrome, or incomplete heart block. Lactic acidosis (>2.0 mmol/L) can be present in blood or cerebrospinal fluid (CSF), or both. Several transfer RNA point mutations have been described in patients with MELAS, but 80% of cases are due to the A3243G mutation in the gene for tRNA leucine.

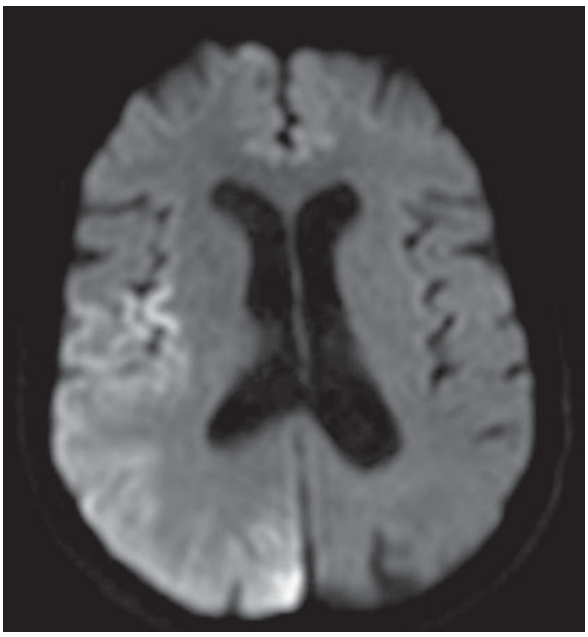

Figure 76.1 *Magnetic Resonance Image in a Patient With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Strokelike Episodes (MELAS).*
Diffusion-weighted image shows cerebral infarction.
(Courtesy of Dr Marc C. Patterson, Mayo Clinic, Rochester, Minnesota. Used with permission.)

Myoclonic Epilepsy With Ragged Red Fibers

Overview and Genetics

Myoclonic epilepsy with ragged red fibers (MERRF) is a maternally inherited multisystem disorder caused by heteroplasmic state of a point mutation in mtDNA.

Clinical Features

MERRF usually begins with cortical myoclonus, followed by seizures, neurogenic weakness, ataxia, and cognitive deterioration. Age of onset of symptoms is typically in childhood, occurring after normal early development, but can be from late childhood to adulthood. Other associated features are hearing loss, short stature, pigmentary retinopathy, optic atrophy, spasticity, peripheral neuropathy, and cardiomyopathy. Lipomas, especially of the neck and trunk, are rare.

Diagnosis

Neuroimaging may show atrophy of the cerebral cortex and basal ganglia calcifications. Echocardiogram and electrocardiogram may show evidence of cardiomyopathy and heart block, respectively.

The histologic hallmark of MERRF is the presence of ragged red fibers representing subsarcolemmal proliferation of mitochondria on modified Gomori trichrome staining of the affected muscle (Figure 76.2). Electron microscopy shows increase in the number and size of mitochondria. Lactic acidosis (>2.0 mmol/L) can be present in blood or CSF. Eighty percent of patients have a point mutation in the mitochondrial gene for tRNA lysine (A8344G, T8356C, G8363A).

Neurogenic Weakness, Ataxia, and Retinitis Pigmentosa

Overview and Genetics

Neurogenic weakness, ataxia, and retinitis pigmentosa (NARP) is a maternally inherited neurodegenerative condition.

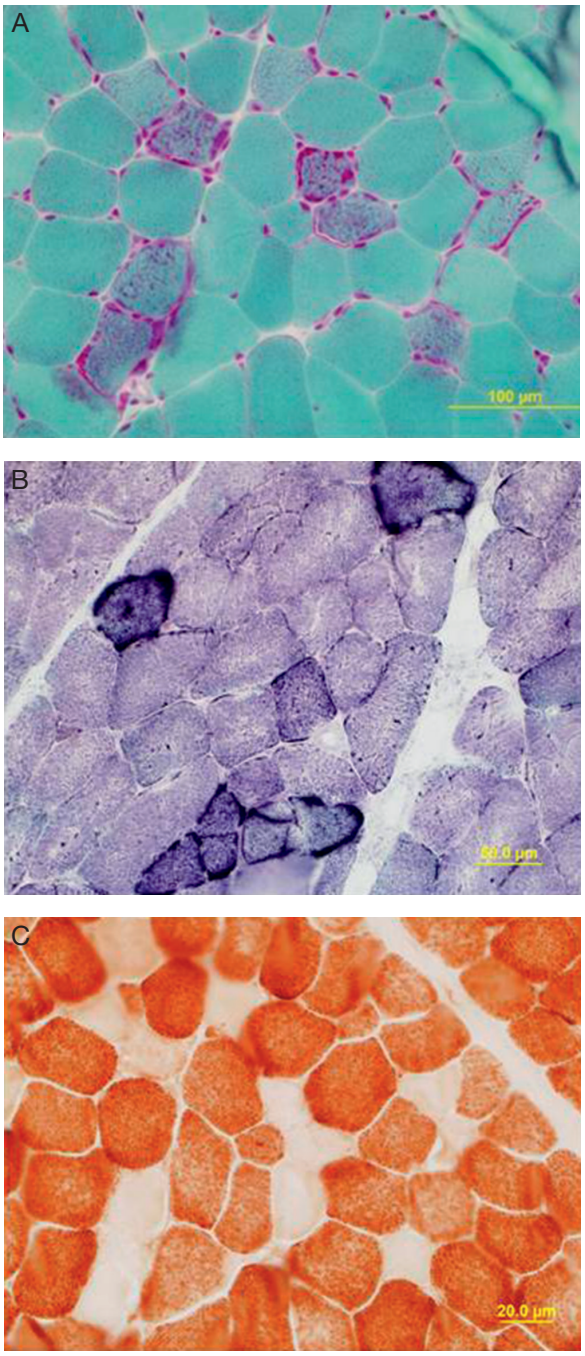

Figure 76.2 *Muscle Histopathology of Myoclonic Epilepsy With Ragged Red Fibers. A, B, and C, Note the "ragged red fibers" representing subsarcolemmal proliferation of mitochondria*
(Courtesy of Dr Duygu Selcen, Mayo Clinic, Rochester, Minnesota. Used with permission.)

Clinical Features

NARP most commonly presents in the first decade of life, but onset of symptoms ranges from childhood to adulthood. Affected individuals have sensorimotor axonal peripheral neuropathy, cerebellar ataxia, and retinitis pigmentosa. Cognitive deficits involve processing speed, visual-spatial orientation, and verbal fluency. In most patients, NARP remains stable for several years, but episodic neurologic deterioration may occur.

Diagnosis

Brain magnetic resonance imaging (MRI) may demonstrate T2 hyperintensities in the putamen and caudate head, as well as cerebellar, cortical, pontine, and cervical cord atrophy. Nerve conduction studies may demonstrate sensorimotor axonal polyneuropathy. Results of muscle biopsy are typically normal. Ophthalmologic examination may reveal pigmentary retinopathy, and electroretinography confirms photoreceptor dysfunction. Lactic acid elevation is more commonly seen in CSF than in blood. Most patients (>55%) have a point mutation in the *MT-ATP6* gene.

Leber Hereditary Optic Neuropathy

Overview and Genetics

Leber hereditary optic neuropathy (LHON) is a maternally inherited disorder affecting males more commonly than females (ratio, 4:1). Approximately 90% of individuals with LHON have 1 of 3 homoplasmic mtDNA point mutations: m.3460G>A, m.11778G>A, or m.14484T>C. These 3 mutations are located in genes encoding complex I subunits and result in decreased adenosine triphosphate production and consequently damage of the retinal ganglion cells. Therefore, the pathologic hallmark of LHON is degeneration of the retinal ganglion cell layer and subsequently their axons and the optic nerve.

Clinical Features and Diagnosis

LHON typically presents in the second decade of life with severe, painless, acute or subacute visual loss. Both eyes may be affected simultaneously, but approximately 50% of patients experience sequential vision loss in both eyes, usually within 2 to 4 months but sometimes up to 1 year. LHON affects the central vision (maculopapillary bundle), and visual impairment is typically worse than 20/200. Visual recovery may occur in some patients.

Visual outcome depends on the age of onset (better prognosis with onset before age 20 years) and the specific causative mutation (patients with m.14484T>C have a better chance of recovery), among other factors. Funduscopic examination shows disc edema and increased vascular tortuosity in the acute phase and optic atrophy in the chronic phase. Cranial neuroimaging is necessary to exclude compressive and infiltrative causes of a bilateral optic neuropathy.

- Strokelike episodes are defined as recurrent neurologic deteriorations resembling stroke, often combined with seizures or encephalopathy but with distinct neuroimaging findings (lesions that most commonly

affect the parietooccipital cortex and are not confined to a single vascular territory).
- Lactic acidosis (>2.0 mmol/L) can be present in blood or CSF, or both, of patients with MELAS.
- The histologic hallmark of MERRF is the presence of ragged red fibers representing subsarcolemmal proliferation of mitochondria on modified Gomori trichrome staining of the affected muscle.
- Patients with NARP have sensorimotor axonal peripheral neuropathy, cerebellar ataxia, and retinitis pigmentosa.
- Leber hereditary optic neuropathy typically presents in the second decade of life with severe, painless, acute or subacute visual loss.

Deletions or Duplications (Large-Scale Rearrangements) of mtDNA

Overview

Deletions or duplications of mtDNA are called large-scale rearrangements. More than one-third of cases are detected on the basis of a common 4.9-kilobase deletion in mtDNA. The clinical manifestations resulting from large-scale rearrangements of mtDNA are grouped into discrete clinical syndromes, such as chronic progressive external ophthalmoplegia (CPEO), Kearns-Sayre syndrome (KSS), and Pearson syndrome. However, considerable clinical variability exists, depending on the tissues involved, and many cases do not fit neatly into one particular category. In contrast to the maternal inheritance of most mtDNA diseases, most cases of deletions or duplications of mtDNA are sporadic.

Chronic Progressive External Ophthalmoplegia

CPEO can also result from mutations in nuclear genes such as *SLC25A4* encoding adenine nucleotide translocase type 1, *C10orf2* encoding twinkle protein, or *POLG1* encoding the catalytic subunit of mtDNA polymerase.

Disease onset can be from the second decade to late adulthood. Patients develop distinct neuro-ophthalmologic features including paresis of extraocular muscles and bilateral ptosis. The disease is slowly progressive, so diplopia is often absent. Proximal myopathy can also develop.

Kearns-Sayre Syndrome

KSS typically presents before the age of 20 years with CPEO and pigmentary retinal cone-rod dystrophy. Patients may also have a cardiac conduction defect with heart block, cerebellar ataxia, or CSF protein level greater than 100 mg/dL. Other rare features include short stature, hearing loss, proximal myopathy, cognitive impairment, renal insufficiency, and diabetes.

Pearson Syndrome (Sideroblastic Anemia and Pancreatic Insufficiency)

Pearson syndrome presents before 5 years of age with neonatal/infantile anemia (80%) and exocrine pancreatic insufficiency (30% by age 4 years). It is often fatal, and up to 60% of patients die before age 4 years. Those who survive beyond age 1 year may have multisystem involvement including liver function impairment, renal tubulopathy, diabetes, hearing loss, or short stature. About one-third have neurologic features including hypotonia, developmental delay, ataxia, or tremor. Some patients may develop signs and symptoms of KSS or Leigh syndrome.

- Patients with chronic progressive external ophthalmoplegia develop distinct neuro-ophthalmologic features including paresis of extraocular muscles and bilateral ptosis.
- Kearns-Sayre syndrome typically presents before the age of 20 years with chronic progressive external ophthalmoplegia and pigmentary retinal cone-rod dystrophy.

Nuclear Gene Mutations

Mitochondria are semiautonomous and depend on nuclear encoded factors for their replication and for the structure and function of the respiratory chain. Therefore, mutations in nuclear genes that are required for mtDNA replication will result in mtDNA depletion, and mutations in nuclear genes that encode subunits of the respiratory chain may compromise the oxidative phosphorylation system. Mitochondrial diseases caused by mutations in nuclear genes are inherited in a mendelian pattern.

mtDNA Depletion Syndrome

Maintenance of the amount of mtDNA is dependent on *POLG1*, which encodes the catalytic subunit of DNA polymerase γ. DNA polymerase γ is the only polymerase responsible for mtDNA replication in mammalian cells. Thus, mutations of this gene lead to mtDNA depletion syndromes. To date, more than 150 mutations in this gene are known. The phenotype varies from mildly affected individuals with peripheral neuropathy to severely affected children with Alpers-Huttenlocher disease.

Recessive *POLG1* mutations have been associated with Alpers-Huttenlocher disease; CPEO; ataxia-neuropathy syndrome comprising mitochondrial recessive ataxia syndrome, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; spinocerebellar ataxia with epilepsy; and idiopathic parkinsonism. Dominant mutations have also been linked to CPEO.

Alpers-Huttenlocher Disease

Alpers-Huttenlocher disease is a rare autosomal recessive hepatocerebral disorder, also referred to as diffuse progressive degeneration of cerebral gray matter or progressive infantile poliodystrophy. It is characterized by the clinical triad of psychomotor retardation, intractable epilepsy, and liver failure. Children with Alpers-Huttenlocher disease may have normal initial development or may have a history of delays. They typically present between 2 and 4 years of age in the setting of intercurrent illness when they develop partial or secondarily generalized seizures. The initial seizures may be followed by status epilepticus (particularly epilepsia partialis continua, consisting of repetitive motor activity of one part of the body), myoclonic seizures, regression of developmental milestones, spasticity, ataxia, and cortical blindness. Liver failure may develop over several months, or it may be precipitated by valproic acid. Therefore, valproic acid is contraindicated.

Most patients die before the age of 3 years. Electroencephalogram may demonstrate slow wave activity and/or epileptic spikes over the involved hemisphere. MRI findings include cerebral atrophy, often worse in the occipital regions, or signal abnormalities in the deep gray matter nuclei.

- Mitochondrial diseases caused by mutations in nuclear genes are inherited in a mendelian pattern.
- Alpers-Huttenlocher disease is characterized by the clinical triad of psychomotor retardation, intractable epilepsy, and liver failure.

Mutations in Nuclear Genes Encoding Respiratory Complex Subunits

Overview

Mutations in the nuclear genes encoding respiratory complex subunits compromise the oxidative phosphorylation system. The most common disease phenotype is Leigh syndrome.

Table 76.4 • Nuclear Genes Encoding Protein Subunits of the Respiratory Complexes Associated With Leigh Syndrome

Complex	Gene
Complex I	*NDUFS1* *NDUFS4* *NDUFS7* *NDUFS8* *NDUFV1*
Complex II	*SDHA*
Complex III	*BCS1L*
Complex IV	*SURF1*

Leigh Syndrome

Overview and Genetics

Leigh syndrome can result from impaired activity of respiratory chain complexes I, II, IV, or V or coenzyme Q. Isolated defects of pyruvate dehydrogenase complex due to mutations in the X-linked *PDHA1* gene encoding the E1 alpha catalytic subunit of the complex can also cause this phenotype. Thus, Leigh syndrome is genetically heterogeneous, and mutations in both nuclear and mitochondrial genes can cause Leigh phenotype (Table 76.4).

Clinical Features

Leigh syndrome, or subacute necrotizing encephalomyelopathy, is a severe mitochondrial neurodegenerative condition characterized by bilaterally symmetrical lesions in the basal ganglia, thalamus, and brainstem. In the majority of cases, onset is in early childhood, usually after an intercurrent illness, and is characterized by psychomotor delay and/or regression with signs and symptoms of brainstem and basal ganglia disease (dystonia, chorea, respiratory failure, swallowing difficulties, persistent vomiting, hypotonia, spasticity). Peripheral neuropathy, optic nerve atrophy, and hypertrophic cardiomyopathy may also develop. The disease course is characterized by episodic neurologic deterioration. About 50% of affected children die by age 2 to 3 years, most often as a result of respiratory or cardiac compromise. Rare adult-onset forms have also been reported.

Diagnosis

Elevated lactic acid levels in both blood and CSF are almost always present, though they may fluctuate in severity. MRI shows evidence of bilateral T2 hyperintense necrotic lesions of the basal ganglia and brainstem. Neuropathologic examination of these lesions shows bilateral symmetrical spongiform necrosis and capillary proliferation.

- Leigh syndrome, or subacute necrotizing encephalomyelopathy, is a severe mitochondrial neurodegenerative condition characterized by bilaterally symmetrical lesions in the basal ganglia, thalamus, and brainstem.

Diagnosis of Mitochondrial Disorders

Multisystemic presentation commonly involving the nervous system and a positive family history should raise the suspicion of an underlying mitochondrial disorder. Diagnosis is based on a combination of clinical, radiologic, biochemical, histologic, and genetic/molecular

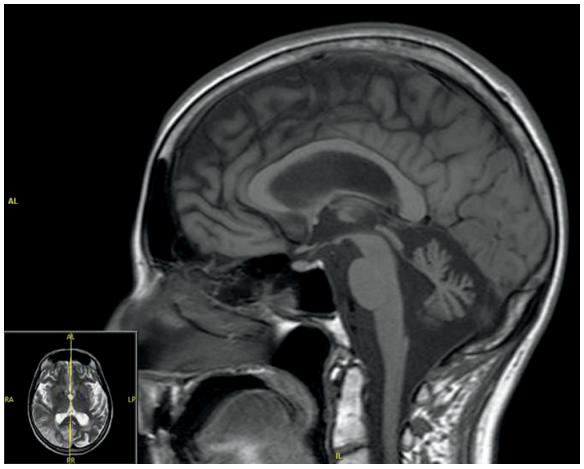

Figure 76.3 *Imaging Findings in Mitochondrial Encephalomyopathy, Lactic Acidosis, and Strokelike Episodes (MELAS). Magnetic resonance image (T1 sagittal) shows atrophy of the cortex, cerebellum, and brainstem.*
(Courtesy of Dr Marc C. Patterson, Mayo Clinic, Rochester, Minnesota. Used with permission.)

investigations. Further confirmation can be done by direct mutation analysis of the mitochondrial or nuclear DNA.

Radiologic Investigations

MRI scan can be normal or show a wide array of abnormalities. It may demonstrate changes consistent with an ischemic stroke that do not correspond to a single vascular territory in MELAS (Figure 76.1); atrophy of the cortex or cerebellum in MERRF, NARP, and mitochondrial depletion syndromes (Figure 76.3); leukodystrophy in complex I deficiency due to specific nuclear DNA mutations; and symmetrical T2 hyperintensities and/or restricted diffusion on diffusion-weighted images in the basal ganglia and brainstem in Leigh syndrome (Figure 76.4). Computed tomogram may show basal ganglia calcification and/or diffuse atrophy. Presence of a lactate peak (1.33 ppm) on magnetic resonance spectroscopy adds to the suspicion of an underlying mitochondrial disorder.

Biochemical Investigations

Testing of blood and/or CSF lactate and pyruvate, plasma amino acids, urine organic acids, and carnitine may be useful in the diagnosis of mitochondrial diseases.

Blood levels of lactate and pyruvate are typically elevated but nonspecific. The blood or CSF lactate to pyruvate ratio reflects the cytoplasmic redox state and can be elevated to greater than 20. The ratio is most commonly elevated during metabolic crisis. Levels can be normal in LHON and KSS.

Plasma amino acids may be measured as an adjunctive test. Hyperalaninemia is typically seen.

Urine organic acid tests show increased excretion of tricarboxylic acid cycle intermediates, ethylmalonic acid, 3-methylglutaconic acid, and dicarboxylic acid. These findings commonly occur but are not specific for any particular mitochondrial disorder. Levels may be normal during periods of clinical stability.

Carnitine analysis may be helpful. Carnitine serves as a mitochondrial transporter for free fatty acids and binds potentially toxic coenzyme A esters. Low free carnitine level and elevated acylcarnitine to free carnitine ratio are typically seen in mitochondrial disorders.

Histologic Investigations

The most severely affected tissue should be biopsied. Muscle is most commonly biopsied. Ragged red fibers representing proliferating mitochondria are seen on modified Gomori trichrome staining as red granular deposits of mitochondria in the subsarcolemmal space. Electron microscopy may show characteristic ultrastructural abnormalities (ie, increased mitochondrial number and size, distorted or absent cristae, and paracrystalline inclusions)

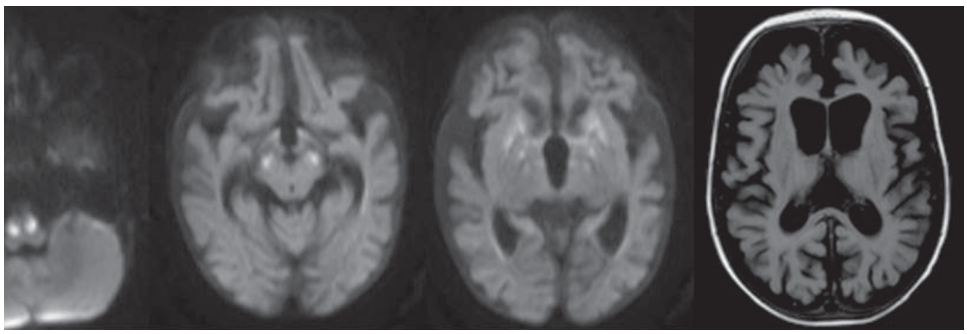

Figure 76.4 *Imaging Abnormalities in Leigh Syndrome. Three images on left, Diffusion-weighted magnetic resonance images (MRI) show restricted diffusion in the brainstem and basal ganglia. Image on far right, MRI (FLAIR) shows marked cerebral atrophy.*
(Courtesy of Dr Marc C. Patterson, Mayo Clinic, Rochester, Minnesota. Used with permission.)

(Figure 76.2). Analysis of mitochondrial enzyme activity (NADH dehydrogenase [complex I], succinate dehydrogenase [complex II], and cytochrome c oxidase [complex IV]) may show reduced activity.

Molecular/Genetic Investigations

Confirmation of the diagnosis can be done by direct mutation analysis (point mutations, deletions, duplications) or sequencing of mtDNA or nuclear genes.

- Testing of blood and/or CSF lactate and pyruvate, plasma amino acids, urine organic acids, and carnitine may be useful in the diagnosis of mitochondrial diseases.
- Blood levels of lactate and pyruvate are typically elevated in mitochondrial disorders but are nonspecific for diagnosis.
- Muscle is the tissue most commonly biopsied in mitochondrial diseases. Ragged red fibers representing proliferating mitochondria are seen on modified Gomori trichrome staining as red granular deposits of mitochondria in the subsarcolemmal space.
- Confirmation of the diagnosis of a mitochondrial disease can be done by direct mutation analysis (point mutations, deletions, duplications) or sequencing of mtDNA or nuclear genes.

Treatment of Mitochondrial Diseases

Management of mitochondrial disorders requires a multidisciplinary approach. No curative therapy is currently available for mitochondrial disorders. A "mitochondrial cocktail" to promote mitochondrial function, consisting of carnitine, coenzyme Q_{10} (ubiquinone), riboflavin, and α-lipoic acid, is typically offered to patients. L-arginine infusion is given in acute metabolic strokes in patients with MELAS. As an electron acceptor and free radical scavenger, idebenone is recommended in patients with LHON because of its ability to bypass the functional impairment of complex I.

Supportive measures are important to improve the quality of life of the patients (eg, ophthalmologic surgery for ptosis, pacemaker for cardiac conduction defects, cochlear implants for hearing loss). Seizures usually respond to conventional anticonvulsants. However, valproic acid should not be used because it inhibits carnitine uptake and can cause liver failure. A correct diagnosis and genetic counseling are of utmost importance.

- A "mitochondrial cocktail" to promote mitochondrial function, consisting of carnitine, coenzyme Q_{10} (ubiquinone), riboflavin, and α-lipoic acid, is typically offered to patients with mitochondrial disease.
- Valproic acid should not be used in mitochondrial disease because it inhibits carnitine uptake and can cause liver failure.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

XII.1. You are asked to evaluate a 1-month-old infant male with obtundation and frequent seizures since shortly after birth. His serum ammonia and glucose levels are normal. Cerebrospinal fluid examination shows a mildly elevated protein level and a glucose level of 17 mg/dL. Which of the following is the most likely diagnosis?
a. Phenylketonuria
b. Maple syrup urine disease
c. Neuronal ceroid-lipofuscinosis
d. Glucose transporter 1 (GLUT1) deficiency
e. Ornithine transcarbamylase deficiency

XII.2. Which of the following disorders is caused by a defect in nucleic acid metabolism?
a. Nonketotic hyperglycinemia
b. Lesch-Nyhan syndrome
c. Carnitine palmitoyltransferase I deficiency
d. Smith-Lemli-Opitz syndrome
e. Propionic academia

XII.3. A 13-year-old adolescent boy is brought to your clinic by his parents for evaluation of exercise intolerance. Since starting basketball this season, he has had 2 transient episodes of dark brown urine after games. He is cognitively normal and has met all developmental milestones in a timely fashion. He has mild symmetric proximal weakness on examination. Which of the following is the most likely diagnosis?
a. Glutaric aciduria type I
b. Pyruvate dehydrogenase complex deficiency
c. Acute intermittent porphyria
d. Multiple carboxylase deficiency
e. Carnitine palmitoyltransferase II deficiency

XII.4. A 17-year-old cognitively normal adolescent boy presents to your clinic with a slowly progressive spastic paraparesis. An electrodiagnostic evaluation shows a length-dependent sensorimotor peripheral neuropathy. Which of the following tests is most likely to lead to the correct diagnosis?
a. Plasma levels of very long-chain fatty acids
b. Leukocyte arylsulfatase A assay
c. *GFAP* mutation analysis
d. Serum cholestanol level
e. Cerebrospinal fluid lactate level

XII.5. You follow a 10-year-old girl in your clinic who has juvenile-onset metachromatic leukodystrophy. Which of the following imaging abnormalities was most likely present on her evaluation?
a. Frontal predominant subcortical T2-signal abnormalities on magnetic resonance imaging (MRI)
b. Prominent *N*-acetylaspartate peak on magnetic resonance spectroscopy
c. Subcortical T2-signal hyperintensities with tigroid stripes on MRI
d. Focal T2-signal hyperintensities in the dentate nuclei on MRI
e. Normal MRI of the brain

XII.6. Mutations in which of the following genes is associated with Pelizaeus-Merzbacher disease?
a. Galactocerebrosidase gene
b. Proteolipid protein (*PLP*)
c. *ABCD1*
d. *Notch3*
e. *PEX7*

XII.7. You are asked to evaluate a 16-year-old cognitively normal adolescent boy with fluctuating painful distal paresthesias. On examination, you note multiple angiokeratomas in the lower limbs; on ophthalmologic evaluation, you note corneal "whorls." On further evaluation, you are likely to find which of the following abnormalities?
a. Sphingomyelinase deficiency
b. Neuraminidase deficiency
c. α-Mannosidase deficiency
d. Hexosaminidase A deficiency
e. α-Galactosidase deficiency

XII.8. In the evaluation of a patient with a syndrome of neurologic developmental regression, you note an X-linked pattern of inheritance. Which of the following diagnoses could fit this pattern?
a. Danon disease
b. Mucopolysaccharidosis type I
c. Glycogen storage disease type II
d. Gaucher disease
e. GM_2 gangliosidosis

XII.9. A 2-year-old girl presents with loss of social smiling followed by progressive generalized cognitive decline and severe myoclonic epilepsy. Which of the following pathologic findings is associated with the most likely diagnosis?
a. Membranous cytoplasmic bodies
b. Subsarcolemmal glycogen deposits
c. Fingerprint bodies
d. Axonal spheroids
e. Periodic acid-Schiff–positive neuronal inclusions

XII.10. Neural tube defects, such as myelomeningocele, result from neurulation defects occurring at which of the following stages of gestation?
a. Days 11 to 13
b. Days 25 to 27
c. Days 42 to 44
d. Days 110 to 114
e. Days 190 to 198

XII.11. You evaluate a 15-year-old adolescent girl who has a new diagnosis of focal epilepsy and secondarily generalized seizures. MRI of the brain shows multiple periventricular nodular heterotopias. Mutations in which of the following genes may lead to this neuronal migration abnormality?
a. *DCX*
b. *ABCD1*
c. *LIS1*
d. *FLN1*
e. *NF1*

XII.12. A 1-year-old boy presents for evaluation of a head circumference well above the 99th percentile. Which of the following diagnoses would suggest communicating hydrocephalus as the cause of the macrocephaly?
a. Glutaric aciduria type 1
b. Primitive neuroectodermal tumor
c. Cowden syndrome
d. Fragile X syndrome
e. Choroid plexus papilloma

XII.13. Which of the following mitochondrial disorders is typically caused by large-scale rearrangement in mitochondrial DNA?
a. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
b. Neurogenic weakness, ataxia, and retinitis pigmentosa (NARP)
c. Chronic progressive external ophthalmoplegia (CPEO)
d. Leber hereditary optic neuropathy (LHON)
e. Myoclonic epilepsy with ragged red fibers (MERRF)

XII.14. A 10-year-old girl is sent for evaluation of a possible mitochondrial disorder. Which of the following statements regarding this category of diseases is most correct?
a. Mitochondrial diseases present exclusively in childhood
b. Mitochondrial genome analysis is all that is required to exclude a disorder of mitochondrial function
c. Mitochondrial disorders, when familial, can be inherited in only a maternal pattern
d. Mitochondrial diseases are frequently associated with multisystemic presentations
e. Highly energy-dependent tissues are usually spared in patients with mitochondrial disorders

XII.15. Which of the following statements about the evaluation of patients with mitochondrial diseases is most correct?
a. Mitochondrial gene sequencing or mutation analysis is more sensitive when performed on affected tissues
b. The most sensitive test for Leber hereditary optic neuropathy (LHON) is serum lactate
c. MRI of the brain is typically normal for adults with mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS)
d. Brain biopsy is preferred over muscle biopsy in the diagnosis of myoclonic epilepsy with ragged red fibers (MERRF)
e. *POLG1* mutations have been associated with only chronic progressive external ophthalmoplegia (CPEO)

XII.16. Which of the following is the most common neurocutaneous disorder?
a. Neurofibromatosis type 1 (NF1)
b. Tuberous sclerosis complex (TSC)
c. Hypomelanosis of Ito
d. Ataxia telangiectasia
e. Sturge-Weber syndrome

XII.17. Which of the following statements about the cutaneous manifestations of neurocutaneous disorders is most correct?
a. Hypomelanosis of Ito is associated with truncal telangiectasias
b. von Hippel-Lindau disease is associated with café au lait spots
c. Neurofibromatosis type 2 (NF2) is associated with ash leaf spots
d. Incontinentia pigmenti is associated with retinal hemangioblastoma
e. Sturge-Weber syndrome is associated with facial port wine stain

XII.18. You are asked to evaluate a 5-year-old girl with headaches. Imaging shows obstructive hydrocephalus due to an intraventricular mass, which, after resection, is shown to be a subependymal giant cell astrocytoma (SEGA). Which of the following neurocutaneous syndromes is most likely to accompany this diagnosis?
a. Neurofibromatosis type 2 (NF2)
b. Tuberous sclerosis complex (TSC)
c. Ataxia telangiectasia
d. von Hippel-Lindau disease
e. Linear sebaceous nevus syndrome

XII.19. A 1-week-old newborn male presents with seizures, encephalopathy, and eventually obtundation. Which of the following categories of diseases is the most likely culprit?
a. Lysosomal storage disease
b. Disorder of peroxisomal biogenesis
c. Neurocutaneous disorder
d. Urea cycle defect
e. Leukodystrophy

XII.20. A 7-year-old girl presents with slowly progressive loss of cognitive skills. On examination, she has coarse features, and radiography shows dysostosis multiplex. Which of the following categories of disease is the most likely culprit?
a. Lysosomal storage disease
b. Disorder of peroxisomal biogenesis
c. Neurocutaneous disorder
d. Urea cycle defect
e. Leukodystrophy

Answers

XII.1. **Answer d.**
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XII.2. **Answer b.**
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XII.3. **Answer e.**
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XII.5. **Answer c.**
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XII.6. **Answer b.**
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XII.14. Answer d.
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XII.17. Answer e.
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XII.18. Answer b.
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XII.19. Answer d.
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XII.20. Answer a.
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Section
XIII

Neurologic Complications of Medical Diseases

Neeraj Kumar, MD, *editor*

77 Electrolyte Disturbance and Acid-Base Imbalance

SARA E. HOCKER, MD

Electrolyte Disturbances

Electrolyte disorders are among the most common clinical problems encountered in critically ill patients. Disorders such as severe burns, trauma, sepsis, acute brain injury, and heart failure lead to disturbances in fluid and electrolyte homeostasis through complex mechanisms involving deregulation or activation of hormonal systems and ischemic or nephrotoxic kidney injury. Inappropriate fluid management should also be considered in the differential diagnosis of electrolyte disturbances in patients in intensive care units. Electrolyte imbalances produce both central and peripheral neurologic dysfunction because electrochemical membrane potentials in brain, nerve, and muscle tissues are particularly sensitive to chemical, ionic, and osmolar shifts. Individual conditions are discussed below and presented in Table 77.1 with a focus on the neurologic manifestations they produce.

Hypernatremia

Hypernatremia (serum sodium >145 mEq/L) is due to impaired thirst or access to water, poor release or effect of antidiuretic hormone (ADH), water loss, or sodium retention. Hypernatremia leads to cell shrinkage. The nervous system can adapt over 1 to 2 days by generating solutes (ie, idiogenic osmoles), such as glutamine, taurine, and urea, to minimize cell shrinkage. ADH is released in response to hypernatremia and results in increased thirst and retention of free water by the kidneys.

When hypernatremia is severe (serum sodium >160 mEq/L) or develops rapidly, these adaptive mechanisms fail and symptoms occur. Symptoms relate more to the hyperosmolar state produced by the hypernatremia than to the electrolyte abnormality itself. The most prominent neurologic manifestations of hypernatremia are restlessness, confusion, and diminished arousability. Generalized seizures are uncommon. Focal neurologic deficits should not be attributed to hypernatremia alone. In patients with comorbid hepatic disease, asterixis and myoclonus may be precipitated by hypernatremia. Other uncommon neurologic manifestations include tremor, rigidity, and chorea.

Hyponatremia

Among hospitalized patients, hyponatremia (serum sodium <135 mEq/L) is the most frequent electrolyte disorder. The evaluation of hyponatremia begins by estimating the volume status. In patients with decreased extracellular volume, the likely culprits are diuretics, hypoaldosteronism, or fluid losses (sweat, diarrhea, polyuria, or third spacing). In the euvolemic state, consider iatrogenic causes (ie, postoperative fluid administration) or the syndrome of inappropriate secretion of ADH (SIADH). In patients with congestive heart failure, end-stage liver disease, or renal failure, hyponatremia is often secondary to hypervolemia. In patients with neurologic conditions, hyponatremia most commonly results from SIADH and cerebral salt wasting from hypernatriuresis (ie, excess renal excretion of sodium).

Neurologic dysfunction occurs with very low sodium levels (<120 mEq/L) or with abrupt changes in serum osmolality resulting from a rapid decrease in the serum sodium level. Symptoms of hyponatremia range from fatigue, nausea, headache, and muscle cramps to vomiting, fasciculations, seizures, and a progressive decline in

Abbreviations: ADH, antidiuretic hormone; CO_2, carbon dioxide; SIADH, syndrome of inappropriate secretion of antidiuretic hormone

Table 77.1 • Comparison of Electrolyte Disorders

Electrolyte Disorder	Causes	Symptoms
Hypernatremia	Water loss Sodium retention Impaired thirst or access to water Poor release of ADH	Restless Confused Poor arousability Seizures (rare)
Hyponatremia	Fluid loss (sweat, polyuria, diarrhea, third space) Fluid overload (CHF, renal failure) Medications (diuretics) Iatrogenic (excess intravenous fluids) SIADH Hypoaldosteronism	Headache, nausea Muscle cramps Seizures Reduced consciousness
Hyperkalemia	Poor elimination (renal failure, mineralcorticoid insufficiency) Iatrogenic Excess potassium release from cells (trauma, burns, status epilepticus)	Rare symptoms Nonspecific weakness Paresthesias
Hypokalemia	Excess gastrointestinal or urinary excretion Distribution away from extracellular space (insulin, β-agonists)	Myalgias Weakness Hyporeflexia
Hypercalcemia	Hyperparathyroidism (primary, secondary, or tertiary) Malignancy Thyrotoxicosis	Headache Fatigue Myalgias Psychiatric symptoms
Hypocalcemia	Renal failure Parathyroid deficiency Acute pancreatitis Hypomagnesemia Rhabdomyolysis Tumor lysis syndrome Vitamin D deficiency Critically ill patients	Paresthesias Chvostek sign Trousseau sign Tetany Altered mental status
Hyperphosphatemia	Renal failure Rhabdomyolysis Tumor lysis syndrome Hypoparathyroidism	Similar to effect of hypocalcemia (high serum concentration of phosphorous lowers the calcium level)
Hypophosphatemia	Impaired absorption Alkalosis Refeeding syndrome Burns Chronic alcoholism Medications (catecholamines, thiazide diuretic, antacid)	Perioral paresthesias Polyneuropathy Inability to wean from ventilator
Hypermagnesemia	Excess magnesium intake (patients with eclampsia or renal failure)	Nausea, vomiting Dry mouth Flushing Generalized weakness, hyporeflexia (severe)
Hypomagnesemia	Critially ill patients Low magnesium intake Poor absorption Excess excretion by kidneys (eg, diuretics)	Tremor Myoclonus Ataxia Tachycardia, sweating, dilated pupils Seizures (severe)

Abbreviations: ADH, antidiuretic hormone; CHF, congestive heart failure; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

consciousness. Life-threatening hyponatremia (serum sodium <110–115 mEq/L or an abrupt decrease in the sodium level) causes cerebral edema, which results in coma.

Rapid correction of hyponatremia may be as detrimental as the disorder itself. A controlled but expeditious correction (at a rate of <12 mEq/L daily) should occur—a more rapid correction may cause central pontine or

extrapontine myelinolysis. Central pontine and extrapontine myelinolysis are more likely to occur in susceptible patients, such as those with chronic illness or alcohol abuse. It is a monophasic demyelinating event predominantly involving the basis pontis, with or without extrapontine lesions in the subcortical white matter, cerebellum, lateral geniculate body, basal ganglia, thalamus, and internal capsule (Figure 77.1). Clinical features may include spastic paraparesis, pseudobulbar palsy and dysarthria from involvement of the corticobulbar tracts, lethargy, confusion, locked-in syndrome, and coma.

Hyperkalemia

Hyperkalemia is defined as a serum potassium concentration more than 5.5 mEq/L. It results from excessive potassium release from cells (eg, trauma, burns, or persistent seizures) or from ineffective elimination (eg, renal failure, mineralocorticoid insufficiency or resistance, or medications that impair urinary excretion).

Hyperkalemia rarely results in neurologic manifestations, but generalized nonspecific weakness, paresthesias, and long tract sensory signs may occur.

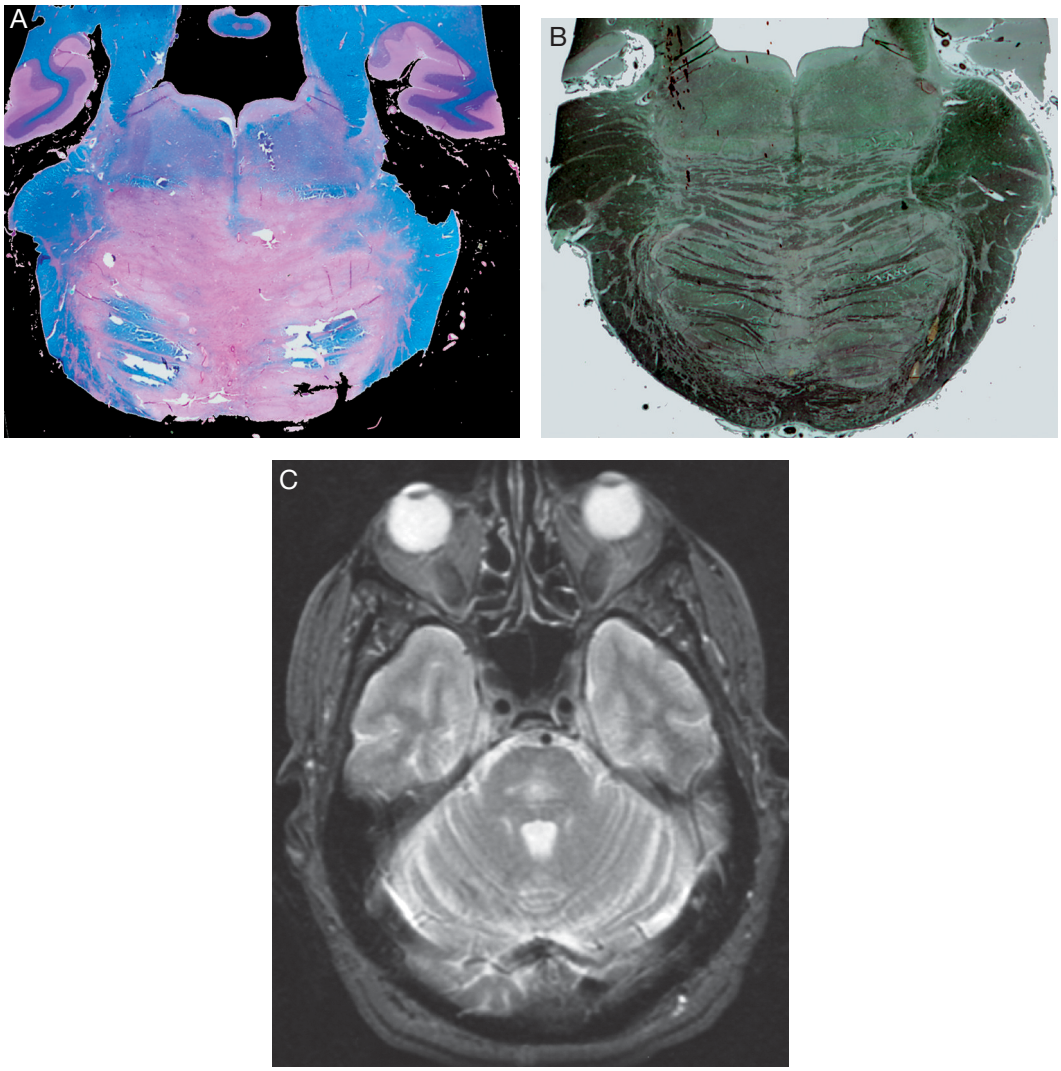

Figure 77.1 *Central Pontine Myelinolysis (CPM).*
A, The basis pontis has undergone symmetric and extensive loss of myelin, with relative sparing of subpial tissue and small patches within the substance of the pons (Kluver-Barrera stain). B, Remarkable preservation of axons is shown in the region of extensive demyelination (silver stain). C, Magnetic resonance imaging (MRI) of a different patient with CPM shows symmetric, increased T2-weighted signal in the pons, corresponding to a region of demyelination (axial T2-weighted MRI sequence).
(Adapted from Mowzoon N. Toxic and metabolic disorders of the nervous system. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 679–92. Used with permission of Mayo Foundation for Medical Education and Research.)

Hypokalemia

Hypokalemia is defined as a serum potassium concentration of less than 3.5 mEq/L. It may result from underconsumption (rarely), excess gastrointestinal or urinary excretion, or distribution away from the extracellular space, such as with the use of β-agonists or insulin. Hypokalemia predominantly affects the peripheral nervous system when potassium levels are less than 2.5 mEq/L. This is because the electrochemical potassium gradient between the extracellular and intracellular spaces is necessary for the cell membrane to repolarize to the resting state after an action potential.

Neuromuscular manifestations of hypokalemia range from myalgias, muscle cramping, and weakness to hyporeflexia, flaccid paralysis, and respiratory depression from severe impairment of skeletal muscle function. Weakness often disproportionately affects the proximal muscle groups of the lower extremities.

Hypercalcemia

The differential diagnosis of hypercalcemia includes primary hyperparathyroidism and malignant disease with or without metastasis.

Neurologic symptoms appear in at least half the patients with increased calcium levels and include headache, fatigue, myalgias, and psychiatric symptoms when levels exceed 12 mg/dL. Psychiatric symptoms may include delusions, agitation, and hallucinations. As the calcium levels increase, patients may become progressively drowsy and eventually comatose. Symptoms are typically reversible with prompt initiation of therapy, which includes hydration with or without drugs that inhibit bone resorption.

Hypocalcemia

Hypocalcemia is defined as a serum calcium level <9 mg/dL or an ionized calcium level less than 4.5 mg/dL. It may result from renal failure, parathyroid deficiency, acute pancreatitis, hypomagnesemia, rhabdomyolysis, tumor lysis syndrome, vitamin D deficiency, or repeated blood transfusions. The calcium level is frequently low in critically ill patients, many of whom do not show outward clinical manifestations of hypocalcemia.

Patients who are symptomatic classically present with tetany, a syndrome consisting of paresthesias in the hands and feet and around the lips followed by muscle spasms, which begin distally and spread proximally in the extremities. Patients with hypocalcemia may demonstrate the Chvostek sign (facial muscle contraction when tapping the facial nerve) or the Trousseau sign (flexor carpal spasm with transient brachial artery compression). Seizures are relatively common and may be focal or generalized. Cognitive changes range from drowsiness to agitated delirium. Severe hypocalcemia may cause laryngeal stridor and opisthotonus.

Treatment involves administration of intravenous calcium gluconate, normalization of serum magnesium levels, and correction of the underlying cause of the hypocalcemia.

Hyperphosphatemia

The differential diagnosis of hyperphosphatemia includes renal failure, rhabdomyolysis, tumor lysis syndrome, and hypoparathyroidism.

The clinical effects of hyperphosphatemia are related to its effects on calcium metabolism. An increased serum phosphorus level decreases the ionized calcium level, the effects of which are discussed above.

Hypophosphatemia

Hypophosphatemia in patients in intensive care units typically results from impaired absorption, alkalosis, burns, refeeding, chronic alcoholism, or pharmacologic agents such as catecholamines, thiazide diuretics, and antacids.

Hypophosphatemia produces cognitive, sensory, and neuromuscular symptoms when serum levels are less than 1 mg/dL. Patients may present with a neuropathy that mimics acute inflammatory demyelinating polyneuropathy, with ptosis, perioral paresthesias, and quadriplegia. Hypophosphatemia may cause diaphragmatic and proximal muscle weakness related to adenosine triphosphate depletion, with the result that patients cannot be weaned from a ventilator. In addition, rhabdomyolysis may occur in hypophosphatemic patients.

Hypermagnesemia

Clinically significant hypermagnesemia is almost always caused by exogenous administration of magnesium. It is most common in the treatment of eclampsia or in patients with underlying renal failure receiving antacids or hemodialysis with a high magnesium content in the dialysate.

Clinical features of hypermagnesemia appear when serum magnesium levels exceed 4 mg/dL. Patients experience nausea, vomiting, dry mouth, and flushing. At higher levels, severe generalized weakness and hyporeflexia occur; magnesium competes with calcium at the neuromuscular junction, impairing release of acetylcholine from the presynaptic terminal and resulting in a clinical picture that resembles Lambert-Eaton myasthenic syndrome.

In general, correction may be allowed to occur naturally with removal of the exogenous magnesium source. If heart block is present, the use of calcium gluconate reverses hypermagnesemia.

Hypomagnesemia

Of the many causes of hypomagnesemia in critically ill patients, most can be attributed to a low-magnesium diet,

poor absorption, or excess excretion by the kidneys. Probably the most common cause in patients in intensive care units is the use of loop diuretics.

Symptoms of hypomagnesemia occur when serum levels are less than 1 mg/dL; symptoms include tremor, myoclonus, and ataxia and episodes of agitation, sweating, tachycardia, and hallucinations, during which the pupils are dilated. Severe hypomagnesemia may also predispose patients to seizures.

- The most prominent neurologic manifestations of hypernatremia are restlessness, confusion, and diminished arousability.
- Symptoms of hyponatremia range from fatigue, nausea, headache, and muscle cramps to vomiting, fasciculations, seizures, and a progressive decline in consciousness.
- Rapid correction of hyponatremia may be as detrimental as the disorder itself. A controlled but expeditious correction (at a rate of <12 mEq/L daily) should occur—a more rapid correction may cause central pontine or extrapontine myelinolysis.
- Neuromuscular manifestations of hypokalemia range from myalgias, muscle cramping, and weakness to hyporeflexia, flaccid paralysis, and respiratory depression from severe impairment of skeletal muscle function.
- Patients with hypocalcemia may demonstrate the Chvostek sign (facial muscle contraction when tapping the facial nerve) or the Trousseau sign (flexor carpal spasm with transient brachial artery compression).

Acid-Base Imbalance

The body maintains a pH of about 7.40 in the extracellular fluid by respiratory excretion of carbon dioxide (CO_2) and renal excretion of nonvolatile acid or base. Acute acid-base disorders may change the arterial pH enough to cause neurologic manifestations (Box 77.1). Buffer systems exist to help maintain the pH by balancing serum bicarbonate and CO_2. If one of these components becomes abnormal, complex respiratory or renal compensation occurs.

Respiratory Acidosis

The primary abnormality in respiratory acidosis is hypercapnia ($Paco_2$ >45 mm Hg), which decreases the arterial pH and produces a compensatory increase in bicarbonate. The degree of hypercapnia and the acuity with which it occurs correlate with the clinical symptoms. Patients with chronic respiratory acidosis are often asymptomatic.

Respiratory acidosis is more likely to produce neurologic manifestations than metabolic acidosis because CO_2 diffuses readily across the blood-brain barrier. Thus, if left untreated, acidemia worsens and may result in coma. Patients with acute respiratory acidosis can present with symptoms and signs of increased intracranial pressure (Box 77.1) from the cerebral vasodilatation that occurs with rapid elevations of $Paco_2$. Common causes of respiratory

Box 77.1 • Neurologic Symptoms and Signs of Acidosis and Alkalosis

- Acidosis symptoms
  - Somnolence
  - Confusion
  - Headache
  - Visual disturbances
  - Tremulousness
- Acidosis signs
  - Encephalopathy, coma
  - Visual impairment
  - Asterixis
  - Signs of increased intracranial pressure (respiratory acidosis)
  - Increased opening CSF pressure
  - Papilledema
  - Pupillary light reflex abnormality
  - Herniation syndromes
- Alkalosis symptoms
  - Light-headedness
  - Dizziness
  - Confusion
  - Headache
  - Tinnitus
  - Blurred vision
  - Syncope
  - Seizure
  - Circumoral and limb paresthesia
  - Cramps
  - Tremulousness
- Alkalosis signs
  - Encephalopathy, coma
  - Seizure manifestations
  - Chvostek sign
  - Tremor
  - Ataxia
  - Myoclonus
  - Tetany

Abbreviation: CSF, cerebrospinal fluid.

Adapted from Yee AH, Rabinstein AA. Neurologic presentations of acid-base imbalance, electrolyte abnormalities, and endocrine emergencies. Neurol Clin. 2010 Feb;28(1):1–16. Used with permission.

acidosis include airway obstruction related to asthma or chronic obstructive pulmonary disease, neuromuscular disorders (Guillain-Barré syndrome, spinal cord lesions at or above C3, amyotrophic lateral sclerosis, or myasthenia gravis), or hypoventilation related to the central nervous system depression that occurs with narcotic or sedative agents.

Respiratory Alkalosis

Respiratory alkalosis results from hyperventilation, which occurs in response to any number of stimuli. Thus, the primary abnormality is hypocapnia ($Paco_2$ <35 mm Hg), with a resultant alkalotic state (serum pH >7.44). Symptoms are related to the decreased serum CO_2 levels and to a secondary decrease in ionized blood calcium and phosphate concentrations.

Respiratory alkalosis lowers the threshold for seizures in susceptible patients. Patients often experience light-headedness, headaches, perioral paresthesias, and confusion. In the intensive care unit, the most common cause of respiratory alkalosis is excessive mechanical ventilation. Other causes include early sepsis, lung diseases in which hypoxia drives ventilation more than CO_2 levels (eg, pneumonia or pulmonary emboli), and liver disease with increased arterial ammonia and pulmonary shunting. Perhaps the most profound respiratory alkalosis occurs in patients who have central neurogenic hyperventilation.

Metabolic Acidosis

Metabolic acidosis occurs with either a depletion of serum bicarbonate or an increase in production of hydrogen ions. Determining whether the anion gap is normal or abnormal is essential to identifying the cause of the acidosis. The anion gap is the difference between unmeasured anions and cations in the serum:

$$\text{Anion Gap} = ([\text{Sodium}]+[\text{Potassium}]) - ([\text{Chloride}]+[\text{Bicarbonate}]).$$

Common causes of anion gap acidosis include ketoacidosis, lactic acidosis, and uremia. Less common causes include toxins (methanol, paraldehyde, and ethylene glycol) and medications (salicylates, metformin, isoniazid, and excessive iron). The most common causes of non–anion gap acidosis are diarrhea and renal tubular acidosis. Other causes include hyperalimentation, carbonic anhydrase inhibitors, and ureteroenteric or pancreaticoduodenal fistulas. Neurologic manifestations are typically nonspecific and include headache, lethargy, stupor, and coma.

Metabolic Alkalosis

Metabolic alkalosis occurs when the serum bicarbonate concentration is greater than 26 mEq/L, producing alkalemia. The condition typically occurs with volume contraction, often with diuretic use or recurrent vomiting. Systemic alkalemia may produce paresthesias and muscle cramping initially and, as the degree of alkalemia progresses, depression of consciousness and seizures.

- Patients with acute respiratory acidosis can present with symptoms and signs of increased intracranial pressure from the cerebral vasodilatation that occurs with rapid elevations of $Paco_2$.
- Common causes of anion gap acidosis include ketoacidosis, lactic acidosis, and uremia. Less common causes include toxins (methanol, paraldehyde, and ethylene glycol) and medications (salicylates, metformin, isoniazid, and excessive iron).

78 Neurologic Complications of Nutritional Disorders[a]

BRENT P. GOODMAN, MD

Introduction

Maintenance of medical and neurologic health requires adequate ingestion and stores of vitamins and minerals. Nutritional disorders may result from deficient intake or malabsorption of critical vitamins and micronutrients. Persons at risk for deficient nutrient intake include the impoverished in developed and underdeveloped countries (where certain nutritional disorders may be endemic), persons with eating disorders, those engaged in dietary fads, persons with chronic alcoholism, and those receiving prolonged, inadequate parenteral nutrition for chronic medical conditions. Malabsorption may result from gastrointestinal surgery, including bariatric surgery for obesity, and from chronic gastrointestinal tract disorders, such as celiac disease, Whipple disease, bacterial overgrowth, and inflammatory bowel disease. Excessive ingestion of certain substances, including vitamins and micronutrients, may result in neurologic impairment directly (eg, vitamin B_6 excess) or indirectly (eg, copper deficiency induced by hyperzincemia). Awareness of the characteristic clinical features of the various nutritional disorders and the conditions associated with them facilitates more timely recognition and treatment and directly affects the prognosis (Table 78.1).

- Malabsorption may result from gastrointestinal surgery, including bariatric surgery for obesity, and from chronic gastrointestinal tract disorders, such as celiac disease, Whipple disease, bacterial overgrowth, and inflammatory bowel disease.

Vitamin B_{12}

Sources, Requirements, and Function

Vitamin B_{12} refers to a group of cobalamins that include adenosylcobalamin, methylcobalamin, and hydroxocobalamin. Methylcobalamin is the primary form of cobalamin in plasma and is disproportionately reduced in cobalamin deficiency. Cyanocobalamin is not found in living organisms but is the most commonly used synthetic agent, requiring conversion to adenosylcobalamin or methylcobalamin to become metabolically active. Foods of animal origin, such as meat, eggs, and milk are the primary dietary sources of cobalamin, although cobalamin can also be found in fortified cereals and some nutritional yeast products. The recommended dietary allowance (RDA) for cobalamin is 2.4 mcg daily in adults, 2.6 mcg daily in pregnant females, and 2.8 mcg daily in lactating females. Normal total body stores of vitamin B_{12} range from 2 to 5 mg. A deficiency may take from 2 to 5 years to develop.

Cobalamin becomes dissociated from other food products in the stomach after exposure to gastric acid and pepsin. It then binds with intrinsic factor (IF) in the small intestine. The cobalamin-IF complex binds to receptors in the ileum, where cobalamin is dissociated from IF, bound to transcobalamin, and absorbed. In addition, 1% of cobalamin is absorbed passively (independently of IF) in the terminal ileum. This explains why large oral dosages of vitamin B_{12} can successfully treat vitamin B_{12} deficiency due to pernicious anemia (loss of IF). Cobalamin is then transported throughout the body bound to transcobalamin.

[a] Portions previously published in Goodman BP. Diagnostic approach to myeloneuropathy. Continuum (Minneap Minn). 2011 Aug;17(4):744–60. Used with permission.

Abbreviations: IF, intrinsic factor; RDA, recommended dietary allowance; TPN, total parenteral nutrition

Table 78.1 • Nutritional Deficiencies

Nutrient	Neurologic Features	Cause of Deficiency	Diagnosis	Treatment
Vitamin B_{12} (cobalamin)	Memory loss Psychosis Myelopathy Neuropathy Myeloneuropathy	Malnutrition Atrophic gastritis Pernicious anemia Gastrointestinal surgery Gastrointestinal disease H_2 antagonists	Serum cobalamin Methylmalonic acid Homocysteine	Vitamin B_{12} 1,000 mcg IM daily for 5 d, then monthly 1,000 mcg orally daily
Folic acid	Same as for cobalamin Folate deficiency in isolation is rare	Alcoholism Chronic gastrointestinal disorders Folate antagonists (methotrexate, trimethoprim)	Serum folate RBC folate Homocysteine	Oral folate 1 mg 3 times daily initially, then 1 mg daily Folate 1–5 mg daily parenterally Folate 0.4 mg daily for women of childbearing age to prevent neural tube defects
Copper	Myelopathy Neuropathy Myeloneuropathy Optic neuropathy	Excessive zinc ingestion Gastric surgery Chronic gastrointestinal disease	Serum copper Ceruloplasmin 24-h urinary copper Serum zinc 24-h urinary zinc	Oral elemental copper 8 mg daily in week 1, 6 mg daily in week 2, 4 mg daily in week 3, and 2 mg daily thereafter
Vitamin E	Myelopathy Neuropathy Myopathy Ophthalmoplegia Ptosis Pigmentary retinopathy	Chronic cholestasis Pancreatic insufficiency Gastrointestinal disease α-TTP deficiency Hypobetalipoproteinemia Abetalipoproteinemia	Serum vitamin E	Vitamin E 200 mg daily to 200 mg/kg daily
Thiamine	Wernicke encephalopathy Korsakoff syndrome Neuropathy Beriberi	Recurrent vomiting Gastric surgery Alcoholism Dieting Critical illness	Urinary thiamine Serum thiamine Erythrocyte transketolase assay RBC thiamine Diphosphate	Thiamine 50–300 mg daily; higher doses may be needed in Wernicke encephalopathy
Niacin	Encephalopathy Neuropathy	Corn as primary food source Alcoholism Malabsorption Hartnup syndrome Carcinoid	Clinical diagnosis Urinary excretion of niacin metabolites	Niacin 25–50 mg orally or IM daily
Vitamin B_6 (pyridoxine)	Peripheral neuropathy	Vitamin B_6 antagonists Alcoholism Chronic gastrointestinal disease	Serum pyridoxal phosphate	Vitamin B_6 50–100 mg orally daily

Abbreviations: α-TTP, α-tocopherol transport protein; IM, intramuscularly; RBC, red blood cell.

Cobalamin is a critical cofactor in several methylation reactions involving proteins, neurotransmitters, and phospholipids. Methylcobalamin is a cofactor in the conversion of homocysteine to methionine. Methionine is adenosylated to *S*-adenosylmethionine and facilitates the formation of formyltetrahydrofolate. Deficient production of *S*-adenosylmethionine results in a decrease in myelin basic protein methylation and white matter vacuolization. A decrease in formyltetrahydrofolate production limits purine and pyrimidine synthesis, resulting in disordered oligodendrocyte growth and myelin production.

Causes of Deficiency

Vitamin B_{12} deficiency has been estimated to affect between 1.5% and 15% of the general population. Conditions known to cause or be associated with vitamin B_{12} deficiency include malnutrition, atrophic gastritis, pernicious anemia, and malabsorption due to gastrointestinal disorders (eg, inflammatory bowel disease) or gastric bypass surgery. Certain medications, including H_2 receptor antagonists and metformin, are known to decrease vitamin B_{12} absorption.

Clinical Features

The neurologic manifestations of vitamin B_{12} deficiency are varied and may be the earliest or only signs of deficiency. Neuropsychiatric manifestations may include memory loss, personality change, psychosis, emotional lability, and, rarely, coma. A myelopathy with or without peripheral neuropathy may occur. Classically, vitamin B_{12} deficiency has been associated with subacute combined degeneration, a form of myelopathy with pyramidal and posterior column signs, including spastic paraparesis, extensor plantar responses, and impairment in vibration sense and proprioception. An axonal peripheral neuropathy may occur with or without myelopathy. Optic neuropathy and orthostatic hypotension may also occur. Other common constitutional symptoms include fatigue, weight loss, and gastrointestinal symptoms. Hematologic manifestations of vitamin B_{12} deficiency include megaloblastic anemia, pancytopenia, neutrophil hypersegmentation, and macrocytosis.

Evaluation

Serum cobalamin levels may be normal in some patients with cobalamin deficiency. If patients have borderline-low cobalamin levels—particularly patients strongly suspected of having vitamin B_{12} deficiency—methylmalonic acid and homocysteine levels should be checked. Methylmalonic acid and homocysteine levels are increased in as many as one-third of patients with low-normal serum cobalamin levels and vitamin B_{12} deficiency.

Treatment

Treatment of neurologic impairment due to vitamin B_{12} deficiency involves the administration of high dosages of oral, sublingual, or intramuscular cobalamin. For patients with malabsorption, 1,000 mcg of cobalamin is administered intramuscularly each day for 5 days and monthly thereafter. Lifelong vitamin B_{12} supplementation therapy is typically necessary.

Nitrous Oxide and Vitamin B_{12}

Nitrous oxide is one of the more commonly used anesthetic agents worldwide, and toxicity may result in myeloneuropathy, myelopathy, peripheral neuropathy, and cognitive changes. Nitrous oxide alters the cobalt core of cobalamin, converting it into an inactive oxidized form, and most reported cases have been associated with low or borderline-low vitamin B_{12} levels. Treatment involves prompt intramuscular injections of cyanocobalamin.

- Classically, vitamin B_{12} deficiency has been associated with subacute combined degeneration, a form of myelopathy with pyramidal and posterior column signs, including spastic paraparesis, extensor plantar responses, and impairment in vibration sense and proprioception.
- If patients have borderline-low cobalamin levels—particularly patients strongly suspected of having vitamin B_{12} deficiency—methylmalonic acid and homocysteine levels should be checked.
- Nitrous oxide alters the cobalt core of cobalamin, converting it into an inactive oxidized form, and most reported cases have been associated with low or borderline-low vitamin B_{12} levels.

Folic Acid

Sources, Requirements, and Function

The active form of folate, tetrahydrofolate, is essential in the modification, acceptance, or transfer of 1-carbon units to substrates used in the synthesis of nucleic and amino acids. Folate is present in animal products, citrus fruits, and green leafy vegetables; 50 to 100 mcg is required daily. Normal body stores of folate range from 500 to 20,000 mcg.

Folate is absorbed in the proximal small intestine and ileum. In the enterocyte, folate is converted into 5-methyltetrahydrofolate, which is exported into the bloodstream and ultimately internalized into various body compartments. Serum folate levels decrease within 3 weeks after diminished intake or malabsorption begins, and clinical signs of folate deficiency may occur within months.

Causes of Deficiency

Folate deficiency is characteristically associated with conditions that result in other nutritional deficiencies. Persons with alcoholism, premature infants, and adolescents are populations at risk. The prevalence of folate deficiency has decreased in the United States and Canada since a mandatory folic acid fortification program was started in 1998. General conditions associated with folate deficiency include disorders that result in malabsorption (eg, celiac disease, bacterial overgrowth, and inflammatory bowel disease), states of reduced gastric acid secretion (eg, after gastric surgery, in the presence of atrophic gastritis, and with the use of medications that decrease gastric acid levels), and administration of medications that inhibit tetrahydrofolate reductase (eg, trimethoprim, triamterene, and methotrexate).

Clinical Features

The neurologic manifestations of folate deficiency may resemble those of cobalamin deficiency, including myelopathy, myeloneuropathy, and neuropathy. Folate deficiency has been associated with neural tube defects, increased risk of vascular disease, venous thrombosis, and possible cognitive impairment.

Evaluation

A low serum folate level (typically <2.5 ng/mL) can establish a diagnosis of folate deficiency. Plasma homocysteine is usually elevated in folate deficiency and is useful to confirm the presence of folate deficiency and to monitor the response to folate supplementation. Serum cobalamin levels should also be checked in patients with suspected folate deficiency.

Treatment

Oral administration of folate is adequate for some patients, although some patients with malabsorption or patients who are acutely ill need parenteral administration of folate. Women of childbearing age with epilepsy should be counseled to supplement with 0.4 mg of folate daily to prevent neural tube defects.

Copper

Sources, Requirements, and Function

Copper is a trace element involved in a number of metalloenzymes that have a critical role in nervous system structure and function. These enzymes include cytochrome-*c* oxidase (involved in electron transport and oxidative phosphorylation), copper-zinc superoxide dismutase (antioxidant defense), tyrosinase (melanin synthesis), dopamine β-hydroxylase (catecholamine synthesis), and lysyl oxidase (cross-linking collagen and elastin).

Copper is present in various foods; particularly rich sources of copper are shellfish, oysters, legumes, organ meats, chocolate, nuts, and whole grain products. The estimated requirement for copper is 0.70 mg daily, and the estimated total body copper content is 50 to 120 mg. Copper absorption occurs in the stomach and proximal small intestine through active and passive transport processes. The Menkes P-type adenosine triphosphatase (ATP7A) is responsible for copper efflux from enterocytes. Menkes disease is a congenital (X-linked) form of copper deficiency resulting from a mutation in the *ATP7A* gene. Copper is bound to ceruloplasmin in the liver and is distributed to liver, brain, kidney, cornea, bone, and pancreas.

Causes of Deficiency

The most common cause of copper deficiency is gastric surgery, which results in copper malabsorption. Copper deficiency may also result from excessive zinc ingestion, and from chronic gastrointestinal conditions that impair copper absorption (inflammatory bowel disease, celiac disease, and bacterial overgrowth). It may also arise as a complication in patients receiving long-term total parenteral nutrition (TPN) with inadequate copper supplementation.

Clinical Features

The most common neurologic manifestation of copper deficiency is a myelopathy or myeloneuropathy, which results in a sensory ataxia (Figure 78.1). The myelopathy may be clinically indistinguishable from the subacute combined degeneration described in association with vitamin B_{12} deficiency. Hematologic manifestations of copper deficiency include anemia and neutropenia.

Evaluation

In the appropriate clinical setting, low serum copper and ceruloplasmin levels establish a diagnosis of copper deficiency. Typically, 24-hour urinary copper levels are decreased, in contrast to the elevation in urinary copper levels with Wilson disease. Serum and 24-hour urinary zinc levels should also be assessed.

Treatment

Treatment of copper deficiency involves the discontinuation of zinc in patients who have excessive zinc consumption and the initiation of copper supplementation. Oral copper supplementation (2 mg daily) is typically adequate. Some patients may require higher daily dosing or short-term parenteral supplementation. Treatment typically results in improvement in hematologic abnormalities (if present) and stabilization but not resolution of neurologic signs and symptoms.

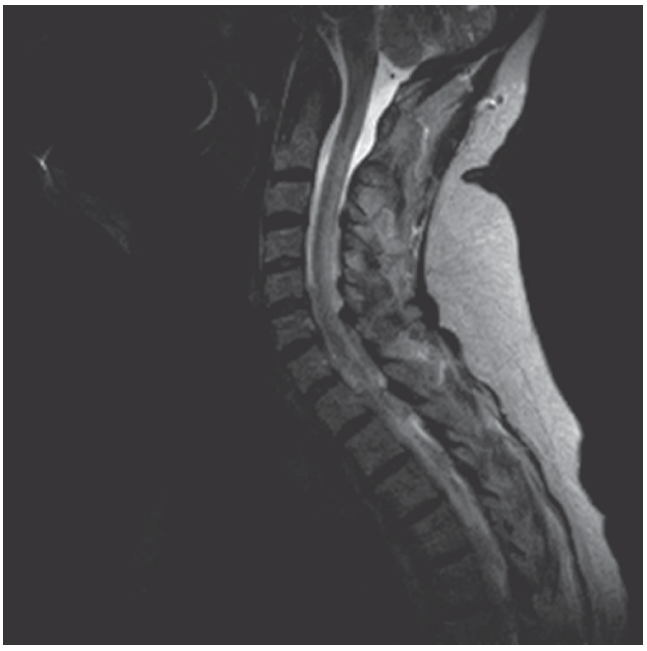

Figure 78.1 *Copper Deficiency Myeloneuropathy. Sagittal T2-weighted magnetic resonance imaging sequence of the cervical spine shows abnormal intramedullary T2 hyperintensity within the dorsal spinal cord.*

- The most common cause of copper deficiency is gastric surgery, which results in copper malabsorption.
- The most common neurologic manifestation of copper deficiency is a myelopathy or myeloneuropathy, which results in a sensory ataxia.
- Treatment of copper deficiency involves the discontinuation of zinc in patients who have excessive zinc consumption and the initiation of copper supplementation.

Vitamin E

Sources, Requirements, and Function

Vitamin E is a fat-soluble vitamin with important antioxidant properties, providing protection against oxidative stress and inhibiting the fatty acid peroxidation of membrane phospholipids. *Vitamin E* refers to a family of tocopherols and tocotrienols, of which α-tocopherol is the most abundant and active biologic form of vitamin E in the human diet. Nuts, seeds, and vegetable oils are among the best sources of vitamin E. The RDA for vitamin E is 15 mg (22.4 international units).

Causes of Deficiency

Vitamin E absorption requires pancreatic and biliary secretions; deficiency may therefore result from chronic cholestasis and pancreatic insufficiency. Other gastrointestinal disorders that may cause malabsorption of vitamin E include celiac disease, inflammatory bowel disease, blind loop syndrome, bacterial overgrowth, effects of radiotherapy, and cystic fibrosis. Long-term TPN with inadequate vitamin E supplementation may result in vitamin E deficiency. Genetic causes of vitamin E deficiency include ataxia (with vitamin E deficiency resulting from α-tocopherol transport protein deficiency), apolipoprotein B mutation (homozygous hypobetalipoproteinemia), and a defect in the microsomal triglyceride transfer protein (abetalipoproteinemia).

Clinical Features

The neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome resembling Friedreich ataxia, myopathy, ophthalmoplegia and ptosis, and a pigmentary retinopathy.

Evaluation and Treatment

Low serum vitamin E levels establish the diagnosis. Serum levels of lipids, cholesterol, and very low-density lipoprotein affect serum vitamin E levels. Vitamin E supplementation may be necessary with dosages ranging from 200 mg daily to 200 mg/kg daily. Parenteral administration may be necessary for some patients, particularly those with severe malabsorption.

- The neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome resembling Friedreich ataxia, myopathy, ophthalmoplegia and ptosis, and a pigmentary retinopathy.

Thiamine

Sources, Requirements, and Function

Thiamine, or vitamin B_1, is a water-soluble vitamin that functions as a coenzyme in the metabolism of carbohydrates, lipids, and amino acids. Foods rich in thiamine include yeast, sunflower seeds, eggs, oatmeal, pork, and whole grains. The RDA is 1.4 mg in most countries, but thiamine requirements are proportional to total caloric intake (proportion of calories from carbohydrates) and are higher during periods of higher metabolic demand (eg, infection, critical illness, malignancy, and pregnancy).

Causes of Deficiency

Thiamine deficiency may occur 1) in conditions associated with increased thiamine requirements, 2) in patients with compromised nutritional status (eg, dieting, alcoholism, AIDS, and inadequate supplementation in TPN), 3) in conditions associated with malabsorption or increased loss (eg, gastrointestinal surgery, vomiting, renal failure, and chronic liver, pancreatic, or gastrointestinal disease), and 4) in states of high carbohydrate intake (with inadequate thiamine supplementation), such as intravenous glucose administration and refeeding after starvation.

Clinical Features

Thiamine deficiency may affect the heart, the central nervous system, or the peripheral nervous system in various combinations. High- or low-output cardiac failure may occur. A rapidly progressive, axonal, sensorimotor peripheral neuropathy may occur. Wernicke encephalopathy, caused by thiamine deficiency, is a subacute or chronic syndrome characterized by a combination of ophthalmoparesis, gait ataxia, and mental status changes. In approximately 80% of patients with Wernicke encephalopathy who survive, Korsakoff syndrome develops. It is an amnestic-confabulatory syndrome with severe anterograde and retrograde amnesia.

Manifestations of thiamine deficiency have been categorized as dry, wet, and infantile beriberi. Beriberi is caused by thiamine deficiency. *Dry beriberi* is a length-dependent, painful, sensorimotor peripheral neuropathy. *Wet beriberi* is characterized by high-output congestive heart failure with peripheral neuropathy. Patients with *infantile beriberi* may present with vomiting, diarrhea, irritability, nystagmus, ophthalmoplegia, and respiratory difficulties.

Evaluation

Thiamine deficiency is often a clinical diagnosis. Serum and urinary thiamine levels do not reliably reflect thiamine status. The erythrocyte transketolase assay or measurement of red blood cell thiamine diphosphate may be used if available, but samples must be taken before supplementation. Elevated pyruvate and lactate levels may be suggestive. Magnetic resonance imaging of the brain may show T2-signal changes in paraventricular regions, including the thalamus, hypothalamus, mammillary body, periaqueductal midbrain, pons, medulla, and cerebellum.

Treatment

Parenteral administration of thiamine, the treatment of choice, must be administered to high-risk patients before glucose or TPN infusions. Long-term oral maintenance with 50 to 100 mg daily may be indicated for some patients.

- Wernicke encephalopathy, caused by thiamine deficiency, is a subacute or chronic syndrome characterized by a combination of ophthalmoparesis, gait ataxia, and mental status changes.
- Beriberi is caused by thiamine deficiency. *Dry beriberi* is a length-dependent, painful, sensorimotor peripheral neuropathy. *Wet beriberi* is characterized by high-output congestive heart failure with peripheral neuropathy. Patients with *infantile beriberi* may present with vomiting, diarrhea, irritability, nystagmus, ophthalmoplegia, and respiratory difficulties.

Niacin

Niacin (or vitamin B_3) is an end product of tryptophan metabolism; niacin deficiency results in pellagra. Pellagra occurs primarily in populations dependent on corn as their primary carbohydrate source (corn lacks niacin and tryptophan), but it also occurs in persons with alcoholism or malabsorption.

Clinically, pellagra may result in diarrhea, dermatitis, dementia, and peripheral neuropathy. Treatment involves administration of oral or parenteral niacin.

- Clinically, pellagra (caused by niacin deficiency) may result in diarrhea, dermatitis, dementia, and peripheral neuropathy.

Vitamin B_6

Vitamin B_6 (or pyridoxine) is converted to pyridoxal phosphate, which acts as a coenzyme in the metabolism of amino acids, lipids, and nucleic acids. It is important in gluconeogenesis and in neurotransmitter and heme biosynthesis. Vitamin B_6 is abundant in meat, fish, eggs, soybeans, nuts, and dairy products. Deficiency may be seen in association with vitamin B_6–antagonist medications, such as isoniazid, hydralazine, and penicillamine.

Infantile seizures may result from dietary vitamin B_6 deficiency or from congenital vitamin B_6 dependency. Dietary insufficiency resulting in infantile seizures is rare and occurs primarily in breastfed infants of malnourished mothers. Pyridoxine-dependent seizures are caused by a mutation in the antiquitin gene, which results in inactivation of pyridoxal phosphate. High-dose vitamin B_6 halts the seizures. Chronic vitamin B_6 deficiency results in a painful peripheral neuropathy. Excessive ingestion of vitamin B_6 (>100 mg daily) may result in a sensory neuropathy or ganglionopathy.

- Excessive ingestion of vitamin B_6 (>100 mg daily) may result in a sensory neuropathy or ganglionopathy.

Vitamin A

Vitamin A is necessary for normal vision. Deficiency may occur in populations with a dietary dependence on rice and wheat (which lack β-carotene), in persons with alcoholism, in the elderly, and in patients with chronic malabsorption. Vitamin A deficiency results in night blindness. Excessive vitamin A consumption (>25,000 international units daily) may result in neurologic manifestations, including headache, insomnia, irritability, and increased intracranial pressure.

- Excessive vitamin A consumption (>25,000 international units daily) may result in neurologic manifestations, including headache, insomnia, irritability, and increased intracranial pressure.

Vitamin D

Vitamin D is a fat-soluble vitamin that exists in 2 ingestible forms, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), and can be synthesized from cholesterol with adequate exposure to sunlight. Causes of vitamin D deficiency include inadequate sun exposure, malabsorption, gastric surgery, and kidney disease. Vitamin D deficiency may result in a proximal myopathy associated with bone pain, and recent studies have suggested a potential relationship between vitamin D deficiency and multiple sclerosis. Vitamin D_2 or vitamin D_3 can be administered orally, with high dosages necessary in cases of malabsorption.

79 Endocrine Disease

WILLIAM D. FREEMAN, MD

Introduction

The endocrine system is involved in creating and distributing hormones that have wide-ranging organ effects and a potential for neurologic complications. Basic pathophysiology is covered in Volume 1, Chapter 15, "Principles of Neuroendocrinology and Hypothalamic Function." Neurologic manifestations related to dysfunction of the thyroid, parathyroid, and adrenal glands are discussed in the present chapter.

Pituitary Disorders

Pathophysiology

The pituitary gland is subdivided into anterior and posterior lobes. The posterior pituitary (neurohypophysis) receives direct neuronal transmission from the hypothalamus (supraoptic and paraventricular nuclei) and secretes prolactin, oxytocin, and vasopressin (antidiuretic hormone [ADH]) (Figure 79.1). Prolactin release is regulated by a negative feedback inhibition mechanism involving dopamine. Lesions of the posterior hypothalamus or other factors that impair the dopaminergic inhibition can lead to release of prolactin, resulting in galactorrhea.

The anterior pituitary (adenohypophysis) makes follicle-stimulating hormone and luteinizing hormone (which are important in the female hypothalamo-ovarian-uterine menstrual cycle), growthhormone, corticotropin (which stimulates cortisol secretion from the adrenal glands), and thyrotropin (which stimulates the thyroid gland). Further details of pituitary pathophysiology are covered in Volume 1, Chapter 15, "Principles of Neuroendocrinology and Hypothalamic Function."

Causes and General Manifestations of Pituitary Dysfunction

Pituitary disorders may result from traumatic, surgical, inflammatory, structural (eg, tumor), and sometimes vascular processes that impair normal function. Symptoms may depend on whether hormone production is disrupted (excess or deficiency) and whether surrounding structures are compromised (eg, third cranial nerve and optic chiasm).

Selected Disorders

Acromegaly

Acromegaly is a condition of excessive growth hormone production from a growth-hormone–producing tumor, which leads to large stature (gigantism) and coarse facial features. These pituitary tumors may grow larger and cause structural compression of the optic chiasm and the surrounding cavernous sinus, resulting in headache and, classically, bitemporal hemianopic visual field loss.

Pituitary Apoplexy

Progressive growth of a pituitary tumor can lead to vascular infarction or hemorrhage of the tumor, which is termed pituitary apoplexy. When it occurs postpartum, it is referred to as Sheehan syndrome. Pituitary apoplexy is a medical emergency that can result in a neuroendocrine crisis from a lack of pituitary hormone production, profound vasopressor-refractory hypotension due to the lack of stress hormones, blindness from optic nerve or chiasm compression, coma, and death. Emergent neuroimaging, such as computed tomography and magnetic resonance imaging, typically shows pituitary apoplexy (Figure 79.2), which can also cause cranial neuropathies within the cavernous sinus (ie, cranial nerves III, IV, or VI). Pituitary apoplexy requires emergency

Abbreviations: ADH, antidiuretic hormone; DKA, diabetic ketoacidosis; HONK, hyperosmolar nonketotic state; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; T_3, triiodothyronine; T_4, tetraiodothyronine

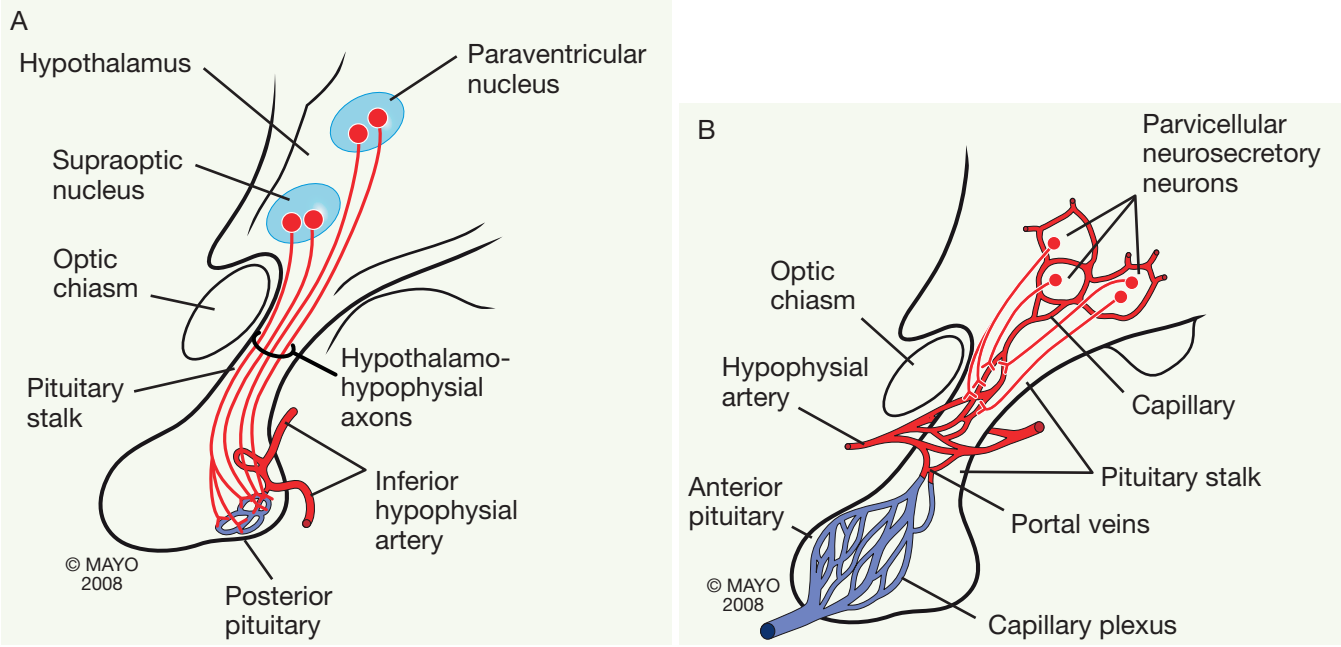

Figure 79.1 *Neuroendocrine Systems of the Hypothalamus and Pituitary Gland. A, Magnicellular system. Neurons of the supraoptic and paraventricular nuclei synthesize arginine-vasopressin or oxytocin and send axons through the pituitary stalk to secrete these hormones into capillaries in the posterior pituitary. B, Parvicellular system. Neurons of the periventricular preoptic, paraventricular, and arcuate nuclei synthesize releasing or inhibitory factors, and their axons deliver these factors to the portal circulation at the level of the median eminence. The portal circulation delivers these factors to the anterior pituitary to control hormonal secretion by the pituitary endocrine cells.*

(Adapted from Benarroch EE, Daube JR, Flemming KD, Westmoreland BF. Mayo Clinic medical neurosciences: organized by neurologic systems and levels. 5th ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. Chapter 16, Part A, The supratentorial level: thalamus, hypothalamus, and visual system; p. 669-99. Used with permission of Mayo Foundation for Medical Education and Research.)

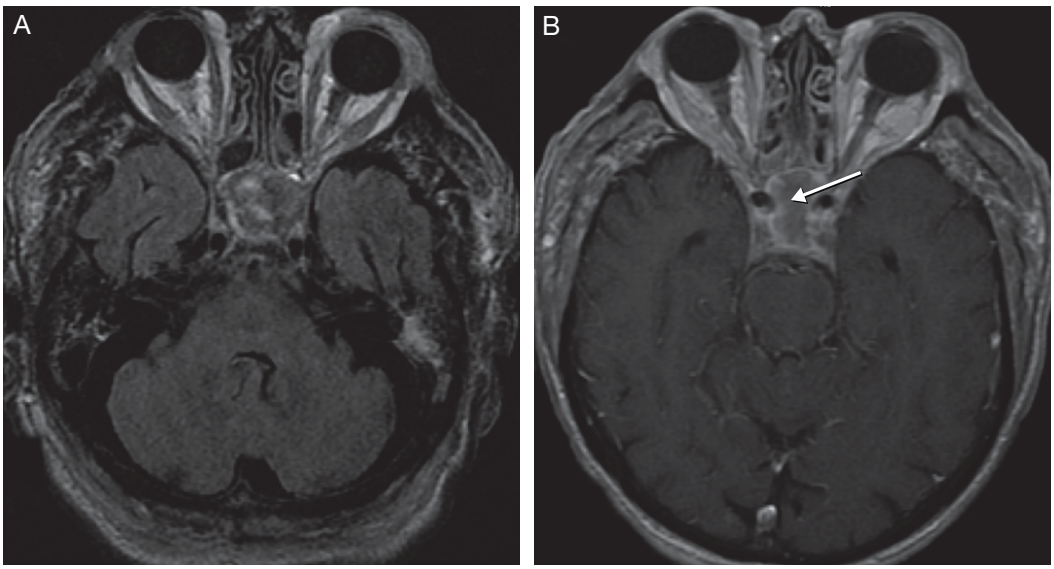

Figure 79.2 *Pituitary Apoplexy.*
Magnetic resonance imaging from a patient with pituitary apoplexy shows heterogeneous signal within a large pituitary adenoma indicative of hemorrhage (arrow in B). A, Axial fluid-attenuated inversion recovery image. B, T1-weighted with gadolinium contrast image.

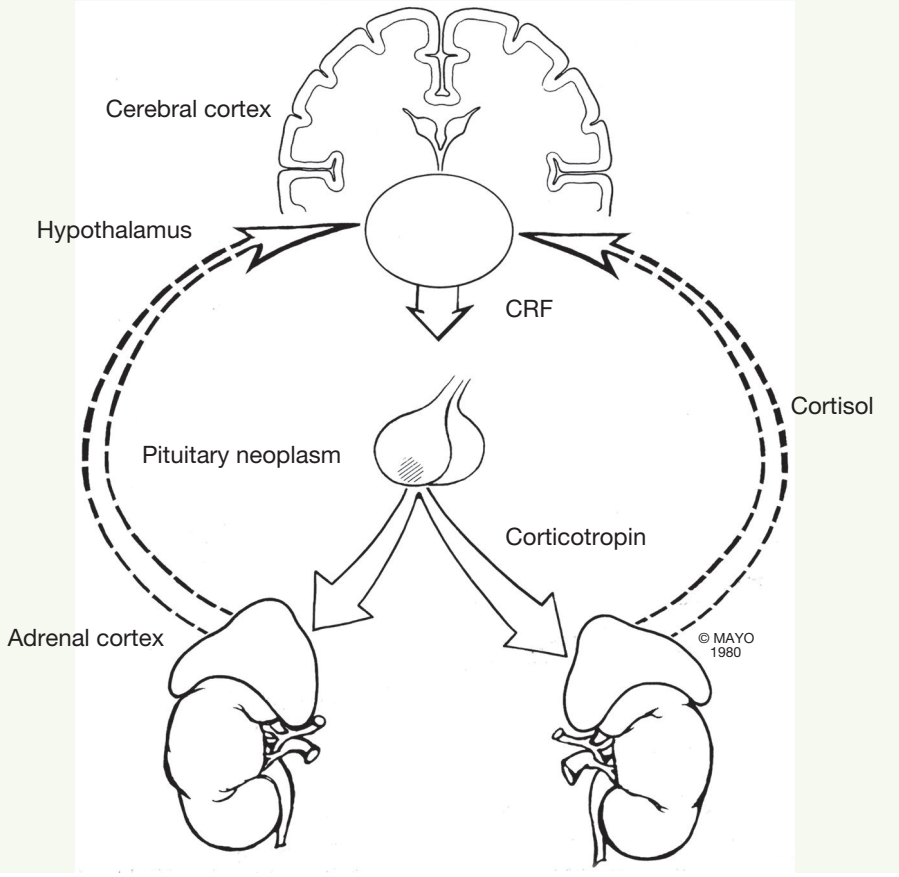

Figure 79.3 *Cushing Disease.*
A corticotropin-secreting adenoma results in excess production of endogenous glucocorticoids and feedback inhibition of corticotropin-releasing factor (CRF).
(Used with permission of Mayo Foundation for Medical Education and Research.)

neurosurgical consultation for possible transsphenoidal surgery to debulk the lesion, stress-dose corticosteroid support because of the lack of corticotropin and cortisol, thyroxine intravenously if thyrotropin is lacking, and desmopressin administration if diabetes insipidus develops.

Syndrome of Inappropriate Secretion of ADH

The overproduction of ADH can lead to the syndrome of inappropriate secretion of ADH (SIADH) with hyponatremia from excessive water absorption in the kidney. SIADH typically causes fluid retention, concentrated, dark urine (with a high specific gravity), and relatively low urine output. Diabetes insipidus typically produces the opposite clinical situation of hypernatremia: hypovolemia, high urine output (>300–500 ml/h), and low urine specific gravity.

Cushing Disease

Cushing disease is caused by a pituitary tumor that causes excessive production of corticotropin from the anterior pituitary (Figure 79.3), leading to excessive cortisol, hyperpigmentation, abdominal striae, dorsal cervical adipose deposition (buffalo hump), and thinning of the skin. Diagnosis is typically confirmed with serum cortisol and corticotropin blood sampling; treatment consists of transsphenoidal surgery and replacement of pituitary hormones as needed. Box 79.1 shows the processes that can affect the

Box 79.1 • Differential Diagnosis of Disorders of the Pituitary-Hypothalamic Axis[a]

S—sellar tumor (pituitary adenoma or prolactinoma) or sarcoid

A—aneurysm (eg, anterior communicating or internal carotid artery)

T—teratoma or tuberculosis

C—craniopharyngioma, cleft cyst (Rathke cyst), or chordoma

H—hypothalamic glioma, hamartoma (of the tuber cinereum), or histiocytosis X (eosinophilic granuloma)

M—meningioma, metastasis, or meningeal lymphomatosis

O—optic nerve glioma, other (eg, Erdheim-Chester disease)

[a] Mnemonic: *SATCHMO*.

hypothalamic-pituitary axis, which can be remembered with the mnemonic *SATCHMO*.

- Pituitary apoplexy is a medical emergency that can result in a neuroendocrine crisis from a lack of pituitary hormone production, profound vasopressor-refractory hypotension due to the lack of stress hormones, blindness from optic nerve or chiasm compression, coma, and death.

Thyroid and Parathyroid Disorders

Pathophysiology

The thyroid gland responds to thyrotropin and produces triiodothyronine (T_3) and tetraiodothyronine (T_4), collectively known as thyroxine. Thyroid hormones modulate the rate of cellular metabolism, and parathyroid glands are important in calcium homeostasis. Deficiencies in T_3 and T_4 lead to hypothyroidism, and excessive amounts of T_3 and T_4 lead to hyperthyroidism.

Causes and General Manifestations of Thyroid Disease

Hypothyroidism may be due to multiple causes (Box 79.2). Neurologic and psychiatric symptoms of patients with hypothyroidism regardless of the cause include depression, anxiety, reduced reflexes (Woltman sign), slowed psychomotor ability, cognitive decline, myopathy, and neuropathy (peripheral painful neuropathy or carpal tunnel syndrome [or both]). Other systemic symptoms include fatigue, weight gain, dry skin, cold intolerance, constipation, hair thinning, oligomenorrhea, and myxedema when severe.

Hyperthyroidism may also be due to several causes (Box 79.2). Neuropsychiatric manifestations of hyperthyroidism may include anxiety, tremor, psychomotor hyperactivity, myopathy, and brisk reflexes. Systemic symptoms include palpitations (atrial fibrillation and malignant arrhythmias can develop in severe cases), exophthalmos (in 25%-50% of patients) (Figure 79.4), onycholysis, and diarrhea.

Determination of the thyrotropin concentration is typically a good screening test for thyroid disorders. If the thyrotropin level is abnormal, determination of free T_3 or free T_4 can be considered along with thyroid antibodies (anti–thyroid peroxidase and anti-thyrotropin receptor) in selected cases (Table 79.1) in addition to seeking an endocrinology consultation.

Selected Disorders

Cretinism

Cretinism results from congenital pituitary failure. Infants have impaired growth and development. Thyrotropin, T_3, and T_4 levels are low.

Box 79.2 • Causes of Hypothyroidism and Hyperthyroidism

- Hypothyroidism
  - Autoimmune thyroiditis
  - Iatrogenic (thyroidectomy, radioiodine therapy, or external neck irradiation)
  - Iodine deficiency or excess
  - Drugs and toxins: many; notable ones include lithium, amiodarone, calcium carbonate, omeprazole, and dopamine
  - Infiltrative diseases (rare)
  - Secondary hypothyroidism (thyrotropin deficiency; eg, pituitary tumor)
  - Tertiary hypothyroidism (thyroid-releasing hormone deficiency; eg, hypothalamic tumor or sarcoid)
- Hyperthyroidism
  - Graves disease
  - Thyrotoxicosis
  - Thyroiditis
  - Toxic adenoma or toxic multinodular goiter
  - Iodine induced (often after load including iodine-based contrast agent)
  - Germ cell tumors (stimulate thyrotropin receptor)
  - Thyrotropin-mediated hyperthyroidism
  - Medication or drug related: excess intake of thyroid replacement, epoprostenol, lithium, or amiodarone

Myxedema Coma

Severe primary hypothyroidism can result in coma, hypothermia, hyponatremia, and hemodynamic instability. Typically,

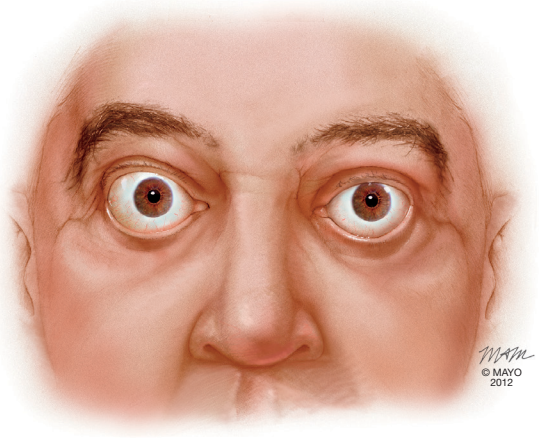

Figure 79.4 *Exophthalmos in Hyperthyroidism.*
(Used with permission of Mayo Foundation for Medical Education and Research.)

Table 79.1 • Diagnosis of Thyroid Diseases

Disease	Thyrotropin	T_3	T_4	Comment
Primary hypothyroidism	↑	↓	↓	Primary thyroid disease
Secondary hypothyroidism	↓	↓	↓	Pituitary dysfunction
Tertiary hypothyroidism	↓	↓	↓	Hypothalamic dysfunction Cannot be distinguished from secondary hypothyroidism biochemically; requires MRI of the brain
Primary hyperthyroidism	↓	↑	↑	Primary thyroid disease or excess intake of thyroid replacement

Abbreviations and symbols: MRI, magnetic resonance imaging; T_3, triiodothyronine; T_4, tetraiodothyronine; ↓, decreased; ↑, increased.

myxedema coma is precipitated by an event in a patient with preexisting hypothyroidism (eg, stroke, cold, burns, sepsis, or medications). These patients require neurologic intensive care evaluation and thyroid hormone replacement with T_4 intravenously or shorter-acting T_3 (5 mcg intravenously every 8 hours) if they are comatose; when the patient is awake, the medication is gradually converted to an oral form. Vitamin B_{12} levels should be checked to exclude concomitant autoimmune thyroiditis with pernicious anemia.

Thyrotoxicosis

Patients with thyrotoxicosis may present with tachycardia (atrial fibrillation), tremors, seizures, and hyperthyroid myopathy. Cardiac arrest may occur. The condition is diagnosed by measuring thyrotropin, T_3, and T_4 levels; testing for thyrotropin receptor antibodies for possible Graves disease; and evaluating the thyroid with ultrasonography (for toxic thyroid adenoma). In an intensive care unit, β-blockers, methimazole, or propylthiouracil (thionamides) may be used to block thyroid hormone synthesis. In these patients, it is important to avoid the use of an iodinated contrast agent. Glucocorticoids also decrease the conversion of T_4 to T_3 and suppress autoimmune cases of thyroid disease (Graves).

Thyrotoxic Periodic Paralysis

In patients with hypothyrodism, periodic paralysis (typically, a few hours of motor weakness ranging from mild proximal weakness to complete flaccid paralysis) may be precipitated by large carbohydrate meals or with rest after exercise (or by use of acetazolamide). Laboratory findings include suppressed thyrotropin and increased T_3 and T_4 levels.

During attacks, laboratory tests may show an increased creatine kinase level, hypokalemia, hypocalcemia, and hypophosphatemia. An electrocardiogram may show transient large QRS complexes during attacks, and an electromyogram may show reduced compound muscle action potential amplitudes during attacks.

Medication Adverse Effects

Drugs used to treat hyperthyroidism can have adverse effects. For example, carbimazole can cause headache and myopathy, and propylthiouracil can cause encephalopathy.

Parathyroid Disorders

Table 79.2 reviews clinical manifestations and recommendations for evaluation in disorders of the parathyroid.

- Typically, myxedema coma is precipitated by an event in a patient with preexisting hypothyroidism (eg, stroke, cold, burns, sepsis, or medications).

Adrenal Disorders

Pathophysiology

The adrenal glands are involved with the synthesis of stress hormones, corticosteroids, and mineralocorticoids. The term *Cushing syndrome* refers to a condition resulting from long-term exposure to excessive glucocorticoids. The syndrome is most commonly caused by the administration of exogenous glucocorticoids. *Cushing disease* refers to a condition with clinical manifestations resulting from excessive corticotropin secretion by the pituitary.

Causes and General Manifestations of Adrenal Disease

Clinical manifestations of both Cushing syndrome and Cushing disease include abdominal obesity, thinning of skin, high blood pressure, and hair thinning. Exogenous corticosteroids can lead to atrophy of the adrenal glands, which then do not respond to produce endogenous corticosteroids in response to stress.

Adrenal insufficiency most commonly results from withdrawal of exogenous corticosteroids used to suppress the immune system. Patients with hypoadrenalism or Addison disease can present with encephalopathy, seizure from hypoglycemia, hypokalemia, stupor or coma, and refractory hypotension. Adrenal insufficiency rarely occurs as a result of pituitary failure (eg, pituitary apoplexy).

- Patients with hypoadrenalism or Addison disease can present with encephalopathy, seizure from hypoglycemia, hypokalemia, stupor or coma, and refractory hypotension.

Table 79.2 • Symptoms, Evaluation, and Management of Parathyroid Disease

Disease State	Symptoms	Evaluation and Management
Hyperparathyroidism	Neurologic Encephalopathy (moderate to severe), headache Proximal myopathy or myalgia Systemic "Stones, bones, abdominal groans, and psychiatric overtones" refers to hypercalciuric kidney stones, osteopenic changes on plain radiographs (changes in the hand or bones), and vague abdominal pain	Parathyroid hormone levels, serum calcium with albumin or ionized calcium Endocrinology consultation
Hypoparathyroidism	Central nervous system Oral, tongue, and acral paresthesia Encephalopathy Hypokinesia Seizures Peripheral nervous system Cramps, fasciculations Carpopedal spasm Chvostek and Trousseau signs (if hypocalcemic) Opisthotonus or tetany (if severe hypocalcemia)	Parathyroid hormone levels, serum calcium with albumin or ionized calcium, and vitamin D levels May see basal ganglia calcification Replace calcium (intravenously if severely low) and vitamin D levels Endocrinology consultation

Diabetes Mellitus and Glucose Dysregulation

Overview

Type 1 diabetes mellitus is typically an autoimmune disease that occurs within the first 2 decades of life. The endogenous insulin deficiency can result in severe hyperglycemia and diabetic ketoacidosis (DKA). Type 2 diabetes mellitus is often an adult-onset disorder (beyond the second decade of life) and is typically associated with impaired end-organ insulin sensitivity and obesity. Type 2 diabetes mellitus, when uncontrolled, can lead to hyperosmolar nonketotic state (HONK), which can also produce acidosis and be life-threatening but is typically devoid of ketone production (ketosis). Diabetes mellitus can lead to several neurologic complications (Box 79.3).

Selected Disorders

DKA and HONK

Both DKA and HONK are associated with volume depletion due to the osmotic diuretic effect of glucosuria on the kidney. Severe dehydration and electrolyte depletion can result. Neurologic manifestations include mental status changes with deterioration to coma, rarely focal neurologic signs (hemiparesis and hemianopsia), and seizures.

Management of DKA and HONK involves replacement with physiologic saline and cautious insulin administration with frequent serum glucose monitoring. The goal is to decrease the serum glucose level from more than 300 mg/dL to approximately 200 mg/dL. This is followed by further slow, steady correction over 24 to 48 hours to minimize the risk of cerebral edema caused by osmolar tonicity shifts in brain parenchyma. Patients with both DKA and HONK require frequent electrolyte monitoring and replacement since acidosis causes intracellular potassium to leach into interstitial and intravascular spaces. Therefore, while acidosis is being corrected, potassium gradually shifts back into cells, and profound hypokalemia may result. Similar depletion of phosphate or severe hypophosphatemia may occur during correction of DKA or HONK and can cause rhabdomyolysis. Coma or seizures (or both) may occur in DKA or HONK.

Hypoglycemia

Hypoglycemia is injurious to brain tissue because its metabolism is based on glucose. Mild hypoglycemia can cause encephalopathy; moderate to severe hypoglycemia (<40 mg/dL), especially when prolonged, can cause seizures and coma. Prodromal somatic symptoms, which occur as serum glucose levels decrease, result from underlying neurohormonal activation of the sympathetic nervous system and stress hormone release of cortisol and adrenaline. The symptoms include diaphoresis, pallor, light-headedness, dizziness, visual disturbance, and tremulousness. They can be blocked partially in patients taking β-blockers. Hypoglycemia can cause focal deficits and, if prolonged and severe, can result in a diffuse hypoxic-ischemic brain injury type of pattern on magnetic resonance imaging and computed tomography, coma, and death. Hypoglycemia should be corrected rapidly with sublingual dextrose or intravenous 50% dextrose to prevent prolonged hypoglycemia. To prevent Wernicke-Korsakoff syndrome, thiamine deficiency should be considered in nutritionally deficient patients before dextrose administration.

- Volume depletion due to the osmotic diuretic effect of glucosuria on the kidney can result in severe dehydration and electrolyte depletion with neurologic manifestations that include mental status changes with

Box 79.3 • Potential Neurologic Complications of Diabetes Mellitus

- Central nervous system
  - Cerebrovascular complications: ischemic or hemorrhagic stroke from small-vessel disease, intracranial large-artery stenosis, or occlusion (large vascular territory infarcts, embolism from aortic atheromatous or carotid artery disease); progressive rapid intracranial vasculopathy; and leukoaraiosis from small-vessel disease
  - Cognitive dysfunction due to hypoglycemia, hyperglycemia, or stroke
  - Eye: retinopathy, ischemia, or hemorrhage
  - Spinal cord: ischemic infarction
- Autonomic nervous system
  - Autonomic neuropathy: Argyll Robertson pupils, syncope or presyncope and orthostatic intolerance, gastroparesis, sudomotor or sweating abnormalities
- Peripheral nervous system
  - Carpal tunnel syndrome and other mononeuropathies
  - Length-dependent, large-fiber neuropathy (stocking glove pattern); Charcot joints
  - Small-fiber (painful) neuropathy
  - Proximal diabetic neuropathies (eg, diabetic lumbosacral radiculoplexus neuropathy)
- Systemic manifestations
  - Syncope, light-headedness, and transient ischemic attack or strokelike spells
  - Hypoglycemia (encephalopathy, seizures, and coma)
  - Hyperglycemia (HONK and DKA) leading to CPM and, if overcorrected, cerebral edema; seizures and coma may occur
  - CPM with normal sodium, from relative hyperosmolar hyperglycemic state

Abbreviations: CPM, central pontine myelinolysis; DKA, diabetic ketoacidosis; HONK, hyperosmolar nonketotic state.

deterioration to coma, rarely focal neurologic signs (hemiparesis and hemianopsia), and seizures.

Congenital Endocrine Disorders and Tumors of the Endocrine System

Multiple Endocrine Neoplasia

Multiple endocrine neoplasia disorders are associated with particular types of endocrine tumors (Box 79.4). Patients with pheochromocytoma may present with episodic headache, hypertension, and hemorrhagic stroke. Diagnosis of pheochromocytoma is typically investigated with measurement of 24-hour fractionated urinary catecholamines and metanephrines.

Box 79.4 • Multiple Endocrine Neoplasia (MEN) Syndromes and Other Endocrine Tumors

- MEN type 1 (gene map locus 11q13)
  - Primary hyperthyroidism (>90%)
  - Pituitary tumors (prolactinoma, GH-secreting tumor, CRH-secreting tumor, and others)
  - Pancreatic tumors
  - Gastrinoma (Zollinger-Ellison syndrome)
  - Insulinoma
  - VIPoma (vasoactive intestinal polypeptide tumor)
  - Glucagonoma
  - Other
- MEN type 2A (gene map locus 10q11.2)
  - Medullary thyroid cancer (>90%)
  - Pheochromocytoma
  - Others (parathyroid hyperplasia and cutaneous lichen amyloidosis)
- MEN type 2B (gene map locus 10q11.2)
  - Medullary thyroid cancer (>90%)
  - Pheochromocytoma
  - Others (intestinal ganglioneuromas, mucosal neuromas, and marfanoid appearance)
- MEN type 3
  - Medullary thyroid carcinoma and pheochromocytoma, marfanoid habitus, mucosal neuromas (oral and ocular), thickened eyelids, and subconjunctival neuromas
- MEN type 4 (gene map locus 12p13.1, *CDKN1B*)
  - Adrenal and extra-adrenal pheochromocytoma, bilateral medullary thyroid neoplasia, parathyroid hyperplasia, and pituitary adenoma
- Other endocrine genetic syndromes with potential neurologic complications
  - Parathyroid adenoma, familial: parathyroid adenoma (*HPRT1* and *HPRT2* [cystic adenomas], gene map locus 1q25-q31)
  - von Hippel-Landau disease
  - Renal cell carcinoma; pheochromocytoma; retinal, cerebellar, or spinal hemangioblastoma; and pancreatic tumors

Abbreviations: CRH, corticotropin-releasing hormone; GH, growth hormone.

Tumors of the thyroid may cause dysphonia from structural compression on the trachea or glottic region, recurrent laryngeal nerve paralysis, and diaphragm weakness.

- Patients with pheochromocytoma may present with episodic headache, hypertension, and hemorrhagic stroke.

80 Neurologic Complications of Cardiac, Pulmonary, Renal, Hepatobiliary, and Hematologic Disease

WILLIAM D. FREEMAN, MD

Introduction

The brain has a higher demand for cardiac output than any other organ, and it strictly relies on oxygen and glucose metabolism. Consequently, the brain is exquisitely sensitive to homeostatic disturbances and extraneural organ dysfunction leading to cardiac, pulmonary, renal, hepatobiliary, and hematologic diseases.

The primary neurologic manifestation of extraneural organic dysfunction is diffuse bihemispheric dysfunction or encephalopathy, which often lacks lateralizing or localizing signs. The common clinical findings are lethargy, difficulty with attention, orientation, sleep-wake disturbance, and psychomotor slowing. As organic dysfunction progresses, a moderate encephalopathy ensues, with worsening cognitive function, gross disorientation, hypoactive or hyperactive psychomotor state, frontal release signs, asterixis, and myoclonus. If organ failure (eg, hepatic or renal) progresses further, stupor and coma may result unless organ function improves. Patients with underlying organic brain disease from degenerative dementia can decompensate out of proportion to neurologically normal counterparts, resulting in encephalopathy even from minor organ dysfunction or infection.

This chapter reviews cardiac, pulmonary, renal, hepatobiliary, and hematologic diseases and their associated clinical and neurologic manifestations.

Cardiac Disease

Mechanism

The central nervous system (CNS) and autonomic nervous system influence the cardiac conduction and contraction system when sympathetic stimulation is applied (eg, stress, pain, or dysautonomia). The resulting sympathetic stimulation increases cardiac output and heart rate through β-receptor stimulation. Secretion of catecholamines by the adrenal glands leads to neurohumoral stimulation of these receptors. Parasympathetic fibers of the autonomic nervous system via vagal efferents slow the heart rate.

An overview of neurologic associations with cardiac disorders is provided in Table 80.1.

Cardiac Manifestations of Neurologic Disease

Neurocardiogenic Stunning

Neurocardiogenic hyperstimulation from severe stress (voodoo death, broken heart syndrome, status epilepticus, or intracranial bleeding, such as subarachnoid hemorrhage) can induce neurocardiogenic injury, acute heart failure, electrocardiographic (ECG) abnormalities (T-wave changes, ST-segment changes, corrected QT interval prolongation, arrhythmias, or tachycardia), and cardiac arrest.

Abbreviations: CKD, chronic kidney disease; CNS, central nervous system; ECG, electrocardiography; EEG, electroencephalography; NINDS, National Institute of Neurological Disorders and Stroke

Table 80.1 • Neurologic Associations With Cardiac Disorders

Cardiac Disorder	Neurologic Association
ECG changes	Syncope, presyncope, cardiac arrest
Troponin elevation	Can occur in myocardial infarction, but also in severe stress (eg, aneurysmal SAH)
Acute heart failure, cardiac arrest	May result from SAH, status epilepticus, or severe emotional stress (takotsubo cardiomyopathy)
Neurocardiogenic (vasovagal syncope)	Syncope, presyncope
Congenital heart defects	Ischemic stroke (hypoperfusion, paradoxical emboli), heart failure, encephalopathy Cerebral aneurysms associated with coarctation of the aorta
Ischemic (CAD), dilated, idiopathic cardiomyopathies	Cardiac encephalopathy, ischemic stroke (embolic or hypoperfusion), anoxic-ischemic brain injury
Takotsubo (stress-induced) cardiomyopathy	Severe brain injury (eg, trauma, SAH)
Atrial fibrillation, ventricular thrombus	TIA or ischemic stroke
Cardiac arrest	Coma, anoxic-ischemic brain injury, persistent vegetative state Cognitive deficits, ataxia Spinal cord ischemia Encephalopathy Myoclonus Lance-Adams syndrome
Sick sinus syndrome	Syncope, stroke
Endocarditis	Embolism, ischemic stroke, cerebral hemorrhage, mycotic aneurysm, meningitis
Rheumatic fever	Heart failure, stroke, syncope
Bradycardia, tachycardia	Syncope, palpitations, cardiac arrest
PEA, VF, VT	Syncope, cardiac arrest
Atrial fibrillation	Ischemic embolic stroke
Central nervous system complications of essential or malignant hypertension	Ocular: retinal vascular disease (decline in vision) Hypertensive emergency or PRES (encephalopathy, seizure) Stroke, small-vessel disease Arterial dissection (pain, ischemia, hemorrhage) Intracerebral hemorrhage (focal deficits, coma)
Cardiac bypass, including ECMO	Stroke, atheromatous emboli Hypoperfusion injury, cerebral edema Cardiac arrest, coma Encephalopathy, phrenic nerve injury
Cardiac transplant	PRES Hypoperfusion, reperfusion, stroke, cardiac arrest Posttransplant lymphoproliferative disorder Encephalopathy, headaches

Abbreviations: CAD, coronary artery disease; ECG, electrocardiographic; ECMO, extracorporeal membrane oxygenation; PEA, pulseless electrical activity; PRES, posterior reversible encephalopathy syndrome; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

The myocardial pathology in neurocardiogenic stunning is due to contraction band necrosis and not to coagulation necrosis, as occurs with a coronary artery occlusion. In fact, coronary angiograms do not show any major coronary artery occlusion.

Neurocardiogenic injury is typically a diagnosis of exclusion, especially in older patients who have coronary risk factors. A thorough cardiac evaluation is needed. The echocardiographic appearance usually associated with stress-induced neurocardiogenic heart failure is takotsubo cardiomyopathy, which is characterized by anterior apical ballooning (Figure 80.1).

Management of neurocardiogenic stunning is aimed at reducing pain, anxiety, and stress and possibly providing β-blockade in patients for whom it is not contraindicated (eg, patients with asthma, chronic obstructive pulmonary disease, or severe hypotension). If severe respiratory and cardiopulmonary failure ensues, ventilator and vasopressor support can be provided.

Neurocardiogenic Syncope

Neurocardiogenic syncope, also known as vasovagal syncope, typically manifests in patients who are startled (emotional distress), have been standing for a prolonged period,

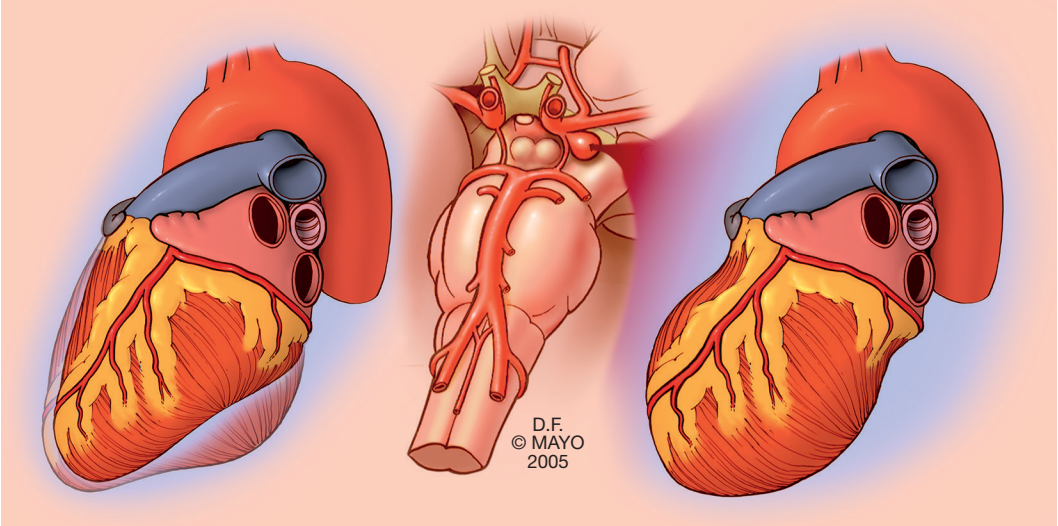

Figure 80.1 *Takotsubo Cardiomyopathy.*
Left, Normal cardiac contraction. Middle, Intracranial aneurysm. Right, Takotsubo cardiomyopathy associated with ruptured intracranial aneurysm and subarachnoid hemorrhage.
(Used with permission of Mayo Foundation for Medical Education and Research.)

are in severe pain, or have been exercising vigorously (especially in a warm environment). The duration of unconsciousness is typically brief (≤30 seconds) and may or may not be associated with a shaking or convulsive syncopal presentation, which is due to reduced cerebral blood flow and not epileptiform activity on electroencephalography (EEG).

Evaluation of patients with syncope should include a complete history and physical examination and a 12-lead ECG to screen for long QT syndrome or other arrhythmias. If there is any question of structural abnormalities, an echocardiogram is warranted. A tilt table examination or Holter monitoring can be performed if repeated syncopal events occur.

Management options include liberal salt intake and hydration, calf- or thigh-high compression hose to improve venous return to the heart, low-dose β-blockers, selective serotonin reuptake inhibitors, and, if severe (eg, repeated syncopal episodes with bodily trauma), cardiac evaluation for consideration of implantable loop recorders or a pacemaker.

Neurologic Manifestations of Cardiac Disease

Structural dysfunction of the heart can lead to various neurologic manifestations. Structural, congenital, functional, vascular, or electrical disturbances can lead to cardiac dysfunction.

Congenital Heart Disease

Patients with congenital disorders, such as tetralogy of Fallot, atrial septal defect, or ventricular septal defect, have evidence of cardiac murmur on examination or cyanosis from left-to-right shunting of oxygenated blood. These disorders are usually discovered within the first year of life, but ventricular septal defect can occur after septal wall myocardial infarction in adulthood. Abnormal heart function can lead to reduced blood flow to end organs (ischemia) and reduced oxygenation (hypoxia). Patients with a chronically reduced left ventricular ejection fraction (ie, heart failure) have a relatively dilated cerebrovascular system for maintaining cerebral blood flow. These patients with chronic heart failure have little cerebrovascular reserve for new additional insults to cardiac function and can become acutely encephalopathic with even minor reductions in cardiac function. Also, patients with progressive chronic heart failure are known to have cognitive dysfunction from low cardiac output states or cardioembolic ischemic stroke events.

Anoxic-Ischemic Injury

Cardiac arrest may lead to anoxic-ischemic injury. This topic is covered in Chapter 5, "Anoxic-Ischemic Encephalopathy."

Cardiac Surgery Complications

Patients undergoing coronary artery bypass graft surgery or valve replacement and patients undergoing extracorporeal membrane oxygenation after cardiac arrest are at risk for cerebrovascular complications—namely, embolic stroke and cerebral hypoperfusion. Atherosclerotic material becomes dislodged during cannulation of the aorta and goes cephalad toward the brain. It can cause discrete thromboembolic cerebrovascular territory infarcts or, if large amounts of atherosclerotic debris are dislodged, a diffuse cholesterol embolization syndrome. Hypoperfusion can occur during the perioperative period from hemodynamic instability or from inadequate bypass pump pressure. Severe anemia and hypoperfusion can result in a diffuse

bihemispheric anoxic-ischemic brain injury pattern from poor cerebral oxygen delivery. An asymmetric hemispheric injury with cerebral edema occurs rarely if the bypass cannula obstructs the brachiocephalic artery or aortic arch at the origin of the left common carotid artery.

Acute ischemic stroke in cardiac surgery patients within the first month after surgery poses a dilemma for treatment with intravenous tissue plasminogen activator because 1 of the exclusion criterion used in the National Institute of Neurological Disorders and Stroke (NINDS) trial was major surgery within 3 months. Intra-arterial stroke intervention such as intra-arterial lower-dose tissue plasminogen activator or mechanical thrombectomy could be considered (but this would be off-label use) if the neurologic deficit is severe enough and if the risks of intra-arterial intervention are discussed with the patient (or the patient's medical surrogate) and the cardiovascular surgeon and if the benefit from such an intervention would outweigh the risks.

Postoperatively, cardiac surgery patients are at risk for atrial fibrillation, lack of transvenous pacemaker wire capture, cardiac arrest, hypotension, and arrhythmias. Patients who receive mechanical heart valves are at risk for cerebral embolic events, especially with a caged-ball valve in the high-risk mitral position.

- Neurocardiogenic hyperstimulation from severe stress (broken heart syndrome) is characterized by anterior apical ballooning on echocardiography and contraction band necrosis on pathology.
- Neurocardiogenic syncope (vasovagal syncope) is characterized by brief episodes of unconsciousness typically triggered by emotional distress, pain, or vigorous exercise.
- Patients undergoing coronary artery bypass graft surgery or valve replacement and patients undergoing extracorporeal membrane oxygenation after cardiac arrest are at risk for cerebrovascular complications—namely, embolic stroke and cerebral hypoperfusion.

Pulmonary Disease

Mechanism

The process of air movement through the lungs is ventilation, and the process of movement of blood through the lungs for gas exchange is perfusion. Ventilation and perfusion are critical to oxygenation of blood.

Neurologic control of respiration starts within the CNS with cortical voluntary control followed by unconscious CNS control in the pontine pneumotaxic center, which functions as a pacemaker between inspiratory and expiratory time and provides input to the lower medullary inspiratory and expiratory neurons. The medullary neurons also have chemoreceptor inputs from changes in blood pH (hydrogen ion concentration) from accumulation of carbon dioxide. Thus, increases in P_{CO_2} or decreases in pH will increase the respiratory rate and depth. Medullary respiratory centers modulate respiration by signaling efferent anterior horn cell motor neurons in the cervical spinal cord at levels C3 through C5. From these levels in the spinal cord, ventral motor roots and the cervical plexus descend from the neck into the chest to innervate the diaphragm (Figure 80.2). Table 80.2 outlines different neurologic breathing patterns in cardiac, systemic, and neurologic disease states.

Pulmonary Manifestations of Neurologic Disease

Coma

Coma may result in altered respiratory patterns. Details are discussed in Chapter 1, "Impaired Consciousness and Coma."

Spinal Cord Disease

Patients with cervical spinal cord disease may have significant respiratory dysfunction, including paradoxical respiration (Table 80.2), due to impaired input to the diaphragm.

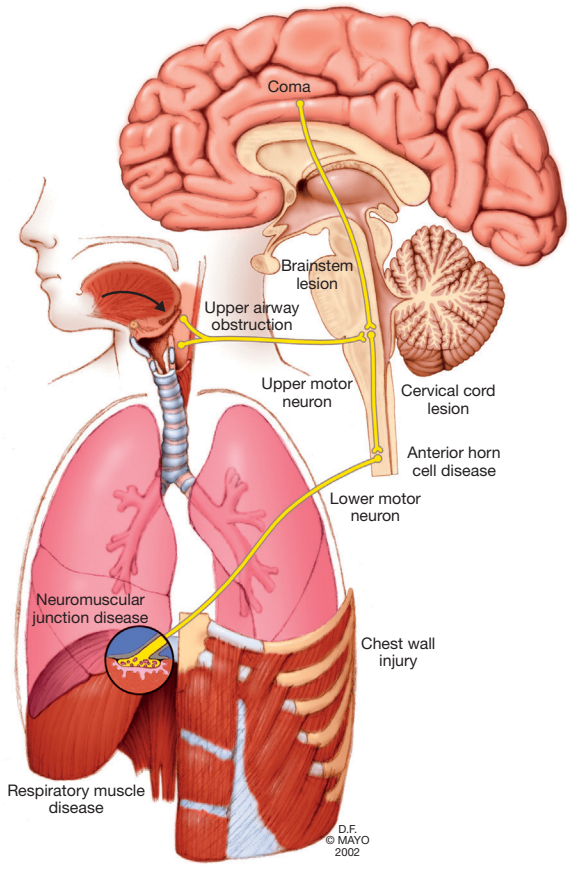

Figure 80.2 *Central and Peripheral Nervous System Structures Involved in Respiratory Control.*
(Used with permission of Mayo Foundation for Medical Education and Research.)

Table 80.2 • Neurologic Breathing Patterns

Breathing Pattern	Description of Pattern	Localization or Cause
Apneustic	Inspiration followed by a prolonged inspiratory pause of 2–3 s followed by expiration	Pontine lesions
Asymmetric chest wall movement	Hemidiaphragm or chest wall respiratory excursion	Pneumothorax (acute) Hemidiaphragm paralysis (eg, traumatic, surgical, or neoplastic phrenic nerve injury) Cervical Brown-Séquard syndrome Large hemispheric stroke (subtle hemithorax movement difference)
Ataxic (Biot respiration) or agonal	Irregular rate, irregular tidal volume	Originally described by Biot in a patient with meningitis Also occurs in end-stage herniation (agonal)
Cluster	Cluster of similar tidal-volume breaths followed by relative hypopnea or apnea	Typically brainstem (pontine) lesions; rarely bihemispheric injury
Central neurogenic hyperventilation	Sustained hyperventilation	Typically pontine or medullary lesions
Central neurogenic hypoventilation (Ondine curse)	Lack of breathing with unconsciousness or sleep	Congenital: undeveloped medullary respiratory control (ie, premature infants or idiopathic) Acquired: rare; brainstem stroke or lesion
Kussmaul respiration	Large tidal volume Consistent respiratory rate	Diabetic ketoacidosis
Paradoxical respiration	No rib cage expansion with inspiration; rather, abdominal wall moves out from diaphragm movement downward ("belly breathing")	Neuromuscular paralysis of cervical spinal cord injury sparing some innervation of the diaphragm (C3 through C5) Generalized Guillain-Barré syndrome Myasthenia gravis Some brainstem strokes
Respiratory failure	Tachypnea Increased work of breathing Nasal flaring Diaphoresis Accessory muscle use (sternocleidomastoids, platysma) Sitting upright to aid diaphragm excursions	Asthma or COPD exacerbation Pulmonary embolus Pneumonia Heart failure Volume overload Progressive fibrotic or interstitial lung disease

Abbreviation: COPD, chronic obstructive pulmonary disease.

Neuromuscular Disease

Patients with acute inflammatory demyelinating polyradiculopathy (Guillain-Barré syndrome), myasthenia gravis, or botulism may present with generalized neuromuscular weakness in addition to respiratory distress. These diseases and specific monitoring aspects of respiration are covered in Chapter 8, "Neuromuscular Disease in the Neuroscience Intensive Care Unit."

Although the diseases noted above often cause acute changes in respiratory function, other neuromuscular diseases may involve the respiratory muscles (Box 80.1).

Neurologic Manifestations of Pulmonary Disease

An overview of neurologic associations with pulmonary disorders is provided in Table 80.3.

Hypoxia and Hypercapnia

Lung disorders typically cause ventilation-perfusion mismatch, resulting in hypoxia or hypercapnia (or both) from impaired gas exchange. Since the brain is the most oxygen-sensitive organ, changes in the ventilation-perfusion status affect the brain's oxidative metabolism. Severe systemic hypercapnia leads to an acute respiratory acidosis, a decline in mental status, obtundation, and coma. Acute hypercapnia causes dilation of cerebral blood vessels and headache. Severe acute hypoxia (Pa_{O_2} <45 mm Hg) without hypercapnia causes acute encephalopathy, with a subsequent metabolic acidosis from failure of oxidative metabolism. Increases in carbon dioxide and low P_{O_2} are strong stimuli for the medullary respiratory centers and result in increased cerebral blood flow.

Pulmonary embolism is a common and potentially fatal form of lung disease caused by deep vein thrombosis and venous thromboembolism into the pulmonary arteries.

Box 80.1 • Neuromuscular Diseases That May be Associated With Involvement of Respiratory Muscles

- Infectious
  - Botulism toxin
  - Polio (and postpolio syndrome)
  - HIV myopathy
- Inflammatory or autoimmune
  - Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
  - Multifocal motor neuropathy with conduction block
  - Myasthenia gravis
  - Parsonage-Turner syndrome (may involve phrenic nerve)
  - Critical illness polyneuropathy and critical illness myopathy
  - Inflammatory myopathies (less common)
- Neoplastic or paraneoplastic
  - Lambert-Eaton syndrome
- Toxic or metabolic
  - Ciguatera toxin
  - Tetrodotoxin
  - Hypophosphatemia
  - Hypokalemia
  - Snake, spider, or scorpion venom
- Medications
  - Paralytic (neuromuscular blocking) agents
- Degenerative
  - Amyotrophic lateral sclerosis
- Genetic or congenital
  - Pompe disease (α-glucosidase deficiency)
  - Myotonic dystrophy
  - Muscular dystrophy (late stage)
  - Facioscapulohumeral muscular dystrophy
  - Congenital myopathies
  - Isolated muscular dystrophy of the diaphragm
  - Mitochondrial myopathy
  - Carnitine palmitoyltransferase deficiency myopathy
- Other
  - Phrenic nerve neuropathy (from trauma, structural compression, infection, or radiotherapy or idiopathic)

Abbreviation: HIV, human immunodeficiency virus.

Clots most commonly migrate from a deep femoral vein. Patients with stroke and spinal cord injury with immobility of limbs are at higher risk than patients who cannot ambulate. Patients with pulmonary embolism may present with various symptoms, such as chest pain, pleurisy, acute dyspnea, light-headedness, or sudden cardiac arrest from saddle embolism.

Table 80.3 • Neurologic Associations With Pulmonary Disorders

Pulmonary Disorder	Neurologic Association
Bacterial (community acquired)	Encephalopathy, coma
Atypical bacterial (*Chlamydophila pneumoniae, Mycoplasma, Legionella*)	Encephalopathy Hyponatremia can be associated with legionnaires' disease and pulmonary infection
Pulmonary embolus	Encephalopathy, shock, cardiac arrest
COPD and asthma	Hypoxic encephalopathy Hypercapnic encephalopathy
Interstitial lung disease	Hypoxia, respiratory failure
Sarcoidosis	Facial neuropathy or mononeuritis multiplex cranialis, CNS sarcoidosis, headache, hypothalamic dysfunction, spinal cord inflammatory disease (transverse myelitis)
Pulmonary edema—cardiogenic or neurogenic (related to injury, hemorrhage, or status epilepticus)	Encephalopathy
Pulmonary hypertension	Headaches related to hypoxia
Carbon monoxide poisoning	Hypoxic stupor, coma
Toxic drug overdose	Coma, narcotics (small pupils)
Neuromuscular respiratory weakness and ventilatory failure	Findings associated with anterior horn cell disease (eg, ALS), nerve disease (eg, AIDP), neuromuscular junction disease (eg, myasthenia gravis), or muscle disease (eg, acid maltase deficiency)
Lung cancer	Headache, brain lesions, subacute cognitive decline, ataxia, seizures
Lung transplant	Headaches, posterior reversible encephalopathy syndrome

Abbreviations: AIDP, acute inflammatory demyelinating polyradiculopathy; ALS, amyotrophic lateral sclerosis; CNS, central nervous system; COPD, chronic obstructive pulmonary disease.

Obstructive Sleep Apnea

Obstructive sleep apnea is covered in Chapter 85, "Clinical Sleep-Related Breathing Disorders."

Treatment

For most patients with pulmonary disease, the initial step is to stabilize the respiratory system by providing adequate systemic oxygenation (Pao_2 >80 mm Hg), and specialized

management for the underlying pulmonary, medical, or neurologic disorder.

Renal Disease

Mechanism

Uremia (ie, increased serum urea nitrogen) from acute or chronic kidney failure leads to decreased cerebral metabolic function. Uremia antagonizes γ-aminobutyric acid and causes a relative excitatory state by promoting *N*-methyl-D-aspartate glutamate transmission.

Renal Manifestations of Neurologic Disease

Although few neurologic diseases cause kidney dysfunction, some neurologic disorders have both neurologic and renal manifestations of the same disease (Table 80.4).

Neurologic Manifestations of Renal Disease

Uremic Encephalopathy

The most common clinical finding in uremia is encephalopathy with myoclonus. Acute kidney disease or injury has a long list of causes, including acute tubular necrosis, acute interstitial nephritis, nephritic and nephrotic syndromes, and vascular, obstructive, ischemic, or embolic (cholesterol) disease. Regardless of the cause, renal failure leads to an accumulation of toxins that are normally excreted by the kidney.

Patients with uremic encephalopathy may have clinical signs of the triad of a fine action tremor, myoclonus, and asterixis. Asterixis and myoclonus are similar brief lapses in motor tone. Asterixis typically occurs in outstretched hands with wrists back, but it also occurs in the face (Figure 80.3) and feet. The EEG is often slowed, with delta and theta frequencies.

Chronic Kidney Disease

Chronic kidney disease (CKD) from hypertension or diabetes mellitus occurs over time and is classified by the glomerular filtration rate and other features. Patients with CKD from chronic hypertension have a higher risk of stroke, severe white matter changes (Binswanger disease), and neurocognitive decline. Chronic hypertension is a common cause of CKD and other neurologic and medical complications, such as cardiac hypertrophy.

In patients with severe CKD (ie, glomerular filtration rate <30 mL/min/1.73 m^2) who receive intravenous gadolinium as a contrast medium for magnetic resonance imaging, an idiopathic, progressive connective tissue disease similar to scleroderma called nephrogenic systemic fibrosis may uncommonly develop. There is no known treatment for nephrogenic systemic fibrosis.

Table 80.4 • Neurologic Associations With Renal Disease

Renal Disease	Neurologic Association
Nephrogenic systemic fibrosis	Progressive muscle weakness, progressive thickening of skin (like scleroderma), burning skin (neuropathic symptoms)
Dialysis disequilibrium syndrome	Length-dependent neuropathy, headache, nausea, muscle cramps, stupor, encephalopathy
Dialysis dementia	Progressive dementia in patients who have received hemodialysis for >3 y Early: speech stammering, arrest Late: dysarthria, dementia, myoclonus, convulsive seizures, asterixis thought to result from brain aluminum accumulation
Polycystic kidney disease	Uremic encephalopathy, subarachnoid hemorrhage
Renal transplant	Stroke Posterior reversible encephalopathy syndrome, seizure Posttransplant lymphoproliferative disorder Fungal CNS infection (eg, meningitis)
Uremia	Encephalopathy, asterixis, coma, seizures (typically late), dysarthria, ataxia, asterixis, myoclonus, restless legs syndrome, length-dependent axonal sensorimotor peripheral neuropathy

Abbreviation: CNS, central nervous system.

Polycystic Kidney Disease

Polycystic kidney disease is an autosomal dominant disorder that leads to progressive cystic changes in the kidney and liver, causes hypertension, and is associated with an increased risk of intracranial berry aneurysms, which can rupture and result in subarachnoid hemorrhage.

Hemodialysis and Renal Replacement Therapy

Hemodialysis or renal replacement therapy is typically indicated in patients with uremic encephalopathy with worsening cognition, myoclonus, or life-threatening hyperkalemia with significant uremia. Kidney transplant, in eligible patients, if successful, can resolve uremic encephalopathy within days.

- Patients with uremic encephalopathy may have clinical signs of the triad of a fine action tremor, myoclonus, and asterixis.
- Patients with CKD from chronic hypertension have a higher risk of stroke, severe white matter changes (Binswanger disease), and neurocognitive decline.
- Autosomal dominant polycystic kidney disease is associated with an increased risk of intracranial aneurysms.

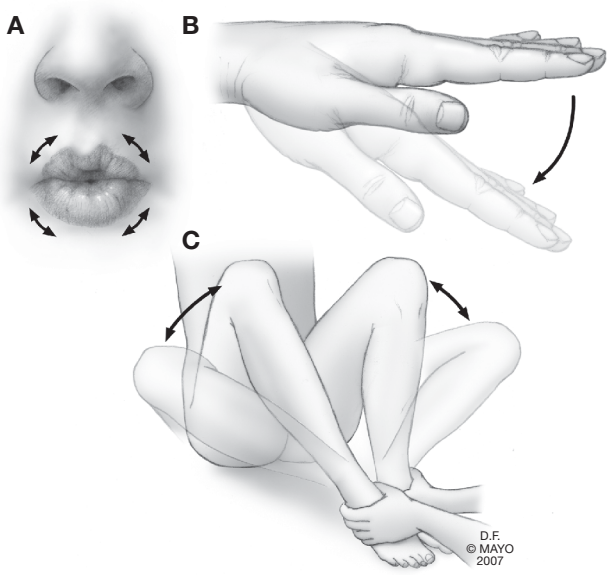

Figure 80.3 *Asterixis. Clinical signs include brief loss of postural tone in the mouth (A), finger extensors (B), and hip adductors (C).*
(Used with permission of Mayo Foundation for Medical Education and Research.)

Hepatobiliary Disease

Mechanism

The liver has a major role in metabolism of nutrients and medications and in detoxification.

Hepatobiliary Manifestations of Neurologic Disease

Wilson Disease

Wilson disease is a disorder with liver and neurologic involvement. Diagnosis is aided by ophthalmologic examination showing Kayser-Fleischer rings on a slit-lamp study and low serum levels of copper and ceruloplasmin. See Chapter 27, "Childhood Movement Disorders."

Storage Disorders

Disorders of glycogen and lysosome storage are often accompanied by neurologic symptoms in addition to hepatomegaly. Examples include mucopolysaccharidoses (eg, Hunter syndrome and Hurler syndrome), Gaucher disease, and Pompe disease. See also Chapter 74, "Lysosomal Storage Disorders."

Neurologic Manifestations of Hepatobiliary Disease

Hepatic Encephalopathy

Liver failure is a well-known cause of encephalopathy and typically occurs from chronic hepatic disease caused by alcoholism or from nonalcoholic steatohepatitis caused by obesity. Hepatic encephalopathy can be graded by the West Haven scale (Box 80.2).

Box 80.2 • Grades of Hepatic Encephalopathy

- Grade 1—subtle cognitive abnormalities, impaired attention
- Grade 2—lethargy, minimal disorientation, subtle personality change or inappropriate behavior
- Grade 3—stuporous but responsive to verbal stimuli, gross disorientation
- Grade 4—coma (Glasgow Coma Scale ≤8), unresponsive to verbal or noxious stimuli

Other causes of hepatic failure to consider in the differential diagnosis include hepatic, pancreatic, or biliary tumors with secondary metastatic involvement or obstruction of biliary pathways.

Patients typically manifest a nonfocal encephalopathy, often accompanied by asterixis. The EEG may show either nonspecific slowing or triphasic waves (Figure 80.4).

The mainstay of encephalopathy management in chronic hepatic disease is lactulose (which reduces ammonium absorption) and either neomycin or rifaximin, which clears ammonia-producing organisms from the bowel. As hepatic disease progresses to end-stage disease, transplant can be a life-saving intervention and can normalize hepatic encephalopathy.

Viral Hepatitis

Acute viral hepatitis and acetaminophen overdose can cause acute liver failure, which can lead to massive transaminitis and hyperammonemic coma. This is a neurologic emergency that can cause global cerebral edema and brain death. Patients with acute liver failure and neurologic involvement are considered first-line candidates for orthotopic liver transplant if they have no contraindications, such as systemic infection.

- The EEG from a patient with hepatic encephalopathy may show either nonspecific slowing or triphasic waves.

Hematologic Disease

Mechanism

Hematologic disease can manifest in various forms depending on the cell line affected. The bone marrow produces 3 major blood cell lines: erythrocytes, leukocytes, and platelets. Within these blood cell lines, various pathologic processes may result in increased or decreased

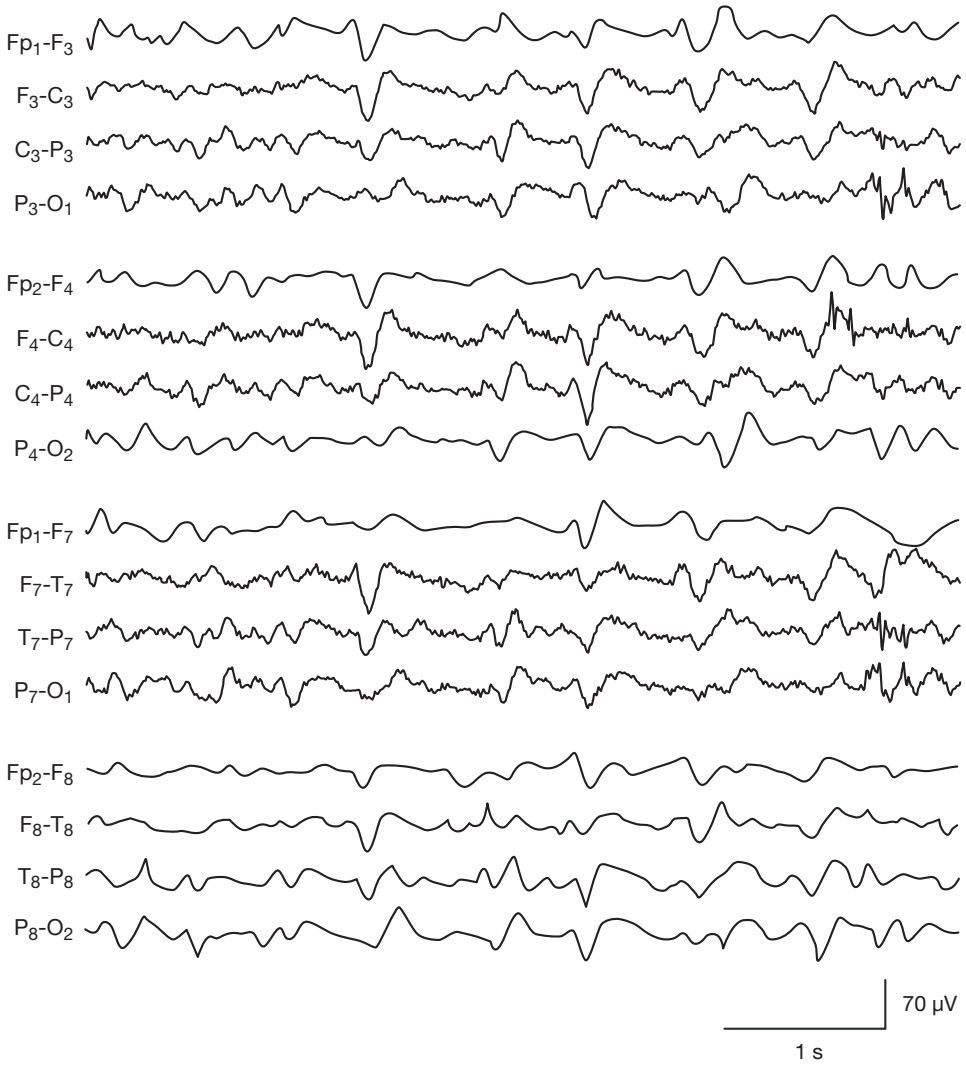

Figure 80.4 *Triphasic Waves.*
Electroencephalogram shows triphasic waves such as those seen in hepatic encephalopathy.

production of cells or dysfunctional cells. Each pathologic process has its own clinical manifestations.

Hematologic Manifestations of Neurologic Disease

Infections

Many neuroinfectious diseases are accompanied by abnormalities in the peripheral white blood cell count and other markers of inflammation. Brucellosis may cause low cell counts in all 3 blood cell lines.

Genetic and Storage Disorders

Select genetic and storage disorders may affect multiple organs, including the brain. Patients with Gaucher disease, for instance, may have mental retardation and seizures in addition to pancytopenia due to splenomegaly. These patients also have hepatomegaly.

Iatrogenic

Chemotherapeutic agents and many of the treatments used for seizure disorders and CNS vasculitis may cause hematologic changes that often require monitoring.

Neurologic Manifestations of Hematologic Disease

Table 80.5 outlines neurologic complications of various hematologic conditions.

Table 80.5 • Neurologic Associations With Hematologic Disorders

Hematologic Disorder	Neurologic Association
Red blood cell line disorders	
Anemia	Encephalopathy, headache, coma (if severe acute anemia from poor cerebral oxygen delivery), death Hyperviscosity may lead to cerebral infarcts and peripheral neuropathy
Polycythemia	Sickle cell (hemoglobin S) disease: sludging (extremity and visceral pain), stroke (ischemic and intracerebral hemorrhage), moyamoya disease, headaches, acute mononeuropathy
Hemoglobinopathies (eg, sickle cell disease, β-thalassemia)	β-thalassemia: cognitive changes, deferoxamine neurotoxicity, blood product transfusion reactions, headaches, vision disturbance, peripheral neuropathy, seizure (less common)
White blood cell line disorders	
Acute lymphocytic leukemia (ALL)	CNS involvement at diagnosis in 5%-10% Leptomeningeal involvement (cranial nerves or peripheral nerve) Intravascular CNS lymphoma may mimic CNS vasculitis
Acute myelogenous leukemia (AML)	AML FAB classification M4: at risk for CNS involvement, chloroma (granulocytic sarcoma)
Chronic lymphocytic leukemia (CLL)	Rarely affects CNS (eg, chloroma)
Monoclonal gammopathy of undetermined significance (MGUS)	Peripheral neuropathy
Multiple myeloma	Demyelinating peripheral neuropathy
Waldenström macroglobulinemia	Hyperviscosity, stroke
POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin abnormalities)	Demyelinating peripheral neuropathy, optic nerve edema, weakness
Histiocytosis X (Langerhans cell histiocytosis)	Multifocal calvarial lesions (Hand-Schüller-Christian disease), exophthalmos, diabetes insipidus
Platelet disorders	
Idiopathic thrombocytopenia (ITP)	Intracranial hemorrhage, anemia
Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)	Encephalopathy, acute renal failure, thrombocytopenia
TTP from clopidogrel or ticlopidine	History of ticlopidine or clopidogrel use
Cancer-related disorders	
Hypercoagulability of cancer	Deep vein thrombosis (DVT), pulmonary embolism (PE), stroke
Nonbacterial thrombotic endocarditis (NBTE)	Stroke
Disseminated intravascular coagulation (DIC)	Hemorrhagic crisis
Radiation vasculopathy	Ischemia or infarction
Graft-vs-host disease	
Bone marrow transplant	Myasthenia gravis symptoms and signs, demyelinating peripheral neuropathy, myositis, CNS angiitis
Bone disease	
Paget disease (osteitis deformans)	Arteriosclerosis (eg, monocular vision loss), pressure on CNS or peripheral nerves from bone overgrowth, deafness, cranial nerve VII palsy

Abbreviations: CNS, central nervous system; FAB, French-American-British.

81 Intoxications and Nontraumatic Neurologic Injury

SARA E. HOCKER, MD

Introduction

Toxins and environmental exposures may result in central or peripheral nerve dysfunction. Toxins may be purposely ingested (eg, substance abuse) or exposure may be accidental (eg, occupational exposure or terrorism). Certain environmental exposures (eg, lightning or high altitude) may also result in neurologic injury. This chapter reviews neurologic clinical syndromes associated with substance abuse and other toxins as well as the physical effects of certain environmental conditions.

Substance Abuse

Drugs of abuse often involve dopaminergic neurotransmission in the mesolimbic system. Despite their common pharmacologic effects, they produce very different intoxication and withdrawal syndromes. This chapter reviews the clinical manifestations of intoxication and withdrawal. The complex psychosocial consequences and treatment of substance abuse disorders are discussed in Volume 1, Chapter 44, "Substance Use Disorders."

Opioids

Opioids comprise natural alkaloids derived from poppy, such as morphine and codeine as well as synthetic compounds like methadone and fentanyl. The opioid receptors μ, δ, and κ each have different subtypes and are located in the brain and spinal cord and at peripheral sites. The differential actions at these various receptor sites account for the variable effects of different agents; however, the mechanisms that underlie the clinical effects of the various opioids, including physical and psychological dependence, are poorly understood.

The predominant action of opioids is to inhibit excitatory (glutamate) or inhibitory (γ-aminobutyric acid) neurotransmission. Although most opiate addicts abuse diacetylmorphine (heroin, a Drug Enforcement Administration [DEA] Schedule I agent), many addicts misuse physician-prescribed opiates, which may be prescribed for their analgesic, antitussive, or antidiarrheal properties (Box 81.1).

Sympathomimetics

Many prescription and over-the-counter drugs have sympathomimetic effects and so are categorized as psychostimulant drugs of abuse. The most commonly abused are amphetamine, dextroamphetamine, methamphetamine, methylphenidate, and cocaine. These are classified as DEA Schedule II drugs. Drugs with amphetamine-like effects are prescribed by physicians for the management of conditions such as attention-deficit/hyperactivity disorder, obesity, narcolepsy, and congestion. The over-the-counter decongestants ephedrine and pseudoephedrine have low abuse potential, but dependence has been described. Symptoms and signs of psychostimulant intoxication and withdrawal are detailed in Box 81.2.

Hallucinogens

During overdose, many drugs of abuse may cause hallucinations along with drug-induced delirium or psychosis. Examples include marijuana, phencyclidine (PCP), methamphetamine, and cocaine. *Hallucinogens* are a class of drugs of abuse that alter perception, mood, and thought without compromising alertness, attentiveness, or memory. Numerous plants have hallucinogenic properties, but the most commonly abused hallucinogens in the United

Abbreviations: DEA, Drug Enforcement Administration; LSD, lysergic acid diethylamide; PCP, phencyclidine

Box 81.1 • Opiate Intoxication and Withdrawal: Symptoms and Signs

- Intoxication
  - Neurologic
    - Analgesia, euphoria, or dysphoria
    - Miosis
    - Drowsiness (suppressed REM sleep); can deteriorate to coma
  - Systemic
    - Pruritus
    - Gastrointestinal tract: nausea and vomiting, dry mouth, biliary tract spasm, reduced gastric secretion
    - Hypothermia, postural hypotension
    - Urinary retention
    - Respiratory depression
- Withdrawal
  - Neurologic
    - Anxiety
    - Mydriasis, lacrimation
    - Muscle spasms, piloerection
  - Systemic
    - Flulike symptoms (abdominal cramps, anorexia, nausea and vomiting, diarrhea, fever, hot flashes, myalgias, rhinorrhea, productive cough)
    - Hypertension, sweating, tachycardia, tachypnea
    - Sweating, yawning
    - Drug craving

Abbreviation: REM, rapid eye movement.

Box 81.2 • Psychostimulant Intoxication and Withdrawal: Symptoms and Signs

- Intoxication
  - Neurologic
    - Alert, euphoria, agitation (sometimes psychosis); poor judgment
    - Mydriasis
    - Headache
    - Increased motor activity (may include chorea, tremor, bruxism, dystonia)
    - Seizure
    - Signs or symptoms of stroke (intracerebral hemorrhage or ischemic)
    - Coma may develop
  - Systemic
    - Insomnia
    - Hypertensive crisis
    - Malignant hyperthermia
    - Cardiac: cardiac arrhythmia, chest pain, dyspnea, diaphoresis, myocardial infarction
    - Pulmonary: pulmonary edema, dyspnea
    - Severe metabolic acidosis
- Withdrawal
  - Neurologic
    - Dysphoria, depression (suicidal)
  - Systemic
    - Fatigue
    - Drug craving

States are psilocybin and psilocin from mushrooms, mescaline from peyote cactus, and the synthetic ergot lysergic acid diethylamide (LSD).

Hallucinogen intoxication first produces dizziness, somnolence, headache, and either anxiety or euphoria. These are followed by visual distortions, palinopsia (prolonged afterimages), and synesthesias (seeing sound or hearing color). The final period includes formed complex hallucinations, which are typically visual in nature. This period may be accompanied by fever, tachycardia, hypertension, tremor, ataxia, mydriasis, and, with high doses, hyperthermia, seizures, and coma.

Ethanol

In the United States, ethanol is the most widely abused drug. Misuse of alcohol is a leading risk factor for premature death and disability worldwide. The predominant physiologic effects of ethanol are the inhibition of glutamatergic neurotransmission and the facilitation of GABAergic neurotransmission. Ethanol is a nervous system depressant at multiple levels of the neuraxis. Symptoms of intoxication correlate with blood alcohol concentration and range from euphoria and impaired inhibition to coma. Either intoxication or withdrawal from alcohol can be fatal.

Acute ethanol intoxication may be associated with hallucinations. Mild withdrawal symptoms may include agitation, diaphoresis, and vomiting. Ethanol withdrawal may be complicated by generalized seizures (typically at 24–48 hours) and delirium tremens (consisting of delirium, hallucinations, and dysautonomia) at 48 to 72 hours. Alcohol withdrawal generally lasts several days to a week. Withdrawal can be monitored with a structured symptom scale such as the Clinical Institute Withdrawal Assessment and generally managed with close monitoring and benzodiazepines.

Chronic alcohol overconsumption may lead to alcoholic hepatitis and cirrhosis, esophageal varices, pancreatitis, hypertension, cardiac dysfunction, increased risk of malignancy, and neurotoxic complications such as cerebellar ataxia or peripheral neuropathy. Dietary insufficiency in patients with chronic alcoholism may lead to thiamine (vitamin B_1) deficiency, resulting in Wernicke encephalopathy or, with more long-standing injury,

Korsakoff syndrome (typically, a confabulatory amnestic syndrome). Urgent thiamine repletion is called for in patients with suspected components of these syndromes. Laboratory evaluation of patients with chronic alcohol abuse may show hepatic dysfunction (elevated aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transferase; diminished synthetic function; and coagulopathy) and an increased mean corpuscular volume. Elevated carbohydrate-deficient transferrin is a sensitive marker of chronic alcohol consumption regardless of end-organ damage.

PCP and Ketamine

PCP and ketamine are similar in mechanism and action. Originally developed as an anesthetic, PCP was withdrawn from clinical use because of psychotic reactions. It emerged as a street drug in the 1970s and continues to be widely used in urban areas.

Clinical effects of PCP are dose dependent and include euphoria or dysphoria, inhibition, distortion of time perception, sensory distortions, analgesia, agitation, and psychosis. Intoxication can mimic the clinical spectrum of schizophrenia. Fever may be present and can progress to malignant hyperthermia. At very high doses, seizures and coma may occur. Death is typically due to frank overdose or from accidents, often resulting from painless self-injury or other violent behavior.

The withdrawal syndrome consists of anxiety, tremor, gastrointestinal tract symptoms, and cold sweats. Ketamine is shorter acting and less toxic than PCP, but intoxication and the withdrawal symptoms are similar to those with PCP.

Marijuana

Marijuana intoxication consists of drowsiness and euphoria but can be accompanied by paranoia, anxiety, and hallucinations. Withdrawal is uncommon because the elimination of marijuana is slow.

- The final period of hallucinogen intoxication may be accompanied by fever, tachycardia, hypertension, tremor, ataxia, mydriasis, and, with high doses, hyperthermia, seizures, and coma.
- Ethanol withdrawal may be complicated by generalized seizures (typically at 24–48 hours) and delirium tremens (consisting of delirium, hallucinations, and dysautonomia) at 48–72 hours.
- Clinical effects of PCP are dose dependent and include euphoria or dysphoria, inhibition, distortion of time perception, sensory distortions, analgesia, agitation, and psychosis.

Other Toxins and Bioterrorism

Heavy Metals and Organic Chemicals

There are many clinical and neurologic features of acute or chronic exposure to heavy metals (Table 81.1) and organic chemicals (Table 81.2).

Table 81.1 • Heavy Metal Toxicities

Toxin	Potential Exposure	Clinical Features
Arsenic	Poisoning	Acute exposure: abdominal pain, nausea, vomiting, headaches, encephalopathy, seizures Chronic, low-grade exposure: abdominal pain, vertigo, headaches, painful peripheral neuropathy, possible optic neuropathy, mees lines (white line on fingernails); hair contains arsenic
Inorganic lead	Lead-based paint	Acute exposure: gastrointestinal tract illness, confusion, coma, seizures Children with chronic, low-grade exposure: behavioral change, psychomotor slowing, sleep disturbance, seizure, clumsiness, ataxia Adult with low-grade exposure: polyneuropathy (motor more than sensory), wrist drop or foot drop common, paresthesias
Manganese	Mine worker inhalation Parenteral nutrition with manganese	Headache, neuropsychiatric changes (memory, hallucinations, aggressive behavior, personality disorder), extrapyramidal syndrome (parkinsonism); MRI shows T1-weighted signal in globus pallidus (pathology shows neuronal loss in globus pallidus and subthalamic nucleus)
Inorganic mercury	Batteries, herbal remedies and cream, chemical industry	Acute exposure: colitis, vomiting, renal failure, delirium Chronic exposure: tremor, peripheral neuropathy, personality changes
Organic mercury	Some fish	Cerebellar ataxia, peripheral neuropathy, cortical blindness, chorea, motor neuron syndrome, cognitive impairment (“mad as a hatter”) with memory loss, hallucinations, psychiatric symptoms
Thallium	Pesticides	Acute exposure: acute gastrointestinal tract illness, confusion, coma Delayed exposure: Painful sensory neuropathy with autonomic features may develop Chronic exposure: alopecia, neuropathy

Abbreviation: MRI, magnetic resonance imaging.

Table 81.2 • Organic Chemical Toxicities

Toxin	Exposure	Clinical Features
Acrylamide	Undercooked food, tobacco smoke	Acute exposure: seizures, encephalopathy Chronic exposure: peripheral neuropathy (axonal); may be preceded by skin peeling
Hexacarbon solvents	Glue sniffing, paint, varnish	Acute exposure: euphoria, hallucinations, headaches Delayed exposure: neuropathy
Toluene	Paint or varnish solvent	Acute exposure: euphoria, headache, confusion, incoordination or ataxia Chronic exposure: euphoria, disinhibition, memory loss, ataxia, optic neuropathy, cranial neuropathies
Trichloroethylene	Manufacturing, dry cleaning	Cranial neuropathies (usually cranial nerve V), involvement of facial and ocular muscles, headaches, dizziness
Methanol (metabolizes to formaldehyde and formic acid)	Accidental poisoning	Acute exposure: headache, dizziness, nausea, visual blurring or loss of vision, encephalopathy, seizures, coma, metabolic acidosis; results in necrosis of optic nerves and putamen
Organophosphates	Insecticide exposure	Acetylcholinesterase inhibitors, resulting in cholinergic toxicity: nausea, hypersalivation; increased bronchial secretions; lacrimation, miosis, fasciculations; seizures, coma Intermediate toxicity (1–3 d after exposure): bulbar and limb weakness with fasciculations; hypertension, tachycardia Delayed toxicity (2–3 wk): polyneuropathy

Ciguatera Poisoning

Clinical syndromes resulting from ciguatera are associated with the ingestion of thermostable polyether toxins. These toxins often affect sodium channels along peripheral nerves causing altered sensory perceptions, including the classic paradoxical perception to temperature, making hot feel cold and vice versa. Ciguatera poisoning can also cause weakness, fatigue, and depressed muscle stretch reflexes. Early treatment with mannitol may significantly improve symptoms.

Snake Bites

Of the 7,000 to 8,000 venomous snake bites that occur annually in the United States, only 5 or 6 result in death. Most deaths are due to envenomation by eastern and western diamondback rattlesnakes. Victims (most commonly men) are most often bitten when attempting to handle or kill the snake. Snake toxins include neurotoxins, hemolytic toxins, and myotoxins. Symptoms depend on the toxicity of the venom, the size of the snake, and the location of the bite. One neurotoxin, α-bungarotoxin (from elapid snakes), irreversibly binds to the postsynaptic acetylcholine receptor, causing paralysis, respiratory failure, and death. The canebrake toxin present in some timber rattlesnake envenomations may cause diffuse clinical myokymia from toxin-induced peripheral nerve hyperexcitability. Supportive measures include immobilization of the envenomation site, inactivity, and hydration.

Chemical Agents and Bioterrorism

Many of the chemical and biological agents that may be used in warfare are directly neurotoxic. Neurologists need to be able to recognize the clinical syndromes produced by these agents (Tables 81.3 and 81.4).

Environmental Disorders

Overview

Although environmental injuries may affect anyone, accidental injuries are a leading cause of morbidity and death among children and young adults. Death is typically due to cardiopulmonary injury and metabolic involvement, and morbidity is often determined by injury to the brain or spinal cord. Management is generally supportive. This section provides an overview of the most common neurologic manifestations of acute environmental injuries.

Thermal Burns

Extensive burns are medically challenging and initially are marked by dramatic metabolic derangements and severe infections. Neurologic complications are common in patients with severe thermal burns but are often not recognized until the initial critical condition is stabilized (Table 81.5). An additional consideration in burn patients is the significant alteration of pharmacokinetics that results from protein loss, sepsis, and multiorgan dysfunction. Drug-binding proteins are decreased by as much as 50%, resulting in an increased free fraction of many drugs, including antiepileptic agents. Patients with epilepsy are predisposed to burn injuries resulting from loss of awareness or consciousness during a seizure. Antiepileptic regimens in these patients may require adjustment during the critical illness.

Table 81.3 • Neurologically Relevant Biological Agents

Agent	Mechanism of Spread	Syndrome	Treatment
Anthrax (*Bacillus anthracis*)	Ingestion, inhalation, or cutaneous exposure	Hemorrhagic meningitis with a characteristic chest radiograph showing mediastinitis without pneumonia or inflammation in the lung parenchyma	Ciprofloxacin, doxycycline
Plague (*Yersinia pestis*)	Infected flea bite or person-to-person transmission	Pneumonia Meningitis Inflamed, hemorrhagic, necrotic lymph nodes (buboes) that release bacteria, which cause sepsis, hypotension, multiorgan failure, and death	Streptomycin, gentamicin, doxycycline
Brucellosis (*Brucella*)	Contracted from infected cattle, goats, sheep, and pigs (easily aerosolized)	Nonspecific flulike illness, bone and joint infections, CNS involvement in 1% of cases (typically chronic meningitis or meningoencephalitis)	Doxycycline combined with an aminoglycoside
Viral encephalitides: EEE, VEE, and WEE (*Alphavirus*)	Insect bites or aerosolized	Common: fever, headache, and myalgias Uncommon: aseptic meningitis; high fever, vomiting, meningismus, drowsiness, and paresis; often, major autonomic disturbances (particularly in EEE) and seizures (particularly in VEE)	Supportive care

Abbreviations: CNS, central nervous system; EEE, eastern equine encephalitis; VEE, Venezuelan equine encephalitis; WEE, western equine encephalitis.

Smoke Inhalation and Carbon Monoxide

Smoke inhalation or exposure to gaseous products of combustion can cause serious injury or death from thermal damage, carbon monoxide and cyanide poisoning, and pulmonary irritation and edema leading to respiratory complications, including acute respiratory distress syndrome. The neurologic manifestations of smoke inhalation injuries result from carbon monoxide and cyanide poisoning.

Carbon monoxide produces personality changes, including irritability and anxiety, profound headache, and eventually diminished responsiveness and coma. Patients may be tachypneic and cyanotic. The classic cherry-red spot may be seen on ophthalmoscopic examination in addition to papilledema and splinter hemorrhages. Magnetic resonance imaging of patients with carbon monoxide poisoning may show symmetric changes in the globus pallidus, centrum semiovale, hippocampus, and cerebellum (Figure 81.1).

Treatment of acute carbon monoxide poisoning is 100% oxygen; hyperbaric oxygen is indicated for patients with a carboxyhemoglobin concentration of more than 30%, coma, signs of myocardial ischemia, or metabolic acidosis or if they are pregnant.

Electrical Burns

Deep conductive electrical burns can result in neurologic injury by multiple mechanisms (Table 81.6).

Table 81.4 • Neurologically Relevant Chemical Agents

Agent	Mechanism of Toxicity	Syndrome	Antidote
Organophosphate nerve agents (sarin, VX)	Rapid inhibition of tissue acetylcholinesterase produces uncontrolled firing at cholinergic synapses	Blurred vision (miosis), sweating, rhinorrhea, salivation, bronchoconstriction, abdominal cramping, nausea, vomiting, diarrhea Fasciculations lead to muscle twitching, flaccid paralysis, and diaphragmatic failure Loss of consciousness and seizures	Pralidoxime, atropine
Botulinum toxin	Interfers with the secretion of acetylcholine from a presynaptic cholinergic synapse	Mydriasis (classically unreactive pupils), cranial nerve palsies, descending flaccid paralysis, including muscles of respiration	Trivalent botulinum antitoxin, supportive care
Cyanide	Combines with iron in cytochrome a_3 to inhibit the enzyme, preventing intracellular oxygen use	Bright red retinal veins, ataxia, hyperventilation, generalized tonic-clonic seizures, coma with absent motor responses, apnea, delayed striatal degeneration with parkinsonism and dystonia	High-flow oxygen, sodium thiosulfate, amyl nitrite, hydroxocobalamin

Table 81.5 • Neurologic Complications of Severe Thermal Burns

Neurologic Syndrome	Mechanism
Burn encephalopathy: generalized tonic-clonic seizures, drowsiness, stupor	Poorly understood but likely multifactorial: reduced cerebral perfusion, cerebral edema, bacterial infection, hemorrhage, demyelination, infarction
Burn delirium: agitation, visual hallucinations, coarse tremor	Fever and other systemic factors Sensory deprivation resulting from bandages Withdrawal from prolonged use of benzodiazepines
Central nervous system infections: septic infarcts, meningitis, cerebral abscesses, epidural abscesses, spinal osteomyelitis	Hematogenous spread in sepsis syndrome
Central pontine myelinolysis or osmotic demyelination syndrome	Rapid correction of hyponatremia
Acute blindness	Bilateral occipital infarcts or anterior ischemic optic neuropathy
Peripheral neuropathies: mononeuritis multiplex, compression neuropathies, critical illness neuropathy	Protein denaturation and clumping within nerve arterioles Faulty position, incorrect splinting, tight dressings Direct result of thermal burns

Lightning Injury

Electrocution produces neurologic injury in much the same way as electrical burns (Table 81.5). An additional mechanism of injury includes direct parenchymal brain damage resulting from a surge of current traversing the brain.

Hypothermia

Accidental hypothermia commonly follows winter outdoor exposure or cold water immersion. Alcohol and homelessness are predisposing factors.

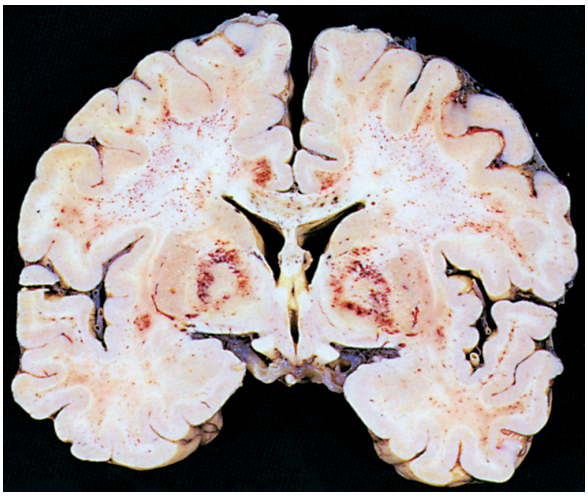

Figure 81.1 *Carbon Monoxide Toxicity.*
Macroscopic appearance of the brain in early carbon monoxide toxicity shows diffuse, scattered, and confluent foci of petechial hemorrhages throughout the white matter, with more prominent hemorrhagic foci in the globus pallidus bilaterally.
(Adapted from Okazaki H, Scheithauer BW. Atlas of neuropathology. New York [NY]: Gower Medical Publishing; c1988. p. 262. Used with permission of Mayo Foundation for Medical Education and Research.)

Profound hypothermia may produce coma and loss of brainstem reflexes, which are reversible with rewarming in the absence of primary brain injury. Brainstem reflexes become depressed, and ventricular arrhythmias occur at temperatures colder than 27°C (Figure 81.2); however, the cutoff is not absolute. Resuscitation efforts should be continued until the patient's core temperature is at least 32°C and preferably normal.

Hyperthermia

Neurologic complications resulting from heatstroke are preventable if early treatment is instituted. Exertion in a hot environment, heat waves in urban areas, and drugs that impair heat loss (eg, anticholinergic agents, phenothiazine derivatives, amphetamines, and monoamine oxidase inhibitors) all predispose to the development of heatstroke.

Table 81.6 • Mechanisms of Neurologic Injury in Electrical Burns

Neurologic Syndrome	Mechanism
Traumatic brain injury	Fall caused by sudden collapse
Anoxic-ischemic encephalopathy	Cardiac arrest resulting from exposure to high voltage
Seizures	Possibly related to traumatic brain injury
Spinal cord injury: ranges from transient paresthesias and weakness resolving within 24 h to permanent quadriplegia	Spinal cord necrosis from electrical heating Demyelination of corticospinal tracts, lateral columns, and fasciculi Thrombosis of arteries supplying the spinal cord
Peripheral nerve damage: polyneuropathy, mononeuropathy, and plexopathies	Indirect injury possibly due to muscle swelling causing nerve entrapment

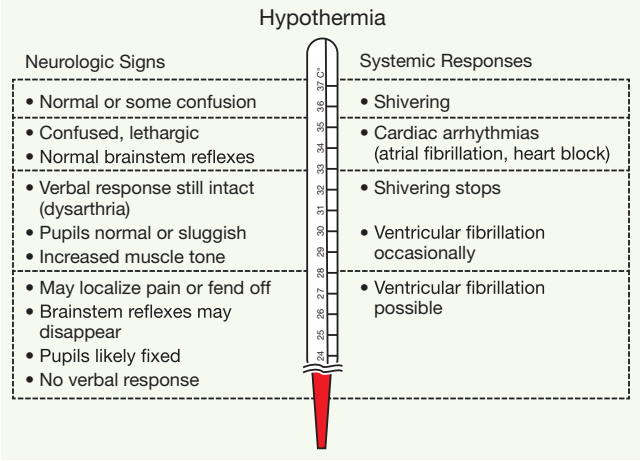

Figure 81.2 *Hypothermia.*
Neurologic signs of hypothermia and systemic responses. (Adapted from Wijdicks EFM. Neurologic complications of critical illness. 3rd ed. New York [NY]: Oxford University Press; c2009. Chapter 17, Neurologic complications of acute environmental injuries; p. 297–315. Used with permission of Mayo Foundation for Medical Education and Research.)

Early symptoms and signs of heatstroke include headache and an acute confusional state, which may include psychosis involving frightening complex hallucinations. Excessive sweating may lead to hyponatremia and painful muscle cramps. The skin is classically dry and hot. Progression to coma is rapid and accompanied by miosis, rigidity, spontaneous extensor posturing, and generalized tonic-clonic seizures. Focal neurologic signs should prompt a search for a primary brain or spinal cord injury that may have caused the hyperthermic state. In the absence of a primary neurologic cause of hyperthermia, neurologic outcome is variable. Death or neurologic morbidity is more common if patients have generalized tonic-clonic seizures at presentation, if they have severe hyperthermia (>42°C), or if they remain comatose after cooling.

Near Drowning

The neurologic evaluation of a patient resuscitated from a near drowning is complex because it may be confounded by hypothermia (from submersion in ice water), drug or alcohol intoxication, or severe electrolyte imbalances (typically hyponatremia and hypoglycemia).

Several neurologic complications are typically associated with near drowning (Table 81.7). When the confounding factors of a near drowning have been carefully considered and eliminated, neurologic prognostication may follow the principles of treatment of coma after cardiac arrest. See Chapter 5, "Anoxic-Ischemic Encephalopathy."

Table 81.7 • Neurologic Complications Associated With Near Drowning

Neurologic Complication	Mechanism
Anoxic-ischemic injury	Hypoxia from the near-drowning event Pulmonary infection from aspiration of contaminated water Acute respiratory distress syndrome
Seizures	Hyponatremia from swallowing large amounts of water
Quadriplegia	Burst fractures of the cervical spine produced during submersion
Coma	Anoxic ischemic injury Severe hypoglycemia

Management focuses on the respiratory complications. Monitoring of intracranial pressure has not led to increased survival or decreased neurologic morbidity.

High-Altitude Illness

Travelers to high altitudes, including hikers, skiers, and rescue workers, are at risk of high-altitude illness, a continuum of disease ranging from mild to moderate acute mountain sickness to the sometimes fatal high-altitude cerebral edema. Risk varies with individual susceptibility and increases with higher elevations and increasing rate of ascent.

The onset of general neurologic signs (ie, encephalopathy and ataxia) signifies the transition from acute mountain sickness to high-altitude cerebral edema (Table 81.8). This transition can occur unpredictably and may require as many as 3 days or as few as 12 hours. Vasogenic edema is a hallmark of high-altitude cerebral edema and is generally reversible except when the disease is prolonged and leads to decreased cerebral blood flow and tissue hypoxia.

Table 81.8 • Neurologic Manifestations of AMS and HACE

Syndrome	Symptoms and Signs
AMS	Headache, fatigue, light-headedness, anorexia, nausea and vomiting, disturbed sleep with frequent awakening, mild shortness of breath with exertion
HACE	Fatigue, ataxic gait, progressive decline of mental function and consciousness (irritability, confusion, and impaired mentation, drowsiness, stupor, and, finally, coma)

Abbreviations: AMS, acute mountain sickness; HACE, high-altitude cerebral edema.

Descent to a lower altitude is the definitive treatment. Supplemental oxygen, dexamethasone, and hyperbaric oxygen may facilitate descent.

Decompression Sickness

Decompression sickness occurs after a person returns from a compressed environment (eg, underground or deep sea) to atmospheric pressure. Oxygen and nitrogen bubbles are liberated on ascent after being loaded (dissolved) in the tissues on descent. These bubbles can block venous plexi or arterial vessels, rupture tissues, and activate clotting or inflammatory cascades.

Neurologic complications of decompression sickness may include damage to the spinal cord (typically upper lumbar or lower thoracic regions), memory loss, ataxia, visual disturbances, and changes in personality, speech, and affect. Treatment consists of hydration, 100% oxygen under hyperbaric pressure, and a mild Trendelenburg position.

- Extensive burns are medically challenging and initially are marked by dramatic metabolic derangements and severe infections.
- In burn patients, drug-binding proteins are decreased by as much as 50%, resulting in an increased free fraction of many drugs, including antiepileptic agents.
- Magnetic resonance imaging of patients with carbon monoxide poisoning may show symmetric changes in the globus pallidus, centrum semiovale, hippocampus, and cerebellum.
- Early symptoms and signs of heatstroke include headache and an acute confusional state, which may include psychosis involving frightening complex hallucinations. Excessive sweating may lead to hyponatremia and painful muscle cramps.
- When the confounding factors of a near drowning have been carefully considered and eliminated, neurologic prognostication may follow the principles of treatment of coma after cardiac arrest.
- Vasogenic edema is a hallmark of high-altitude cerebral edema and is generally reversible except when the disease is prolonged and leads to decreased cerebral blood flow and tissue hypoxia.
- Neurologic complications of decompression sickness may include damage to the spinal cord (typically upper lumbar or lower thoracic regions), memory loss, ataxia, visual disturbances, and changes in personality, speech, and affect.

82 Neurology of Pregnancy

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Introduction

Pregnancy is a time of many physiologic and systemic changes that may predispose women to new neurologic diseases or alter the course of preexisting disease. Management of neurologic diseases during pregnancy is complicated by the fact that risks and benefits to both mother and fetus must be weighed when selecting diagnostic tests and therapeutic options.

Preeclampsia and Eclampsia

Preeclampsia is defined as hypertension associated with organ damage occurring from the 20th week of pregnancy to 2 weeks post partum. Risk factors include multigestational pregnancies, first pregnancy, advanced maternal age (>35 years), and a history of preexisting diabetes mellitus, hypertension, or kidney disease. Preeclampsia may progress to eclampsia manifesting as encephalopathy and seizures and should be considered when new-onset seizures occur during pregnancy.

The prevailing theory for the pathophysiology of eclampsia is that a severe and abrupt increase in blood pressure results in cerebral autoregulatory dysfunction manifesting as vasoconstriction, cerebral edema, hypoperfusion, and ischemia. Eclampsia has occurred with disorders within the cerebral vasoconstrictive spectrum, including posterior reversible leukoencephalopathy and reversible cerebral vasoconstriction syndrome (also known as postpartum angiopathy when it occurs following parturition).

The typical presentation includes headaches, nausea, vomiting, abdominal pain, irritability, oliguria, visual disturbances, and blood pressure higher than 140/90 mm Hg. Some patients may be normotensive or have an abrupt increase in blood pressure above baseline. Seizures and encephalopathy may precede hypertension. Eclamptic encephalopathy presents subacutely and progresses over 1 to 2 days. On examination, patients may have edema of the hands and face, reduced visual acuity, visual field deficits, and hyperreflexia. Findings from a detailed ophthalmologic examination may include cotton wool spots, papilledema, and retinal hemorrhages.

Diagnostic studies include computed tomography (CT) of the head or magnetic resonance imaging (MRI) of the head (or both); however, these studies should be used cautiously in the first trimester. Limiting the dose of radiation to the fetus should always be a priority if CT is necessary. Although there is no evidence that MRI causes harm to mother or fetus, gadolinium is contraindicated because it has been shown to enter fetal circulation and the amniotic sac. Imaging characteristics of eclampsia are consistent with posterior reversible leukoencephalopathy. CT of the head may show relatively symmetric hypodensities in the parietal or occipital regions, which correspond to white matter hyperintensities on T2-weighted MRI that are consistent with vasogenic edema.

Treatment is focused on control of seizures and blood pressure. Intravenous magnesium sulfate is first-line therapy for eclamptic seizures, and seizures usually resolve within hours to days. Seizure control often improves blood pressure, and controlled reduction of blood pressure is important in avoiding placental hypoperfusion. General guidelines suggest decreasing mean arterial pressure by 20% to 25% within the first 2 hours. Labetalol and nicardipine are first-line agents in hypertensive emergencies. Nitroprusside should be avoided because it can increase intracranial pressure. The

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; RLS, restless legs syndrome

only cure for eclampsia or preeclampsia is delivery. It may take up to 6 weeks post partum for symptoms of organ damage to resolve. If treatment is initiated promptly, mortality is less than 5%. For recurrent encephalopathy after treatment, magnesium toxicity should be a consideration.

- Preeclampsia is defined as hypertension associated with organ damage occurring from the 20th week of pregnancy to 2 weeks post partum.
- Preeclampsia may progress to eclampsia often heralded by headaches, seizures, visual changes, and encephalopathy.
- Imaging features with eclampsia are similar to those with posterior reversible leukoencephalopathy syndrome.
- Treatment of preeclampsia and eclampsia involves treatment of blood pressure, treatment of seizures, and delivery of the baby.

Headache

Tension and migraine headaches are the most common causes of headaches in pregnancy. Although primary headaches are benign, a few studies have identified an association between preeclampsia and gestational hypertension. Migraines improve in up to two-thirds of women during pregnancy. Secondary headaches are less common but may cause significant morbidity and mortality in the peripartum period and should always be considered in the headache differential diagnosis, even if women have a history of primary headaches. A thorough history should establish the presence of any red flags since systemic changes during pregnancy predispose women to secondary causes of stroke, which may manifest as headaches (Table 82.1).

Table 82.1 • Secondary Causes of Headache in Pregnancy

Systemic Effect	Differential Diagnosis
Impaired vascular tone	Subarachnoid hemorrhage Preeclampsia or eclampsia Posterior reversible leukoencephalopathy Postpartum angiopathy CADASIL
Hypercoagulability	CVT Ischemic stroke TIA TTP-HUS
Increased ICP	Meningitis or encephalitis Pseudotumor cerebri

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CVT, cerebral venous thrombosis; ICP, intracranial pressure; TIA, transient ischemic attack; TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic uremic syndrome.

(See Chapter 50, "Introduction and Approach to Headache," for a more detailed overview of the approach to headache.)

For primary headache, initial conservative therapies include exercise, hydration, sleep, relaxation, physical therapy, and biofeedback. Abortive analgesics can be considered next.

Acetaminophen has the safest profile throughout pregnancy. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in the third trimester because of the risk of premature closure of the fetal ductus arteriosus. NSAIDs can be considered during lactation; however, aspirin can be excreted in breast milk, so frequent use is discouraged during lactation because of the risk of Reye syndrome. Although triptans (eg, sumatriptan) and antiemetics (eg, ondansetron and promethazine) are generally in US Food and Drug Administration category C, there is no established evidence to support adverse outcomes during pregnancy. Opiates can also be used at the lowest effective dose but should be avoided before delivery to decrease the risk of neonatal withdrawal and respiratory depression. Supplementation with magnesium is safe for migraine prevention during pregnancy (category B) and may reduce the risk of eclampsia. Herbal supplements such as coenzyme Q_{10}, riboflavin, and butterbur have unknown safety profiles and are category C. However, feverfew should be avoided because it may slow clotting and cause early contractions. In severe cases, preventive agents to consider include β-blockers, calcium channel blockers, selective serotonin reuptake inhibitors, tricyclic antidepressants, gabapentin, and pregabalin (all in category C). Topiramate (category D) and valproate (category X) should not be used.

- Tension and migraine headaches are the most common causes of headaches in pregnancy.
- Potentially serious causes of headaches during pregnancy or the postpartum state are noted in Table 82.1.

Epilepsy

Epilepsy is a chronic disease defined by recurrent unprovoked seizures. This is typically a manageable illness with a therapeutic goal of seizure freedom. Seizure frequency before conception is predictive of the level of control during pregnancy. Approximately 80% to 90% of women who achieved seizure freedom 1 year before pregnancy report no worsening during the peripartum period. Most pregnancies in this population have good outcomes. Eclampsia should be considered in patients with epilepsy who present with seizure during pregnancy.

Pregnancy in women with epilepsy brings a host of complex discussions surrounding management options and the risk and benefits they pose to mother and fetus.

Table 82.2 • Antiepileptic Drugs and Factors Relevant to Their Use in Pregnancy

Drug	FDA Category	Risk of MCM, %[a]	Teratogenesis
Levetiracetam	C	1–4	Possible minor skeletal deformities
Lamotrigine	C	1–3	Possible craniofacial defects
Carbamazepine	D	2–4	Craniofacial, cardiac, or urinary defects Spina bifida IUGR
Phenytoin	D	1–5	Fetal hydantoin syndrome Hemorrhage
Topiramate	D	3–7	Craniofacial defects
Phenobarbital	D	3–9	Cardiac defects
Valproate	X	6–13	Spina bifida Hypospadias IUGR Craniofacial and skeletal defects Cardiac anomalies Rare anencephaly

Abbreviations: FDA, US Food and Drug Administration; IUGR, intrauterine growth retardation; MCM, major congenital malformations.
[a] In first-trimester exposure.

Ideally, these discussions should occur before conception. Since most antiepileptic drugs are teratogenic, it is reasonable for patients planning for pregnancy with seizure freedom of 9 to 12 months to discontinue antiepileptic agents before conception. These medications should be tapered slowly to decrease the risk of status epilepticus. Women should be informed that major congenital malformations occur in 2% of pregnancies in the general population and that discontinuing medications does not guarantee the absence of a malformation. For those who need to continue their antiepileptic agents, the type, number, and dosage of these agents may need to be changed.

Levetiracetam, lamotrigine, carbamazepine, and phenytoin have the safest profiles, with reported congenital malformation rates of approximately 2.5% (Table 82.2). Because there is a dose-dependent risk of major congenital malformation with these agents, the lowest effective dose should be used. Phenobarbital, topiramate, and valproate should be avoided, particularly during the first trimester. If valproate must be used for refractory seizures, a dosage less than 700 mg daily should be used to minimize the risk of congenital malformations. Polypharmacy, particularly with valproate, should be avoided because of the high association of birth defects during the first trimester and poor cognitive outcomes with use thereafter. Dosages may need to be adjusted owing to changes in pharmacokinetics (absorption and distribution) and increased clearance (increased hepatic metabolism through cytochrome P450, glucuronidation and renal clearance) during pregnancy. Total and free levels of antiepileptic drugs should be monitored monthly.

Supplementation with folic acid before conception and during pregnancy has been shown to reduce the risk of lower verbal IQ, miscarriage, and neural tube defects. The recommended dosage for patients with epilepsy is 10-fold higher (4 mg daily) than for the general population (0.4 mg daily). Oral vitamin K supplementation (10–20 mg daily) should also be administered to patients receiving enzyme-inducing antiepileptic drugs (ie, phenytoin, carbamazepine, phenobarbital, or primidone) to reduce the risk of neonatal hemorrhagic complications.

- Approximately 80%–90% of women who achieved seizure freedom 1 year before pregnancy report no worsening during the peripartum period.
- Levetiracetam, lamotrigine, carbamazepine, and phenytoin have the safest profiles, with reported congenital malformation rates of approximately 2.5%.
- Supplementation with folic acid before conception and during pregnancy has been shown to reduce the risk of lower verbal IQ, miscarriage, and neural tube defects.

Peripheral Neuropathy

Approximately 1% of pregnancies are complicated by symptoms consistent with a length-dependent peripheral neuropathy. Risk factors include nulliparity and a prolonged second stage of labor. The symptoms usually occur during the third trimester and delivery, and they typically improve, lasting an average of 2 months.

Carpal Tunnel Syndrome

Carpal tunnel syndrome is the most common neuropathy during pregnancy. Carpal tunnel syndrome is thought to be secondary to compression of the median nerve at the carpal tunnel from fluid retention and edema in the tissues surrounding the nerve. It usually occurs during the third trimester with sensory dysfunction that is more pronounced than motor dysfunction. The diagnosis is usually established on clinical grounds alone.

Conservative management such as wrist splints at night, a low-salt diet, and analgesics are first-line treatments. If symptoms are refractory to conservative measures or are severe and persistent after delivery, surgery can be considered. One study found that 50% of patients with pregnancy-induced carpal tunnel syndrome improved within 1 year and up to 70% improved by 3 years.

Table 82.3 • Common Compressive Neuropathies in the Pregnant Patient

Nerve	Mechanism	Sensory Distribution	Motor Deficit
Lumbosacral plexus	Fetal head descent Forceps	Diffuse lower limb	Foot drop Hip adductor and quadriceps weakness
Common peroneal nerve	Direct compression from stirrup or bedrails	Mainly dorsal side of foot	Foot drop
Femoral nerve	Prolonged lithotomy position Retractors	Anteromedial side of thigh	Quadriceps weakness
Lateral femoral cutaneous nerve	Uterus compressing nerve at inguinal ligament Retractors	Anterolateral side of thigh	None
Obturator nerve	Prolonged lithotomy position Pudendal block	Medial side of thigh	Hip adductor weakness

Bell Palsy

Bell palsy (or idiopathic facial neuropathy) is 3 to 4 times more frequent in pregnant women than in nonpregnant women. Typical onset is between the third trimester and early postpartum period. Bell palsy in pregnancy is likely secondary to reactivation of latent viruses in the geniculate ganglion owing to relative maternal immunosuppression. Studies have identified associations with chronic hypertension, diabetes mellitus, preeclampsia, and gestational hypertension. Generally, outcomes are excellent with nearly complete or complete resolution. However, the rate of recovery from complete facial paralysis is less for pregnant women than for the general population.

Initial treatment is administration of corticosteroids within the first week of symptom onset to maximize facial nerve recovery. Corticosteroids should be used with caution in the first trimester. The use of antivirals is controversial because there is no clear evidence that they provide benefit. Thus, they are generally not instituted in pregnant patients.

Maternal Obstetric Compression Neuropathies

Compression neuropathies are common during the third trimester and during delivery (Table 82.3). Epidural anesthesia during delivery is a major risk factor because sensory loss impairs patient-prompted repositioning. Maternal obstetric neuropathies are self-limited and usually resolve by 6 weeks postpartum. If the presentation is atypical or prolonged, an electromyogram should be performed for localization and prognostication. Spinal cord or nerve root injury is very rare (<0.1%).

- Carpal tunnel syndrome is the most common neuropathy during pregnancy.

Movement Disorders

Restless Legs Syndrome

Restless legs syndrome (RLS) is a movement disorder and a sleep disorder that is characterized by an unrelenting urge to move the lower extremities and, sometimes, by uncomfortable sensations. It is exacerbated during periods of rest and is relieved by activity. RLS may be a primary entity or secondary to uremia, diabetes mellitus, radiculoneuropathies, iron deficiencies, and pregnancy. The prevalence of RLS in the general population is approximately 5% to 10%. However, its prevalence in pregnancy is upwards of 10% to 26%, with peak onset during the third trimester. This increased prevalence is thought to be caused by the high demands for iron and folate and by high estradiol and progesterone levels. Gestational diabetes and polyneuropathies have all been postulated to contribute to the higher incidence during pregnancy.

Among women with preexisting RLS, two-thirds report that RLS worsens in pregnancy, and one-third report no change or improvement. After delivery, the severity of symptoms reverts to previous levels. Patients with new-onset RLS during pregnancy usually improve after delivery. However, 1 study reported an associated 4-fold increase in chronic RLS developing in the future.

Screening laboratory tests should include total iron-binding capacity and serum levels of hemoglobin and ferritin. Ferritin is considered the most accurate reflection of iron stores. Initial treatment includes abstinence from caffeine and other medications that may exacerbate symptoms (ie, antidepressants, neuroleptics, antiemetics, and sedating antihistamines). Iron supplementation can be initiated if ferritin levels are less than 50 mcg/L. For severe symptoms, the clinician may consider opiates, dopaminergic agents, and antiepileptic agents, such as carbamazepine, gabapentin, and benzodiazepines. The lowest effective doses should be instituted for the shortest possible period so as to minimize maternal augmentation and fetal adverse

effects. The safety profile of dopaminergic agents in pregnancy is unknown. In animal studies with dopamine agonists, the animals have had intrauterine growth retardation, digit malformation, and fetal demise. In 1 small case series of 11 pregnant patients who used pramipexole and ropinirole, there were no fetal malformations. Some evidence also exists for the safety of levodopa in pregnant patients with Parkinson disease.

Chorea Gravidarum

Onset of chorea during pregnancy is termed chorea gravidarum. Chorea gravidarum occurs in 1 per 2,000 to 3,000 pregnancies, with onset in the first trimester. It originally described pregnant patients with acute rheumatic fever, rheumatic heart disease, or a history of Sydenham chorea. However, with the advent of antibiotics, the incidence of rheumatic fever has decreased. Other causes of chorea gravidarum to consider during pregnancy include drugs, systemic lupus, antiphospholipid syndrome, vascular insults causing focal lesions, thyrotoxicosis, Wilson disease, and Huntington disease, all of which require different therapies and carry different prognoses.

Chorea gravidarum spontaneously resolves before delivery in one-third of patients, with the remainder resolving after delivery. Treatment is centered on the underlying cause. In severe cases that result in rhabdomyolysis and hyperthermia, treatment should be focused on managing these complications. Dopamine antagonists and depleting agents are useful for symptomatic management of chorea gravidarum. Neuroleptics such as haloperidol, chlorpromazine, and pimozide are in category C and are used in the second and third trimester in low dosages for symptomatic management. Dopamine-depleting agents, such as tetrabenazine used for Huntington disease, can also be considered. However, these agents should be avoided during fetal organogenesis, and use in the first trimester is not advocated.

- The prevalence of restless legs syndrome during pregnancy is 10%–26%, compared with 5%–10% in the general population.
- In pregnant women with restless legs syndrome, the hemoglobin, ferritin, and total iron-binding capacity should be tested.
- Chorea gravidarum occurs in 1 per 2,000–3,000 pregnancies, with onset in the first trimester.

Autoimmune and Inflammatory Diseases

Multiple Sclerosis

Although women of childbearing age may present with multiple sclerosis, presentation during pregnancy is unusual. Many studies have shown a reduction in multiple sclerosis relapse rates during the third trimester when compared with before. However, the risk of relapse is increased during the first 3 weeks post partum. Although no multiple sclerosis therapies have established teratogenicity, the risk of acute and long-term therapies must be considered. Corticosteroids are thought to be safe after the first trimester and may be used for relapses during pregnancy. Among the disease-modifying agents, glatiramer acetate has the safest profile and is in category B. Interferon-β is in category C; conflicting data link it to miscarriages and abortions. Fingolimod, mitoxantrone, and teriflunomide have been associated with fetal congenital malformations in animal studies.

Myasthenia Gravis

Women of childbearing age commonly present with myasthenia gravis. Pregnancy may unmask myasthenic symptoms, but overall its effect on preexisting myasthenia gravis is variable. About 20% of patients with myasthenia gravis in pregnancy have a respiratory crisis and should be monitored carefully throughout pregnancy. Affected women may fatigue during active labor and require delivery-assistance devices such as vacuums or forceps. Transient neonatal myasthenia gravis may develop in up to 20% of infants born to mothers with myasthenia gravis. This is a self-limited disorder due to maternal antibodies crossing the placenta and circulating in the neonate's bloodstream; it may last up to 3 to 6 weeks. Perinatal mortality of infants born to mothers with myasthenia gravis is 5 times higher than among infants in

Table 82.4 • Immunosuppressive Medications and Their Associated Teratogenicity in Pregnancy

Medication	FDA Pregnancy Category	Neonatal Risks and Teratogenicity
Cyclosporine	C	Abortions Low birth weight Premature births
Rituximab	C	B-cell lymphocytopenia lasting <6 mo in infants
Azathioprine	D	Major multiorgan system congenital malformations
Mycophenolate mofetil	D	Abortion in the first trimester Major multiorgan system congenital malformations

Abbreviation: FDA, US Food and Drug Administration.

the general population. A high-risk obstetrician and a neurologist should be involved in the care of these higher-risk infants.

Magnesium sulfate should be avoided in myasthenia gravis patients with preeclampsia or eclampsia. Phenytoin may be an appropriate alternative for seizures. If a cesarean delivery is indicated, regional anesthesia should be used. If general anesthesia is necessary, curariform paralytics should be avoided.

Pyridostigmine for symptom control can be considered for pregnant patients who have moderate symptoms. Considered safe in low doses, pyridostigmine may require higher doses during pregnancy because of altered metabolism. Overuse may lead to uterine contractions and preterm labor. Corticosteroids may also be used during pregnancy; however, if used in the first trimester, they increase the risk of gestational diabetes, preeclampsia, and fetal oral or cleft malformations. For acute exacerbations, intravenous immunoglobulin and plasma exchange therapies are used, but they carry a theoretical risk of abortion and should be considered in severe cases when the benefit outweighs the risk. Diligent monitoring is necessary for hyperviscosity and volume overload with intravenous immunoglobulin and for hypotension with plasma exchange. The use of immunosuppression during pregnancy is discouraged (Table 82.4).

- About 20% of patients with myasthenia gravis in pregnancy have a respiratory crisis and should be monitored carefully throughout pregnancy.
- Transient neonatal myasthenia gravis may develop in up to 20% of infants born to mothers with myasthenia gravis.
- Magnesium sulfate should be avoided in myasthenia gravis patients with preeclampsia or eclampsia.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

XIII.1. What is the only evidence-based therapeutic intervention shown to be neuroprotective in patients with cardiac arrest due to ventricular fibrillation or ventricular tachycardia?
a. Mechanical ventilation
b. Hypothermia
c. Corticosteroids
d. Mannitol
e. Hyperbaric oxygen

XIII.2. Which of the following describes an apneustic pattern of breathing?
a. Inspiration followed by a prolonged inspiratory pause followed by expiration
b. Breathing characterized by irregular rate and tidal volume
c. Rapid, shallow breathing
d. Breathing characterized by absence of rib cage expansion with inspiration
e. Lack of breathing with unconsciousness or sleep

XIII.3. Which of the following is a therapeutic option used in hepatic encephalopathy?
a. Lactulose
b. Kidney transplant
c. Thiamine
d. Diazepam
e. High-protein diet

XIII.4. Which of the following chemical or biological agents with terrorism potential causes a hemorrhagic meningitis?
a. *Bacillus anthracis* (anthrax)
b. *Yersinia pestis* (plague)
c. *Brucella* (brucellosis)
d. Cyanide
e. Eastern equine encephalitis virus

XIII.5. Paradoxical sensory disturbance (making hot feel cold and vice versa) is a feature of poisoning related to which of the following?
a. α-Bungarotoxin
b. Ciguatera
c. Organophosphates
d. Cyanide
e. Botulinum toxin

XIII.6. What is the definitive treatment of high-altitude cerebral edema?
a. Dexamethasone
b. Diuretics
c. Oxygen
d. Mechanical ventilation
e. Descent to lower altitude

XIII.7. Recognized causes of copper deficiency include which of the following?
a. Irritable bowel syndrome
b. Zinc toxicity
c. Cardiac surgery
d. Chronic nutrition through an enteral feeding tube
e. Pernicious anemia

XIII.8. A myeloneuropathy can result from which of the following?
a. Vitamin B_{12} toxicity
b. Nitrous oxide deficiency
c. Copper toxicity
d. Vitamin E deficiency
e. Vitamin D deficiency

XIII.9. Thiamine deficiency can result in which of the following?
a. Peripheral neuropathy
b. Myopathy
c. Progressive bulbar palsy
d. Dyspraxia
e. Alexia

XIII.10. What is the most common movement disorder associated with pregnancy?
a. Chorea gravidarum
b. Essential tremor
c. Myoclonus
d. Restless legs syndrome
e. Tics

XIII.11. Folic acid supplementation to prevent neural tube defects is most important during which weeks of pregnancy (calculated from ovulation)?
a. Weeks 1 to 6
b. Weeks 6 to 12
c. Weeks 13 to 20
d. Weeks 21 to 27
e. Weeks 33 to 36

XIII.12. Which of the following statements is true about headaches and pregnancy?
a. Severe migraines during pregnancy increase obstetric complications
b. Triptans have been proved to be safe during pregnancy
c. Headaches during pregnancy may be due to preeclampsia or eclampsia
d. Migraine headaches generally worsen in pregnancy
e. Magnetic resonance imaging and magnetic resonance angiography should be performed if pregnant women have worsening migraines

XIII.13. Which of the following is secreted by the posterior pituitary?
a. Thyrotropin
b. Oxytocin
c. Luteinizing hormone
d. Corticotropin
e. Growth hormone

XIII.14. Pituitary apoplexy is commonly associated with which of the following?
a. Anosmia
b. Hypertension
c. Coma
d. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
e. Hyperthyroidism

XIII.15. Subacute onset of a painful, asymmetric, predominantly proximal lower limb weakness in a diabetic patient is most suggestive of which of the following?
a. Radiculoplexus neuropathy
b. Multiple mononeuropathies
c. Spinal cord disease
d. Myopathy
e. Cerebrovascular disease

XIII.16. An anion gap acidosis can result from which of the following?
a. Neuromuscular ventilatory failure
b. Ethylene glycol poisoning
c. Acetaminophen toxicity
d. Chronic obstructive pulmonary disease
e. Diarrhea

XIII.17. Respiratory alkalosis can result from which of the following?
a. Insufficient mechanical ventilation
b. Sepsis
c. Narcotic overdose
d. Central sleep apnea
e. Methanol poisoning

XIII.18. SIADH is associated with which of the following?
a. Hypovolemic hypocalcemia
b. Euvolemic hyponatremia
c. Hypervolemic hyperchloremia
d. Euvolemic hyperkalemia
e. Hypervolemic hypokalemia

Answers

XIII.1. Answer b.
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XIII.3. Answer a.
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XIII.12. Answer c.
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XIII.13. Answer b.
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XIII.17. Answer b.
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Section
XIV

Sleep Disorders

Pablo R. Castillo, MD, *editor*

83 Polysomnography and Other Sleep Testing

PABLO R. CASTILLO, MD; MICHAEL F. PRESTI, MD, PHD

Introduction

There are multiple methods for evaluating patients' sleep complaints: clinical screening instruments, sleep diaries, polysomnography (PSG) with multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT), and actigraphy. This chapter reviews tools used to assess patients with sleep complaints.

Sleep-Related Questionnaires

Screening tools (such as questionnaires) are used to stratify patients on the basis of their clinical characteristics and their risk factors. Patients at high risk may need urgent PSG or further treatment.

The Berlin Apnea Questionnaire and Epworth Sleepiness Scale are 2 widely used prescreening tools for persons who may have sleep apnea and other sleep disorders. The Berlin Apnea Questionnaire identifies people at risk of obstructive sleep apnea (OSA). A positive response to the questionnaire is also associated with resistant hypertension. The questions are targeted toward the 3 key symptoms of snoring behavior, daytime sleepiness, and the presence of obesity or hypertension.

The STOP (snoring, tiredness, observed apnea, and high blood pressure) Questionnaire and the STOP-Bang (STOP plus body mass index, age, neck circumference, and gender) Questionnaire have been validated on presurgical patients. The existence of moderate or severe OSA can be predicted with the STOP-Bang and the Berlin Apnea questionnaires; they have the highest sensitivity and specificity, respectively.

The Epworth Sleepiness Scale is a subjective measure of sleepiness; it assesses the level of daytime sleepiness by having patients rate the likelihood of dozing during 8 different daytime situations. The scale ranges from 0 to 24. A score more than 10 indicates excessive daytime sleepiness.

- Questionnaires and other screening methods are used to stratify patients according to clinical characteristics and risk factors.
- The STOP-Bang questionnaire is a useful screening tool for sleep apnea.

Polysomnography

PSG is defined as the attended recording of multiple physiologic variables during sleep. PSG is currently the clinical standard for diagnostic investigation of sleep apnea. PSG is also time-consuming and not readily available in most hospitals.

The standard PSG recording consists of a combination of alternating-current and direct-current amplifiers. The alternating-current (differential) amplifiers are used to record signals of high frequency such as the electroencephalogram, electrocardiogram, and electro-oculogram. The alternating-current amplifiers have both a high-frequency and a low-frequency filter. The direct-current amplifiers record low-frequency signals such as oxyhemoglobin saturation and body temperature. The direct-current amplifiers do not have a low-frequency filter. PSG is usually performed in a sleep laboratory with multiple channels for recording data (Box 83.1; Figure 83.1).

Abbreviations: Bang, body mass index, age, neck circumference, gender [questionnaire]; MSLT, multiple sleep latency test; MWT, maintenance of wakefulness test; OSA, obstructive sleep apnea; PSG, polysomnography; REM, rapid eye movement; SOREMs, sleep-onset rapid-eye-movement periods; STOP, snoring, tiredness, observed apnea, high blood pressure [questionnaire]

Box 83.1 • Data Recorded During Polysomnography

- Electroencephalogram
- Electro-oculogram (measures the movement of the corneo-retinal difference within the eye)
- Surface electromyogram on chin and legs (records the summation of many motor potentials)
- Electrocardiogram and body-position sensors
- Nasal and oral airflow
- Oxygen saturation
- Video and audio recording of behavior and snoring
- Optional trial of continuous positive airway pressure or other interventions

Portable monitoring refers to various devices with fewer physiologic parameters than standard PSG. Portable monitoring is used to diagnose OSA in the ambulatory setting, usually unattended in the patient's home. Portable monitoring has the advantages of improved access, decreased cost, and expedited diagnosis and management of patients with a high pretest probability for OSA. Further studies are needed, but the use of portable monitoring will likely increase in the near future.

- Polysomnogram is the standard tool used to evaluate for OSA.

Multiple Sleep Latency Test

Purpose

The MSLT is used to objectively determine sleeping ability, which is a function of the sleep-promoting areas of the brain.

When excessive daytime somnolence is a prominent symptom, patients should have a baseline daytime sleep

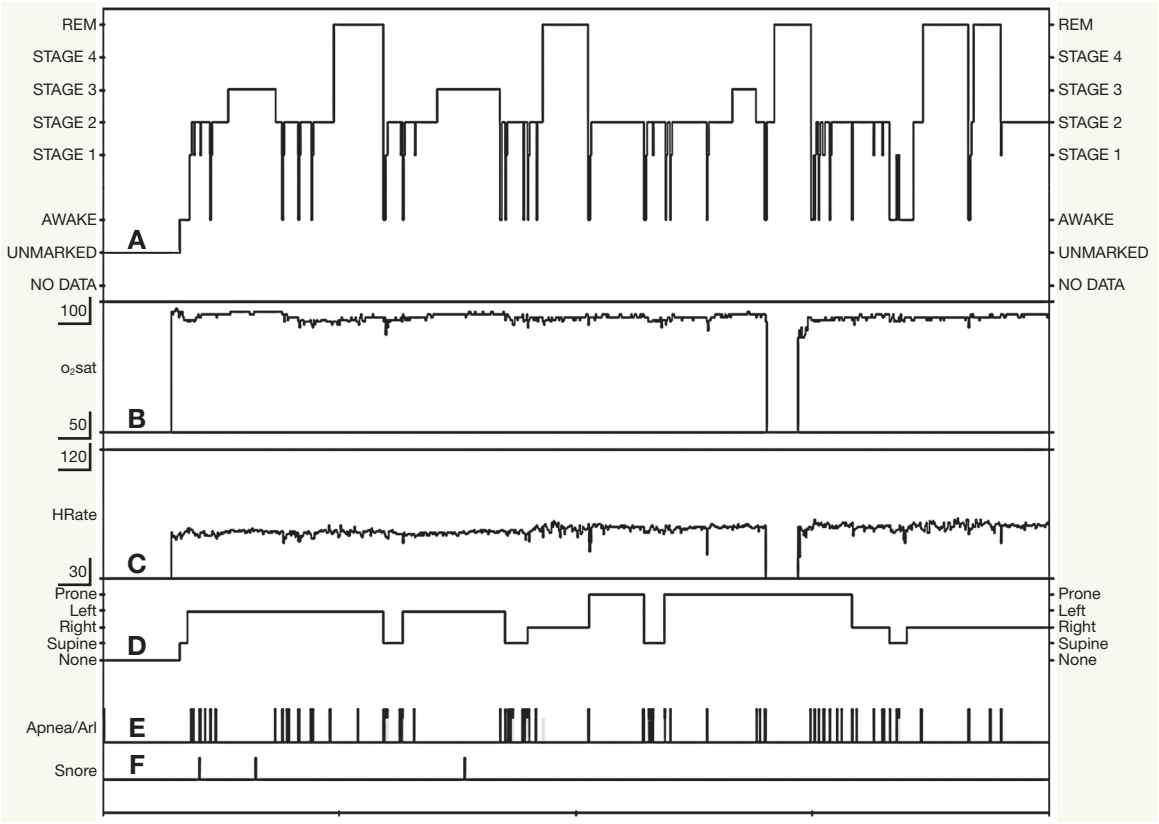

Figure 83.1 *Normal Hypnogram.*
A, Distribution of individual sleep stages throughout the night. B, Oxygen saturation (O2sat). C, Heart rate (HRate). D, Body position. E, Number of sleep-disordered breathing events and arousals (Arl). F, Snoring. Note the transient signal dropout of oxygen saturation and heart rate due to displacement of the recording probe in the second half of the tracing (third rapid-eye-movement [REM] sleep period).
(Adapted from Young TJ, Tippmann-Peikert M. Neurology of sleep disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 719–52. Used with permission of Mayo Foundation for Medical Education and Research.)

study to determine whether they have OSA or poor sleep quality due to other conditions. If, during overnight PSG, no OSA is found and sleep of adequate quality and duration is recorded, daytime recordings (ie, MSLT) can be conducted.

The Test

The MSLT requires special preparation and a complete review of ongoing pharmacologic therapies. Use of medications such as rapid-eye-movement sleep (REM)–suppressing agents (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors) needs to be discontinued at least 2 weeks before MSLT; in the case of a long-acting agent (eg, fluoxetine), 4 weeks may be needed. Urine drug screening can also be performed the morning of the MSLT. Ideally, the MSLT should be conducted on the patient's usual sleep-wake schedule or circadian time, and patients should be advised to obtain adequate sleep for 1 to 2 weeks before MSLT.

The MSLT is valid only after documented adequate sleep time (ie, no less than 6 hours of sleep) the night before by PSG. Sleep time lost during the week before MSLT can also alter the results. For this purpose, 7 to 14 days of wrist actigraphy or sleep logs are used.

During MSLT, the patient relaxes in a dark room and is asked to sleep. If the patient falls asleep, the patient is allowed to sleep a maximum of 15 minutes. Five sequential naps are performed. The patient has pathologic sleepiness if the mean sleep onset, or latency, of all naps to any stage of sleep is less than 5 minutes. A mean sleep latency from 5 to 10 minutes is considered a diagnostic gray zone, and a sleep latency of more than 10 minutes is normal.

Sleep-onset REM periods (SOREMs) are considered abnormal, but there is a prevalence of 4% to 9% in the general population. SOREMs can occur in other states of prior REM deprivation, including insufficient sleep, sleep apnea, withdrawal from REM-suppressing medications (eg, selective serotonin reuptake inhibitors, tricyclic antidepressants), major depression, and delayed sleep-phase syndrome. During MSLT, 39% of patients with Parkinson disease may have SOREM periods. The presence of more than 2 or 3 SOREMs during MSLT has a specificity of 99% for the presence of narcolepsy.

- Multiple sleep latency test (MSLT) is used to determine sleeping ability, or the function of the sleep-promoting portions of the brain.
- If no OSA is found on overnight PSG, daytime MSLT can be conducted.
- Sleep-onset rapid-eye-movement periods (SOREMs) are considered abnormal although they are present in <10% of the general population.
- More than 2 to 3 SOREMS during MSLT is highly specific for narcolepsy.

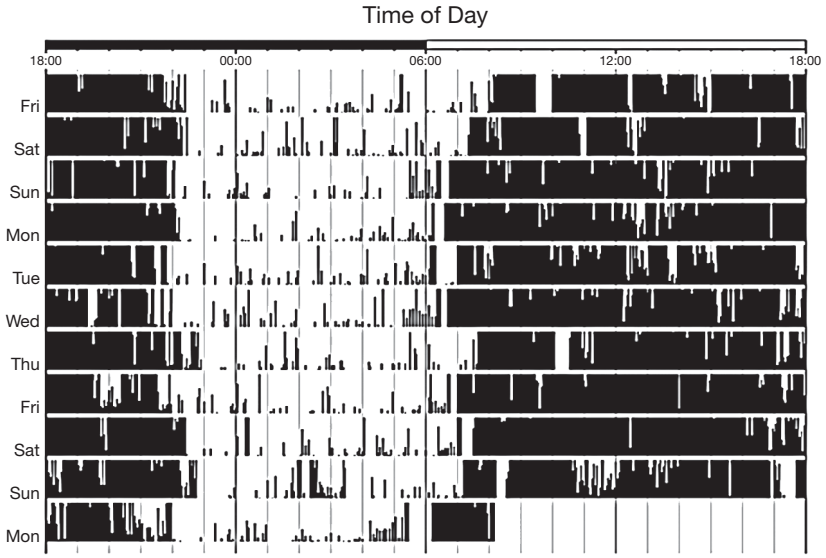

Figure 83.2 *Actigraphy Recording.*
Dark areas indicate movements or increased activity; white areas indicate presumed sleep or quiescence. Normal circadian rhythm with quite regular bed times and somewhat variable wake times. Occasional decrease in activity levels may represent nap periods.
(Adapted from Young TJ, Tippmann-Peikert M. Neurology of sleep disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 719–52. Used with permission of Mayo Foundation for Medical Education and Research.)

Maintenance of Wakefulness Test

Purpose

The MWT measures a subject's volitional ability to stay awake in a calm, nonstimulating condition. This test may be considered the stress test of the arousal system.

The MWT is used to evaluate response to therapy for patients with hypersomnia who need to demonstrate their ability to stay awake for public or personal safety and employment purposes such as airline pilots or commercial drivers.

The Test

Besides different instructions ("try to stay awake") and body position, the recordings for MWT are similar to those of the MSLT and include electroencephalogram, electrooculogram, and electromyogram.

The MWT consists of 4 trials to assess the patient's ability to stay awake in a quiet, dark room for 20 to 40 minutes (40 minutes preferred). Mean sleep latency less than 8.0 minutes on the 40-minute MWT is considered abnormal; values longer than this on MWTs of less than 40 minutes are of uncertain significance.

- The maintenance of wakefulness test (MWT) is used to demonstrate response to therapy (ability to stay awake) for hypersomnia patients.

Actigraphy

Purpose

Actigraphy can be used for the assessment of periodic limb movements, circadian rhythm disorders, and total sleep duration. Other applications in sleep medicine remain controversial.

The Test

Activity-based monitoring (ie, actigraphy) utilizes a motion sensor known as an accelerometer to monitor the occurrence and degree of motion. The actigraph records activity level resulting from movements; paucity of movements results in absence of signal and is assumed to represent sleep periods (Figure 83.2). The recording device can be placed on an upper or lower limb. Extended monitoring (5 days or longer) is necessary to increase the reliability of the test.

- Actigraphy is used to assess periodic limb movements, circadian rhythm disorders, and sleep duration.

84 Neuropharmacology of Sleep

PABLO R. CASTILLO, MD

Introduction

Sleep disorders often respond to both pharmacologic agents and nonpharmacologic therapies. This chapter reviews the pharmacology of and indications for specific sleep agents. The mechanisms of sleep agents are provided in Figure 84.1.

Sleep-Promoting Agents

Overview

Most of the agents approved by the US Food and Drug Administration for insomnia, with the exception of antidepressants and ramelteon, act by modulating the function of the γ-aminobutyric acid (GABA)-A receptor complex. The ventrolateral preoptic nucleus (VLPO) plays a critical role in sleep initiation and maintenance. GABA is the primary inhibitory neurotransmitter of the VLPO. Medications used for sleep promotion include benzodiazepines, chronobiotics, sedating antidepressants, histamine blockers, and γ-hydroxybutyric acid (GHB).

Benzodiazepines

Traditional GABA agonists act downstream on VLPO targets, namely, the arousal system. The benzodiazepines bind to all of the α-unit isoforms of the GABA-A receptor complex, an action that may explain why they have a wide range of pharmacologic effects in addition to sleep induction.

The newer nonbenzodiazepine GABA receptor agonists (including zolpidem, zaleplon, indiplon, and eszopiclone) have relatively greater selectivity for the α-1 subunit, which may correspond with less nonsleep adverse effects. Zolpidem-induced sleepwalking is well documented, and this drug should be avoided in patients with a personal or family history of sleepwalking.

Chronobiotics

Ramelteon acts on melatonin receptor 1 and receptor 2 in the suprachiasmatic nucleus to dampen alerting signals in the brain and thereby help foster sleep.

Melatonin receptor agonists improve quality of sleep, but response may develop over several weeks.

Sedating Antidepressants

Several groups of antidepressants are available for the treatment of insomnia and reduction of cataplexy episodes in patients with narcolepsy. These include first-generation antidepressants (such as tricyclic antidepressants) and second-generation antidepressants (such as selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, serotonin receptor antagonists, and mirtazapine). Many of the antidepressants can potentially worsen rapid-eye-movement sleep behavior disorder and restless legs syndrome.

Commonly used sedating antidepressants include amitryptiline, nortryptiline, mirtazapine, trazodone, and doxepin (Table 84.1).

Histamine Blockers

The inhibition of postsynaptic excitatory histamine$_1$ receptors leads to the sleepiness effects of over-the-counter antihistamines such as diphenhydramine (Benadryl), doxylamine (NyQuil), dimenhydrinate (Dramamine), and brompheniramine (Dimetapp). Antihistamines are also found in combination with pain relievers, such as acetaminophen, to help treat insomnia associated with pain.

Abbreviations: GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyric acid; VLPO, ventrolateral preoptic nucleus

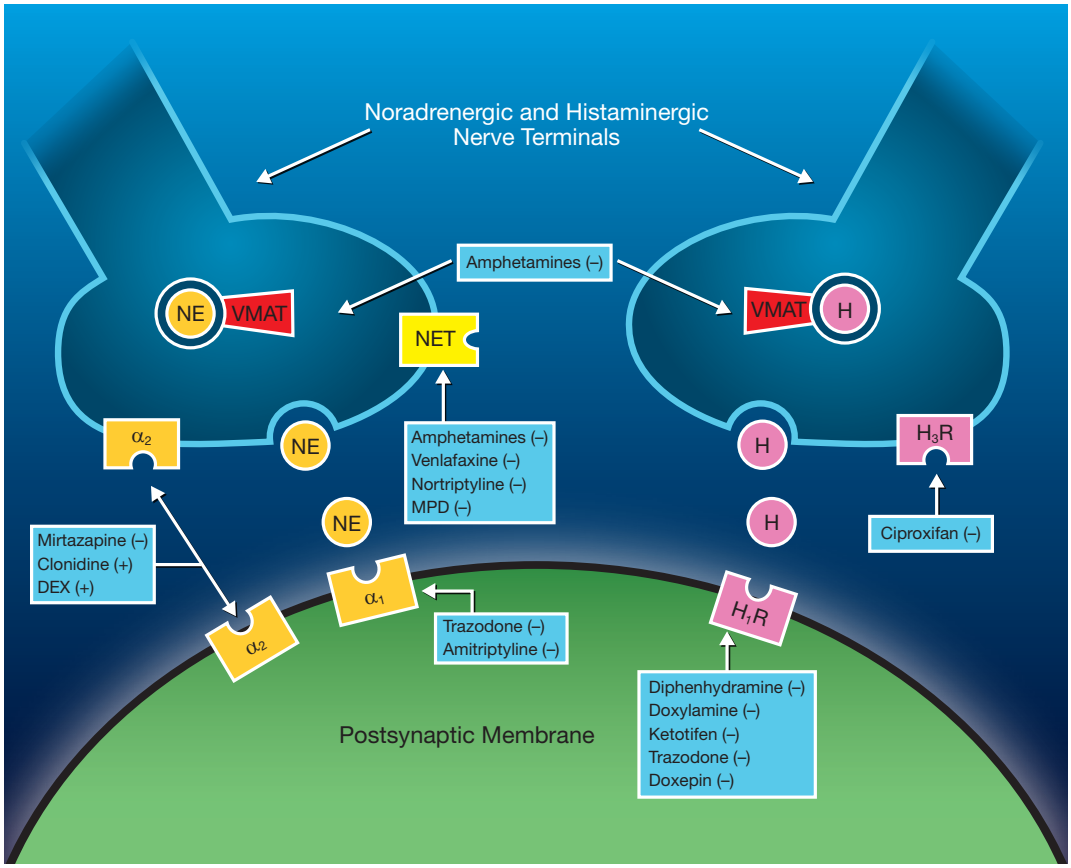

Figure 84.1 *Pharmacology of Sleep Agents.*
α_1 indicates α_1-adrenergic receptors; α_2, α_2-adrenergic receptors; DEX, dexmedetomidine; H, histamine; H_1R, histamine$_1$ receptor; H_3R, histamine$_3$ receptor; MPD, methylphenidate; NE, norepinephrine; NET, norepinephrine transporter; VMAT, vesicular monoamine transporter; –, antagonist or inhibitor; +, agonist.

Diphenhydramine is the most common ingredient in over-the-counter sleep aids. Its limited benefits for sleep should be balanced against its potential anticholinergic adverse effects and rapid onset of tolerance.Diphenhydramine can also exacerbate restless legs syndrome.

The histamine$_3$ autoreceptor is a key presynaptic inhibitory regulator of histamine release and other excitatory amines associated with wakefulness and cognitive performance. Histamine$_3$ blockage would increase the release of histamine and acetylcholine and other

Table 84.1 • Commonly Used Sedating Antidepressants

Medication	Mechanism of Action	Adverse Effects
Amitryptiline Nortryptiline	Interferes with transfer, release, and storage of catecholamines by blockade of serotonin transporter and norepinephrine transporter	Heart block Dry mouth Constipation
Mirtazapine	Blocks central presynaptic α_2 autoreceptors and heteroreceptors and increases serotonin transmission Antagonist of histamine receptor	Weight gain Worsening of REM sleep disorder Orthostatic hypotension
Trazodone	Dose-dependent multifunctional antagonist actions at the serotonin, histamine$_1$, and α_1-adrenergic receptors	Postural hypotension Headache exacerbation Priapism
Doxepin	Tricyclic antidepressant At low doses (up to 6 mg), is preferential antagonist for the histamine$_1$ receptor	At high doses, anticholinergic adverse effects

Abbreviation: REM, rapid-eye-movement.

monoamine transmitters and thereby increase wakefulness.

Thioperamide and ciproxifan are investigational drugs that act on the brain's histamine$_3$ receptor with resulting increased wakefulness and cortical fast rhythms on electroencephalography.

γ-Hydroxybutyric Acid

Sodium oxybate is the sodium salt of the central nervous system depressant GHB. GHB is derived from GABA in the human brain. Sodium oxybate is approved by the US Food and Drug Administration for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

Sodium oxybate therapy has a potential for dependence and a very short half-life (requiring patients to wake up at night for a middle-of-the-night dose). These factors are to be balanced against its benefits for improving sleep continuity and consolidating rapid-eye-movement sleep.

Relative restrictions to the use of GHB include coexisting sleep-related breathing disorders, alcohol intake, concurrent use of sedatives, and epilepsy.

- Most agents approved by the US Food and Drug Administration for insomnia act by modulating the function of the GABA-A receptor complex.
- Medications used for sleep promotion include benzodiazepines, chronobiotics, sedating antidepressants, histamine blockers, and GHB.
- Sleepwalking is a well-documented adverse effect of zolpidem use; its use should be avoided in those with a family history of the behavior.

Alerting Agents

Overview

Many important wake-inducing signals emanate from histaminergic, serotonergic, dopaminergic, and noradrenergic neurons that diffusely innervate the forebrain, regulating cortical and hypothalamic function. With the exception of modafinil, most traditional stimulants enhance alertness by activation of monoaminergic wake-inducing signals.

Modafinil and Armodafinil

Modafinil blocks dopamine transporters and increases dopamine in the human brain including the nucleus accumbens. An additional mechanism proposed for modafinil is the enhancement of thalamocortical activity by increasing gap junction coupling between cortical interneurons. Headaches can be induced by this drug.

Modafinil and its R-enantiomer, armodafinil, are used to promote wakefulness in patients with treated obstructive sleep apnea who have residual sleepiness, shift work disorders, and narcolepsy.

Amphetamines and Related Drugs

The traditional stimulants include the amphetamines and methylphenidate. They are used to treat excessive daytime somnolence in patients with narcolepsy or idiopathic hypersomnia.

The neuronal dopamine transporter, vesicular monoamine transporter, and norepinephrine transporter are some of the targets of amphetamines. Vesicular monoamine transporters are responsible for the translocation of monoamines from the cytoplasm into synaptic vesicles (Figure 84.1).

Caffeine

Adenosine activates sleep-active neurons in the VLPO through excitatory adenosine A_{2A} receptors. Cholinergic neurons in the nucleus of Meynert in the basal forebrain are under tonic inhibition by adenosine. Caffeine, a xanthine derivative, is a nonselective antagonist for adenosine receptors. Caffeine indirectly reduces the inhibition of the cholinergic nucleus of Meynert and hence increases some aspects of central nervous system cholinergic function. Caffeine has a variable half-life of 3.5 to 5 hours.

- Many important wake-inducing signals emanate from histaminergic, serotonergic, dopaminergic, and noradrenergic neurons.
- Modafinil blocks dopamine transporters and increases dopamine in the human brain.

Miscellaneous Drug Therapies for Sleep Disorders

A number of other sleep disorders may require pharmacologic therapy. These are listed in Table 84.2.

Future Therapies

Dexmedetomidine

Dexmedetomidine is a selective agonist of the α_2 receptors with resulting inhibition of the locus ceruleus, which disinhibits the VLPO firing. The increased release of VLPO GABA inhibits histaminergic tuberomammillary nucleus firing, which is required for the induction of sleep.

The drug has unique sedative characteristics with potential for sleep architecture–preserving effect. Its short elimination half-life with light sedation allows for daily awakening and assessment for neurologic, cognitive, and respiratory functions.

Table 84.2 • Drug Therapies for Miscellaneous Sleep Disorders

Sleep Disorder	Therapy
Nightmares	Prazosin (posttraumatic stress disorder), nefazodone
REM sleep behavior disorder	Clonazepam, melatonin, quetiapine (in pervasive cases)
Sleep-related painful erections	Propranolol
Nocturnal leg cramps	Magnesium citrate; quinine is no longer recommended
Enuresis	Desmopressin
Cataplexy	SSRIs, TCAs, GHB

Abbreviations: GHB, γ-hydroxybutyric acid; REM, rapid eye movement; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

This agent was introduced for sleep induction in the intensive care unit and is administered by infusion. Currently, it is not used in the outpatient setting. However, it is also efficiently absorbed after intranasal administration and has great potential as a sleep inducer.

Orexin System

Orexins ensure state stabilization during cortical activation, and pharmacologic blockage of orexin receptor induces somnolence. Because most patients who have narcolepsy with cataplexy have orexin deficiency, orexin replacement therapy may be a new option. Orexin antagonists are also promising new agents for the treatment of insomnia and have shown encouraging results in preliminary clinical trials. Currently, both treatment approaches are unavailable.

Serotonin System

Wake-promoting effects of serotonin likely act through excitatory serotonin 2A receptor. Future sleep compounds are antagonists of the serotonin 2A receptor and are designed to suppress stimulatory effects of serotonin at specific G-protein–coupled receptors. Ketanserin and ritanserin are examples of serotonin 2A-preferring antagonists reported to increase slow-wave sleep.

85 Clinical Sleep-Related Breathing Disorders[a]

VICHAYA ARUNTHARI, MD; MARA CVEJIC, DO

Introduction

Sleep-related breathing disorders are classified into the following categories: obstructive sleep apnea (OSA) syndromes, central sleep apnea syndrome, and sleep-related hypoventilation or hypoxic syndromes (CSAS). These disorders can occur in adults or in children. Clinical features, diagnosis, and treatment are discussed in this chapter.

Obstructive Sleep Apnea

Overview and Epidemiology

Sleep apnea occurs when there is recurrent complete (apnea) or nearly complete (hypopnea) cessation of airflow, accompanied by preservation of respiratory drive manifested as persistent respiratory muscle effort. Apnea is defined as the cessation of airflow for more than 10 seconds using a valid measure of airflow. Hypopnea is a reduction of airflow of at least 30% from baseline lasting at least 10 seconds and accompanied by an oxygen desaturation of 4% or more.

The prevalence of OSA depends on how it is defined. If hypersomnolence, which is a common symptom of OSA, is required as part of the definition of OSA syndrome, 4% of men and 2% of women meet this criterion. However, when a cutoff apnea-hypopnea index (AHI) score of 5 or more is used, it is thought to affect approximately 24% of men and 7% of women in the general population of middle-aged adults.

As obesity increases at younger ages, American children are at increasing risk for OSA. OSA may lead to poor school performance and excessive daytime sleepiness.

Pathophysiology

OSA is a condition of abnormal pharyngeal narrowing and closure during sleep that develops as a result of the summation of various predisposing anatomic and physiologic aberrations in the maintenance of upper airway patency during sleep. Upper airway patency depends on the balance of forces acting on the walls (ie, transmural pressure) and the resistance of the walls to collapse (ie, wall elastance). Patients with OSA seem to have varying degrees of anatomic narrowing in combination with reduced neuromuscular dilatory compensatory mechanisms during sleep. In sleep-disordered breathing conditions, there is a high incidence of accompanying autonomic dysfunction and metabolic alterations.

Clinical Presentation

The presentation of OSA among affected patients depends on several factors, including age, sex, race, and comorbidities. Snoring is the most common symptom of OSA; however, it is not specific for OSA because it is so common in the general population. Bed partners often report that the patient has periods of witnessed breathing cessation that

[a] Portions previously published in Lee-Chiong TL, Polnitsky CA. Sleep breathing disorders. In: Barkoukis TL, Avidan AY, editors. Review of sleep medicine. 2nd ed. New York (NY): Elsevier; c2007. Used with permission.

Abbreviations: AHI, apnea-hypopnea index; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CSAS, central sleep apnea syndrome; CSR, Cheyne-Stokes respiration; OSA, obstructive sleep apnea; PCSA, primary central sleep apnea

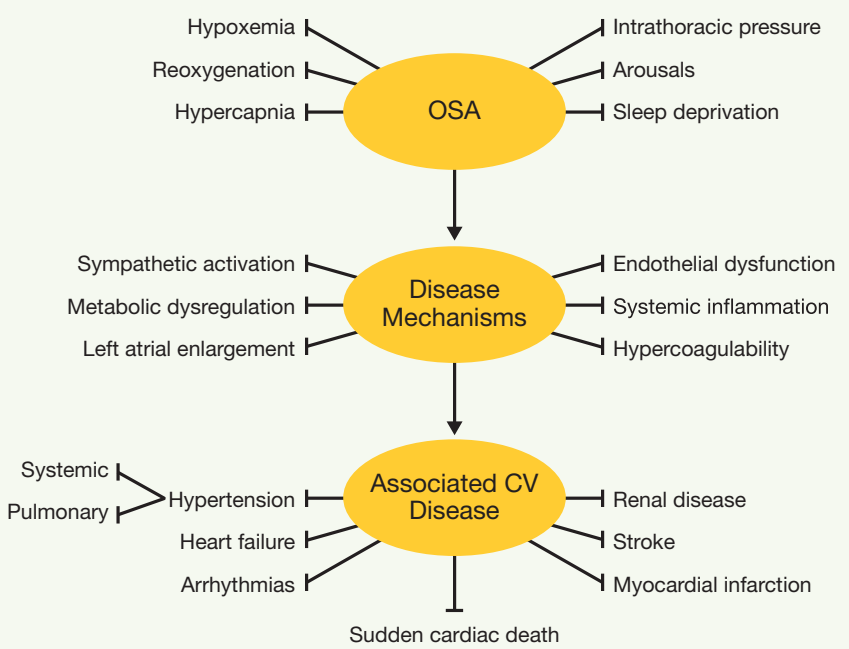

Figure 85.1 *Pathophysiologic Components of Obstructive Sleep Apnea (OSA), Mechanisms of Cardiovascular (CV) Disease, and Consequent Development of Established Cardiovascular Disease.*
(Adapted from Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. Circulation. 2008;118:1080–111. Errata in: Circulation. 2009 Mar 31;119[12]:e380 and Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol. 2008 Aug 19;52(8):686–717. Used with permission.)

can end up with an episode of choking, gasping, or snorting followed by resumption of normal breathing. Excessive daytime sleepiness is also a common symptom and is thought to be caused by sleep fragmentation. Standardized questionnaires used to inquire about excessive daytime sleepiness are the Epworth Sleepiness Scale and Stanford Sleepiness Scale. Other presenting symptoms or signs include morning headaches, restless sleep, obesity, nocturia, and dry mouth.

Health Risks

The main health risks associated with untreated OSA are cardiovascular disease (Figure 85.1), metabolic abnormalities, and accident risk due to excessive sleepiness. Hypertension, myocardial infarction, congestive heart failure, atrial fibrillation, and stroke are examples of cardiovascular disorders that are associated with OSA. There is also evidence supporting a connection between OSA and increased risk for various metabolic changes including insulin resistance and the metabolic syndrome. Furthermore, there is considerable evidence linking untreated OSA to increased risk of automobile accidents due to excessive sleepiness.

Diagnosis and Treatment

Supervised in-laboratory polysomnography remains the standard evaluation for diagnosis of OSA. Various sensors are applied to the patient (eg, oral nasal airflow, thoracic and abdominal excursion, oximetry, body position, and electroencephalography channels) to identify sleep stages and documented arousals. Apneas and hypopneas during sleep are recorded to provide an AHI, which is used to grade severity. An AHI of 5 to 14 is ranked as mild, 15 to 30 as moderate, and more than 30 as severe.

Treatment includes behavioral modifications (ie, avoidance of alcohol or sedatives and positional therapy), weight loss, and OSA-specific therapies. Positive airway pressure (ie, continuous positive airway pressure [CPAP] and bilevel positive airway pressure [BiPAP]) remains the first-line treatment for most patients. CPAP titration is performed after a diagnosis is made, and a specific CPAP value is determined that achieves virtual elimination of apneas. Because 10% to 25% of patients refuse further use of CPAP after the first night, alternative treatments have been used. Oral appliances including mandibular advancement devices and tongue stabilizers are useful in reduction of snoring and the

AHI in mild OSA. Surgical options for sleep-disordered breathing remain controversial and include radiofrequency surgery, uvulopalatopharyngoplasty, tongue-base reduction surgery, genioglossus advancement, maxillary and mandibular advancement, and tracheostomy.

Electrical stimulation of the hypoglossal nerve, which recruits lingual muscles, results in improvement in upper airway collapsibility and OSA severity in both animals and humans. Future research is needed.

- Sleep apnea occurs when there is recurrent complete (apnea) or nearly complete (hypopnea) cessation of air accompanied by persistent respiratory muscle effort.
- The incidence of autonomic dysfunction and metabolic alterations is high in patients with sleep-disordered breathing.
- Snoring is the most common symptom of OSA.
- Excessive daytime sleepiness is another common symptom of OSA.
- Additional presenting symptoms or signs of OSA include morning headaches, restless sleep, obesity, nocturia, and dry mouth.
- Cardiovascular disorders associated with OSA are hypertension, myocardial infarction, congestive heart failure, atrial fibrillation, and stroke.
- Supervised in-laboratory polysomnography is the standard evaluation for diagnosis of OSA.
- CPAP and BiPAP are first-line treatments for OSA.

Upper Airway Resistance Syndrome

Upper airway resistance syndrome is subsumed under the diagnosis of OSA because the pathophysiology does not differ substantially from that of OSA. Upper airway resistance syndrome is characterized by repetitive episodes of increase in resistance to airflow in the upper airways associated with arousals from sleep but without apneas or hypopneas. Frequent arousals result in sleep fragmentation and symptoms similar to those of OSA.

Central Sleep Apnea Syndrome

Overview

CSAS can be idiopathic or secondary. Examples of secondary CSAS include Cheyne-Stokes respiration (CSR) or disrupted breathing due to high altitude, a medical condition, or adverse effect of a drug or substance.

CSAS is characterized by loss of ventilatory output from the central respiratory generator in the brainstem to the respiratory pump. There is gradual or abrupt cessation of airflow resulting from the lapse in controller signaling. Heightened ventilatory response to carbon dioxide leads to instability of respiratory control during wake-sleep transition and may persist into non–rapid eye movement sleep.

During polysomnography, respiratory effort is absent at least 10 seconds with loss of airflow, which can be associated with oxygen desaturation, arousals, and sleep fragmentation.

Primary Central Sleep Apnea

Primary central sleep apnea (PCSA), also referred to as idiopathic central sleep apnea, is a relatively uncommon condition afflicting persons with high chemoreceptor responsiveness that results in lower baseline $Paco_2$, close to the apneic threshold. The arousals and ventilatory pattern in PCSA are not cyclical, but waxing and waning as seen in CSR.

Clinical features of PCSA include fragmented sleep with frequent awakenings that may lead to daytime hypersomnolence.

Treatment options for patients with PCSA who have sleep disruption or daytime functional sequelae include CPAP, supplemental oxygen, and acetazolamide.

Cheyne-Stokes Respiration

CSR is a breathing pattern characterized by crescendo-decrescendo tidal volumes with intervening CSAs. This waxing and waning pattern has also been referred to as periodic breathing. Although central nervous system disease is a known cause of CSR, congestive heart failure is the most frequent cause. Arousals from sleep in CSR tend to occur at the height of the hyperpneic phase following apnea, as opposed to OSA, in which arousals typically occur with apnea termination. In overt congestive heart failure, there is a long circulation with resulting time delay in the nadir of the oxyhemoglobin saturation recording. CSR may develop in unilateral supratentorial stroke involving autonomic (insula) and volitional (cingulate cortex, thalamus) respiratory networks. As such, CSR partly resolves within weeks.

In most cases, treatment is directed toward the underlying congestive heart failure. Other treatment options for CSR include supplemental oxygen, inhaled carbon dioxide, theophylline, acetazolamide, and positive airway pressure such as CPAP, BiPAP, and adaptive servoventilation.

- In patients with central sleep apnea syndrome, respiratory effort is absent for ≥10 seconds on polysomnography, which can be associated with oxygen desaturation, arousals, and sleep fragmentation.
- Cheyne-Stokes respiration is characterized by crescendo-decrescendo tidal volumes and intervening central sleep apnea.
- Congestive heart failure is the most frequent cause of Cheyne-Stokes respiration; central nervous system disease is also a known cause.

Sleep-Related Hypoventilation or Hypoxemic Syndromes

Congenital Central Hypoventilation Syndrome

Congenital central hypoventilation syndrome is a disorder resulting in hypoxemia and hypercarbia during sleep because of ventilatory abnormalities due to autonomic nervous system dysregulation. A mutation in *PHOX2B* leads to decreased tidal volumes and monotonous respiratory rates during sleep and a paradoxic lack of arousal response to these physiologic changes. Depending on the type of mutation, they are associated with tumors of neural crest origin and Hirschsprung disease.

Clinical manifestations include tachycardia, diaphoresis, and cyanosis, which varies depending on disease severity. Onset occurs during the newborn period and consists of episodic apnea, cyanosis, feeding difficulties, or bradycardia. Chronic hypoxemia can lead to pulmonary hypertension, cor pulmonale, developmental delay, seizures, and growth retardation. Arrhythmias, seizures, syncope, esophageal dysmotility, ophthalmologic abnormalities, Hirschsprung disease, renal impairment, mental impairment, and tumors of the neural crest have been reported.

Congenital central hypoventilation syndrome should be distinguished from other congenital syndromes associated with abnormalities in respiratory control, such as Prader-Willi syndrome and familial dysautonomia. Other causes of chronic hypoventilation such as cardiopulmonary, neuromuscular, and metabolic disorders should also be excluded.

Affected children are treated with home ventilatory support, typically positive-pressure ventilators via tracheostomy, BiPAP, negative-pressure ventilators, or diaphragm pacing.

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome is characterized by the presence of severe obesity and hypercapnia during wakefulness. Hypercapnia develops as a result of the increased production of carbon dioxide (because of greater work of breathing) and decreased ventilation. In addition, the ventilatory response to hypercapnia and hypoxemia is decreased. Patients may present with hypersomnolence, decreased attention or concentration, peripheral edema, or cyanosis. Treatment is targeted for weight loss and may require noninvasive positive-pressure ventilation or respiratory stimulants.

- Congenital central hypoventilation syndrome produces hypoxemia and hypercarbia during sleep caused by ventilatory abnormalities caused by autonomic system dysregulation.
- Obesity hypoventilation syndrome is characterized by the presence of severe obesity and hypercapnia during wakefulness.

86 Hypersomnias and Sleep-Related Movement Disorders[a]

VICHAYA ARUNTHARI, MD; MARA CVEJIC, DO

Introduction

Hypersomnias are disorders characterized by excessive daytime sleepiness. This symptom may occur in other disorders. Thus, the hypersomnia disorders must exclude other causes of excessive daytime sleepiness. Specifically, hypersomnias refer to disorders associated with excessive daytime sleepiness not related to sleep deprivation, disturbed nocturnal sleep, circadian rhythm disturbances, sleep-related breathing disorders, or medical condition. This chapter reviews the primary insomnias of narcolepsy and idiopathic hypersomnia.

Sleep-related movement disorders, including restless legs syndrome and periodic limb movements of sleep, are commonly encountered in clinical practice. These common syndromes are also reviewed in this chapter.

Hypersomnias

Narcolepsy

Overview and Epidemiology

Narcolepsy is defined as a pentad of symptoms that include excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, hypnagogic hallucinations, and sleep paralysis.

The prevalence rate of narcolepsy is approximately 1 in 4,000 in North America and Europe and much higher in Japan. The age at onset of narcolepsy varies from early childhood to the fifth decade of life, with a peak in the second decade.

Pathophysiology

The proposed mechanism of narcolepsy suggests a loss of hypocretin-1–secreting cells in the hypothalamus on an autoimmune basis. Low to absent levels of cerebrospinal fluid hypocretin-1 levels coincide with postmortem confirmation of 80% to 90% volume loss of hypocretin-producing neurons in the hypothalamus. Normal levels of cerebrospinal fluid hypocretin-1 range from 230 to 320 pg/mL, whereas patients with narcolepsy who have cataplexy have levels less than 100 pg/mL. A linkage to the histocompatibility antigen HLA DQB1*0602 and DQA1*0102 has been shown, present in almost all patients with narcolepsy, compared with the lower prevalence (10%–40%) in the general population. Diagnosis can be complicated in patients without cataplexy because cerebrospinal fluid hypocretin levels are most often normal and HLA results are negative.

Interestingly, narcolepsy is insufficiently explained by the presence of HLA DQB1*0602 and DQA1*0102 antigen positivity in that monozygotic twins have shown discordance with expression of the disease—only 25% to 30% of both twins will manifest symptoms. Although genetic susceptibility plays a large role, it is believed that a significant and stressful life event such as illness, injury, or traumatic emotional experience can trigger the onset.

Secondary narcolepsy can develop as a result of structural lesions of the brainstem or diencephalon and in certain diseases such as Niemann-Pick type C disease, Prader-Willi syndrome, myotonic dystrophy, Norrie disease, and Coffin-Lowry syndrome.

[a] Portions previously published in Avidan AY. Narcolepsy and idiopathic hypersomnia. In: ACCP sleep medicine board review 2008: course syllabus. Northbrook (IL): American College of Chest Physicians; c2008. p. 35–50. Used with permission.

Abbreviations: MSLT, multiple sleep latency test; PLMS, periodic limb movements of sleep; REM, rapid eye movement; RLS, restless legs syndrome; SOREMP, sleep-onset REM period

Clinical Features

Narcolepsy often begins in childhood or the teenage years and persists into adulthood. Patients present with excessive daytime sleepiness and the irresistible urge to fall asleep. In children, napping beyond the age of 5 years or the misperception of laziness should be sought in the history. Cataplexy, hypnagogic hallucinations, and sleep paralysis can accompany the daytime sleepiness.

Cataplexy is characterized by sudden episodes of bilateral skeletal muscle weakness or paralysis triggered by intense, usually positive, emotions such as laughter, excitement, and sexual arousal, associated with partial or complete muscle atonia, hyporeflexia, or areflexia. Respiratory muscles and consciousness are spared. Cataplexy occurs in the majority of narcolepsy patients (approximately 70%). Cataplexy usually develops within a few months or years of the onset of the sleepiness. Approximately 10% to 15% of patients do not have cataplexy until 10 to 40 years after the onset of sleepiness. Status cataplecticus is also known as continuous cataplexy or limp-man syndrome. Patients present with excessive daytime sleepiness and frequent episodes of sudden buckling of the knees without falls. Status cataplecticus should be considered in the differential diagnosis of psychogenic gait disorders.

Hypnagogic and hypnopompic hallucinations occur in 20% to 40% of patients with narcolepsy. Mostly visual dreamlike hallucinations are common, although there may be auditory, vestibular, or tactile hallucinations. These typically occur just before falling asleep and also on awakening. Hypnopompic hallucinations occur as an intrusion of rapid-eye-movement (REM) sleep onto wakefulness as one awakens, and hypnogogic hallucinations occur at the transition of wakefulness to sleep. These disturbing auditory and visual out-of-body experiences tend to abate with age.

Sleep paralysis refers to the inability to move during sleep onset or on awakening that lasts a few seconds or minutes. It occurs in 25% to 50% of patients with narcolepsy. The paralysis resolves spontaneously or with sensory stimuli.

Diagnosis

A clinical history of excessive daytime sleepiness and features described above are highly suggestive of a diagnosis of narcolepsy. Tools used for assessment of excessive daytime sleepiness include the Epworth Sleepiness Scale and the Stanford Sleepiness Scale. A sleep diary, which includes a sleep log of several weeks in duration, may provide important information about a patient's sleep habits. Sleep studies are generally required for an accurate diagnosis of narcolepsy because of various conditions that can cause excessive sleepiness. Typically, polysomnography is followed by the multiple sleep latency test (MSLT). Polysomnography findings of narcolepsy include sleep disruption, repetitive awakenings, and decreased REM sleep latency. The occurrence of REM-sleep onset occurs in approximately 50% of patients with narcolepsy and cataplexy. A sleep-onset REM period (SOREMP) at night is highly predictive of narcolepsy.

MSLT is performed the day after nocturnal polysomnography. The criteria for narcolepsy include a mean sleep latency of less than 8 minutes and 2 or more SOREMPs. Urine drug screens are performed routinely on patients who seem to fall asleep too quickly because a lifelong diagnosis should exclude any surreptitious drug use.

Cerebrospinal fluid hypocretin measurements can be useful when use of REM sleep–suppressant medications cannot, for medical reasons, be stopped in preparation for MSLT. In narcolepsy-cataplexy cases, cerebrospinal fluid-hypocretin is undetectable.

Nonpharmacologic Treatment

The patient and family members should be educated and counseled about the syndrome. Adequate sleep at night is important because sleep deprivation or insufficient sleep aggravates symptoms. Patients should take "power" naps, such as one to three 20-minute naps during the daytime. Emphasize the importance of good sleep hygiene and the risks associated with sleepiness while driving and in the workplace.

Pharmacologic Treatment

For excessive daytime sleepiness, central nervous system stimulants such as methylphenidate, dextroamphetamine, methamphetamine, or modafinil are used to improve alertness.

Modafinil is often used as a first-line agent because of longer half-life and duration of action with acceptable adverse effects. Adverse effects are uncommon but include headache, nausea, dry mouth, anorexia, and diarrhea. Methylphenidate and amphetamines are central nervous system stimulants and potent wakefulness-promoting drugs. These are considered second-line agents because of their sympathomimetic adverse effects.

Cataplexy and sleep paralysis are usually treated with REM sleep–suppressing drugs and γ-hydroxybutyrate. Medications that increase noradrenergic and serotoninergic signaling suppress REM sleep and reduce cataplexy. These include tricyclic antidepressants such as protriptyline, imipramine, clomipramine, and nortriptyline. Antidepressants that selectively inhibit the reuptake of norepinephrine or serotonin include venlafaxine, atomoxetine, and fluoxetine. γ-Hydroxybutyrate (or sodium oxybate) is approved by the US Food and Drug Administration for treatment of cataplexy. It is given as a liquid at bedtime with another dose 2.5 to 4 hours later. Adverse effects include nausea, dizziness, urinary incontinence, worsening of sleep walking, nocturnal confusion, and respiratory depression.

Idiopathic Hypersomnia

This disorder of unknown cause is characterized by nonrefreshing sleep with difficulty waking up from nocturnal sleep or daytime naps. It is further categorized as idiopathic hypersomnia with a long sleep time (>10 hours) and idiopathic hypersomnia without a long sleep time (≤10 hours). Patients have excessive daytime somnolence with unrefreshing naps.

Diagnoses are primarily those of exclusion by differentiating from other disorders such as insufficient sleep syndrome, narcolepsy, untreated sleep-disordered breathing, medication effect, status post–head injury, and psychiatric disorders. Objective measures of sleepiness are obtained using the scales described earlier and with the MSLT and are important for the diagnosis. On MSLT the mean sleep latency may be less than 8 minutes but with fewer than 2 SOREMPs. Actigraphy and sleep diaries are also helpful to document the 24-hour sleep-wake schedule. Cerebrospinal fluid levels of orexin or hypocretin-1 are normal.

Treatment is similar to that of narcolepsy with various degrees of success. Naps are long and not refreshing and therefore are not indicated.

Recurrent Primary Hypersomnia

Kleine-Levin syndrome typically affects adolescents experiencing episodes of excessive daytime sleepiness lasting a minimum of 2 days or up to 4 weeks. These are followed by return to normal cognitive and psychosocial function for several weeks or months. The hypersomnia is often accompanied by variable disturbances of mood and cognition, increased appetite, and very aggressive or hypersexual behavior. Episodes recur at least once or twice a year but may occur up to 10 times a year. The cause is unclear, but intermittent hypothalamic dysfunction or autoimmune causes have been proposed. Kleine-Levin syndrome is usually a self-limited condition but difficult to treat. There have been some reports of improvement with lithium. Stimulants have not been shown to be of great benefit.

Other Hypersomnias

Menstrual-associated hypersomnia is a poorly characterized condition in which episodic sleepiness coincides with the menstrual cycle; it is postulated to be due to hormonal influences.

Other categories of hypersomnia include behavioral-induced insufficient sleep syndrome, hypersomnia due to a medical condition, hypersomnia due to drug or substance use, hypersomnia not due to a substance or known physiologic condition, and physiologic hypersomnia.

- Narcolepsy is defined as a pentad of symptoms that include excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, hypnagogic hallucinations, and sleep paralysis.
- The proposed mechanism of narcolepsy suggests a loss of hypocretin-1–secreting cells in the hypothalamus on an autoimmune basis.
- Secondary narcolepsy can develop as a result of structural lesions of the brainstem or diencephalon.
- Patients who have narcolepsy present with excessive daytime sleepiness and the irresistible urge to fall asleep.
- Cataplexy, hypnagogic hallucinations, and sleep paralysis can accompany the daytime sleepiness of narcolepsy.
- For the diagnosis of narcolepsy, typically, polysomnography is followed by the MSLT.
- The criteria for narcolepsy include a mean sleep latency of less than 8 minutes and 2 or more SOREMPs.
- Modafinil is often used as a first-line agent for treatment of narcolepsy because of longer half-life and duration of action with favorable adverse effects.
- Kleine-Levin syndrome typically affects adolescents experiencing episodes of excessive daytime sleepiness.
- The hypersomnia of Kleine-Levin syndrome is often accompanied by variable disturbances of mood and cognition, increased appetite, and very aggressive or hypersexual behavior.

Sleep-Related Movement Disorders

Restless Legs Syndrome

Overview and Epidemiology

Restless legs syndrome (RLS) is a sleep disorder characterized by unpleasant leg sensations that occur at bedtime and interfere with sleep onset and disrupt sleep. The prevalence of RLS is between 5% and 15% and is more common in women. Up to 80% of patients have associated periodic limb movements of sleep.

This disorder may occur in 2% of children and adolescents, typically those with a parental history suggestive of the disorder. There is a link between attention deficit hyperactivity disorder and RLS.

Clinical Features

The unpleasant sensations may be described as creepy crawling, burning, throbbing, crazy legs, jittery, or itching. Symptoms are worse at rest and improve with movement or stimulation, such as walking, rubbing, or stretching. The discomfort most commonly involves the lower extremities but has been described in the upper extremities and trunk. The disrupted sleep may lead to insomnia or daytime sleepiness.

When RLS develops without a known predisposing or exacerbating condition, it is considered primary. Primary RLS usually has an early age at onset and a positive family history

consistent with autosomal dominant inheritance. RLS can also be due to another condition, especially iron deficiency, pregnancy, and renal failure. Secondary RLS occurs in association with conditions or disorders that result in iron deficiency, including pregnancy and end-stage renal disease, and the symptoms reverse with adequate iron replacement therapy. Several other comorbid conditions, including primary sleep disorders, Parkinson disease, neuropathies, rheumatoid arthritis, and metabolic disturbances, have been associated with RLS. Several medications can worsen or cause symptoms of RLS, including antidepressants (serotonergic), antihistamines, and dopamine receptor blockers.

Diagnosis

Diagnosis of RLS is a clinical diagnosis with clinical features consistent with RLS, and polysomnography is unnecessary. Laboratory evaluation for predisposing conditions is usually performed, such as tests for iron, ferritin, folate, and vitamin B_{12}. Differential diagnosis includes nocturnal leg cramps, painful legs and moving toes syndrome, peripheral neuropathy, radiculopathy, and restlessness associated with anxiety disorders.

Treatment

The treatment of RLS in patients who have frequent or intense symptoms includes both nonpharmacologic and pharmacologic approaches. Nonpharmacologic measures include education, moderate exercise, smoking cessation, alcohol avoidance, caffeine reduction or elimination, and discontinuing use of offending medications if it is safe to do so. Iron supplementation should be given to patients who are iron deficient, particularly if the serum ferritin level is less than 50 µg/L.

Dopamine receptor agonists are first-line pharmacologic treatments. The dopamine receptor agonists that are approved by the US Food and Drug Administration are ropinirole and pramipexole, taken 2 to 3 hours before bed. Intermittent use of short-acting dopaminergic medications, particularly levodopa/carbidopa, may also provide satisfactory treatment, but over time rebound or augmentation with increasing severity of symptoms may develop and symptoms may recur early in the day and spread to involve other body parts. Other agents that are being used include benzodiazepines, gabapentin, and opioids. Clonidine, clonazepam, ropinirole, pramipexole, and gabapentin are not approved by the US Food and Drug Administration for use in children; however, they are often used with careful monitoring.

Painful Legs and Moving Toes Syndrome

Painful legs and moving toes syndrome is an adult-onset disorder characterized by neuropathic pain in the feet or legs associated with writhing movements of the toes that can be unilateral. The toe movements cannot be voluntarily reproduced by the patient. Indistinguishable toe movements may occur without pain, referred to as painless legs-moving toes. The pathophysiology of painful legs-moving toes is unknown, but in most cases there is an association with a peripheral root or nerve lesion. Central reorganization at the level of the spinal cord is speculated to be responsible for the pain and movements. Treatment is often disappointing with little or no response to dopamine agonists.

Periodic Limb Movements

Periodic limb movements of sleep (PLMS) are rhythmical extensions of the big toe and dorsiflexion of the ankle with occasional flexions of the knee and hip pain that usually occur during the first part of the night. The prevalence of PLMS increases with age. PLMS is present in 5% to 6% of all adults and in 30% to 86% of adults 60 years or older.

During an overnight sleep study, PLMS are scored if they are part of a series of 4 or more consecutive movements lasting 0.5 to 5 seconds with an interval of 4 to 90 seconds (Figure 86.1). A periodic limb movement index of more than 15 movements per hour of sleep is generally considered increased in adults. PLMS are commonly associated with other sleep disorders. The most notable is the occurrence of PLMS and the majority of RLS patients. PLMS also has been described in obstructive sleep apnea, narcolepsy, and REM sleep-behavior disorder.

Patients with complaints of insomnia or hypersomnia who have PLMS and no other sleep disorder are considered to have periodic limb movement disorder.

Treatment is controversial. Some believe that PLMS are significant if they are associated with arousals. Nevertheless, dopamine agonists, similar to treatment of RLS, are indicated if marked sleep fragmentation results from PLMS-associated arousals.

Bruxism

Bruxism is characterized by teeth grinding or jaw clenching. Patients may present with abnormal wear of the teeth, jaw muscle discomfort or pain, jaw lock on awakening, and masseter muscle hypertrophy on voluntary forceful clenching. Dental treatments consisting of soft mouth guards or hard occlusal splints reduce damage to the teeth. Clonidine (adverse effects include REM suppression and morning hypotension) and clonazepam can be used to treat this condition if it is severe.

Sleep-Related Leg Cramps

Sleep-related leg cramps involve sudden, involuntary, usually very painful, and mostly unilateral contractions in the muscle or muscle groups of the legs or feet during the sleep period. They occur most commonly in the calf but can also include the foot or thigh. The contraction is usually relieved by forceful stretching of the affected muscles, which leads to relaxation of the contraction.

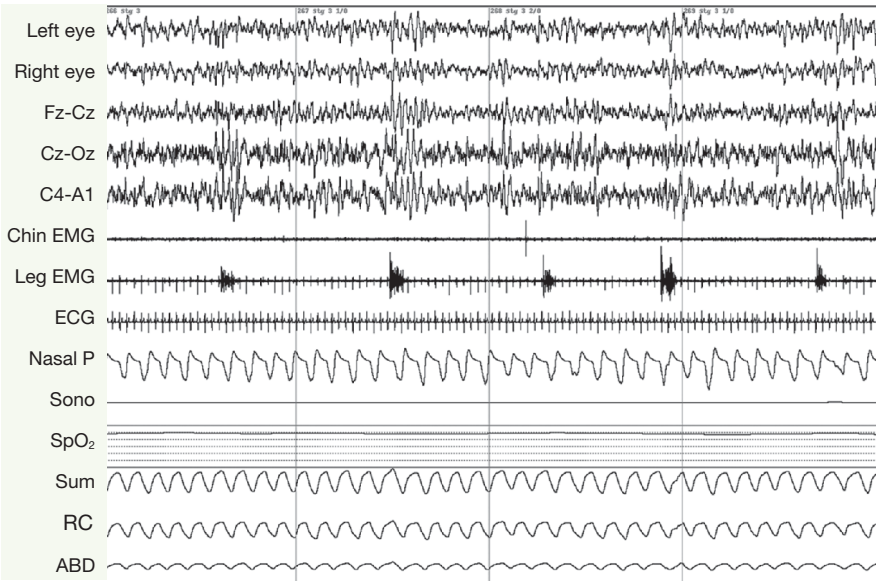

Figure 86.1 *Polysomnogram for Patient With Periodic Limb Movements of Sleep.*
Note the periodicity; no associated arousals are seen (120-second epoch). ABD indicates abdominal respiratory band; ECG, electrocardiogram; EMG, electromyogram; Nasal P, nasal airflow; RC, rib cage respiratory band; Sono, snore microphone; SpO_2, oxygen saturation; Sum, sum of RC.
(Adapted from Young TJ, Tippmann-Peikert M. Neurology of sleep disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 719–52. Used with permission of Mayo Foundation for Medical Education and Research.)

Any basic chemical imbalance could contribute to this condition, including peripheral vascular disease with neuropathy. Stretching and regular exercise of the muscles are preferred treatments to reduce the occurrence. Medications that have been reported to have some possible benefit for more severe cases include verapamil and diltiazem. There are limited data for the use of quinine and vitamin E.

- Restless legs syndrome (RLS) is a sleep disorder characterized by unpleasant leg sensations that occur at bedtime and interfere with sleep onset and disrupt sleep.
- RLS can also be due to another condition, especially iron deficiency, pregnancy, and renal failure.
- For the diagnosis of RLS, laboratory evaluation for predisposing conditions is usually performed, such as tests for iron, ferritin, folate, and vitamin B_{12}.
- The treatment of RLS in patients who have frequent or intense symptoms includes both nonpharmacologic and pharmacologic approaches.
- Dopamine receptor agonists are first-line pharmacologic treatments of RLS.
- Periodic limb movements of sleep (PLMS) are rhythmical extensions of the big toe and dorsiflexion of the ankle with occasional flexions of the knee and hip pain that usually occur during the first part of the night.

87 Circadian Disorders, Insomnia, and Parasomnias[a]

VICHAYA ARUNTHARI, MD

Introduction

This chapter reviews circadian disorders, insomnias, and parasomnias. These are common sleep disorders encountered in clinical practice. Each requires a careful review of potential contributing factors and a multifaceted approach to treatment.

Circadian rhythm disorders have a misalignment between a desired sleep schedule and the circadian sleep-wake rhythm. Many persons experience this condition with jet lag. Other common circadian rhythm disorders include delayed sleep-phase disorder (DSPD), advanced sleep-phase disorder (ASPD), and shift-work sleep disorder (SWSD).

Insomnia is one of the most common medical complaints and increases in prevalence with age. Patients may have difficulty initiating sleep or maintaining sleep and generally have poor quality of sleep. Causes of insomnia are multifactorial and reviewed below.

Parasomnias are abnormal states of behavior and experience in which basic instincts are inappropriately unleashed during sleep; these experiential or physical phenomena are often undesirable and nondeliberate. Parasomnia disorders include sleepwalking, sleep terrors, nightmares, and other common disorders.

Circadian Rhythm Sleep Disorders

Overview

Like most organisms, humans have daily behaviors that are regulated in a circadian (24-hour) manner. Circadian rhythm sleep disorders are caused by a recurrent or persistent misalignment between a desired sleep schedule and the circadian sleep-wake rhythm (Figure 87.1). These disorders can be associated with insomnia or excessive sleepiness and may lead to impairment of social, occupational, or other areas of functioning as the consequence of the disruption.

Delayed Sleep-Phase Disorder

The prevalence of DSPD is unknown but is estimated in adolescents and young adults to be between 7% and 16%. The pathophysiologic mechanism is unknown but has been postulated to be a phase delay of the endogenous circadian pacemaker in relation to conventional sleep-wake schedules with an inability to phase advance in order to correct the disturbance.

In DSPD, the major nocturnal sleep occurs later than the conventional or socially acceptable bedtime. Patients who have DSPD are night owls. Typically, sleep onset is between 1 AM and 6 AM and wake time is from 10 AM to 1 PM. Patients often have complaints of sleep-onset insomnia or difficulty waking up at the desired time. When patients are allowed to follow their preferred schedule, the circadian phase of sleep is delayed and the quality of sleep is normal. They often report feeling most alert in the evening and sleep in the early morning.

DSPD should be differentiated from other disorders associated with sleep-onset insomnia such as psychophysiologic insomnia, idiopathic insomnia, other psychiatric conditions, and poor sleep hygiene. Diagnosis is based on

[a] Portions previously published in Avidan AY. Parasomnias and movement disorders of sleep. Semin Neurol. 2009 Sep;29(4):372–92. Epub 2009 Sep 9; and Reid KJ. Overview and description of circadian rhythm sleep disorders. In: Kushida C. Encyclopedia of sleep. London: Elsevier; c2013; p. 11–15. Used with permission.

Abbreviations: ASPD, advanced sleep-phase disorder; DSPD, delayed sleep-phase disorder; NES, night eating syndrome; NREM, non–rapid-eye-movement; RBD, REM sleep-behavior disorder; REM, rapid eye movement; SWSD, shift-work sleep disorder

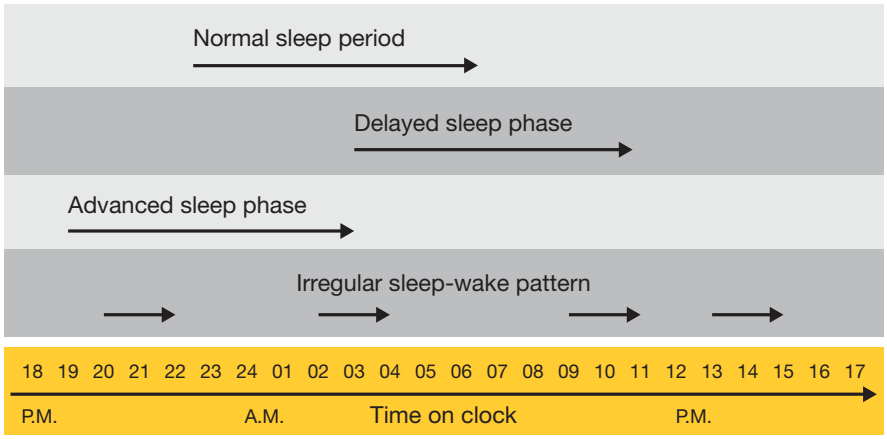

Figure 87.1 *Circadian Rhythm Disorders.*
Sleep periods for normal subjects and several circadian rhythm disorders.
(Adapted from Young TJ, Tippmann-Peikert M. Neurology of sleep disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 719–52. Used with permission of Mayo Foundation for Medical Education and Research.)

a detailed history. Diagnostic studies such as actigraphy and sleep diaries for at least 1 week can be helpful for confirming the DSPD pattern, and polysomnography is not required other than to rule out other sleep disorders.

Treatment consists of chronotherapy with protocols of either progressive phase delay or progressive phase advancement and schedule shift techniques. Light therapy can also be used with timed early-morning exposure and evening avoidance of bright light. Evening administration of melatonin has also been found to be effective for treating DSPD. Strict adherence to desired sleep-wake schedule is crucial because the risk of relapse is high.

Advanced Sleep-Phase Disorder

ASPD is more common among middle-aged and older adults; the estimated prevalence is 1%, and it increases with age. Pathogenesis may be related to deficiency in the ability to delay the sleep phase, an overly dominant phase advance capability, a natural faster circadian rhythm, or a very short endogenous period. Social and behavior factors also may contribute. Familial ASPD was the first recognized mendelian circadian rhythm trait. Persons with familial ASPD have very early sleep onset and offset due to altered posttranslational regulation of period homolog 2.

In ASPD there is a stable shift in the major sleep period to an earlier time relative to desired or conventional bedtimes. This is characterized by early evening sleepiness and wake-up times that are several hours earlier. Sleep typically occurs from 6 PM to 9 PM, and waking up occurs from 2 AM to 5 AM.

Evaluation of ASPD includes consistent history along with activity or sleep diaries for at least 1 week. Polysomnography is not generally indicated other than to rule out other sleep disorders. Treatment consists of phototherapy such as early-evening bright-light exposure and early-morning light restriction.

Non–24-Hour Sleep-Wake Disorder

Hypernyctohemeral syndrome is rare in the general population. It occurs in association with neurologic dysfunction, such as in persons with brain injury, dementia, or mental retardation and in institutionalized elderly persons.

The retinohypothalamic tract is a component of the optic nerve that transmits information about environmental luminance to regions of the hypothalamus that control circadian rhythms. One of these regions includes the suprachiasmatic nucleus, which is entrained by light via the retinohypothalamic tract. Blind persons with lesions of the retinohypothalamic tract frequently have non–24-hour sleep-wake disorder. Hypernyctohemeral syndrome and DSPD often coexist or are associated.

Nonentrained sleep-wake disorder is characterized by a steady daily delay of 1 or 2 hours in which the intrinsic circadian pacemaker is not entrained to a physical and social 24-hour cycle. Patients may complain of insomnia and excessive daytime sleepiness.

Evaluation includes sleep logs and actigraphy performed over 1 to 2 weeks. Neurologic evaluation is recommended to exclude any occult central nervous system abnormality. Evening administration of melatonin has been described to entrain the circadian sleep-wake schedule. Phototherapy such as morning-light exposure can be provided for patients with light perception. Nonphotic entrainment also may be useful with strict regulation of the timing of bedtime, arising time, activities, and planned napping.

Shift-Work Sleep Disorder

SWSD is characterized by complaints of insomnia, nonrestorative sleep, or excessive sleepiness that occurs in relation to work hours that are scheduled during the usual sleep time. Several types of shift-work scheduling are rotating shifts, nightshifts, and early-morning shift. The risk of work-related and vehicle accidents is increased. Symptoms typically remit with termination of shift work. Not every shift worker has SWSD, and tolerance to nonconventional sleep-wake schedules is variable.

Evaluation of SWSD consists of a sleep log or actigraphy, and polysomnography is not routinely indicated. Therapy should include maintenance of a regular and comparable sleep-wake schedule during both work and nonwork days. Other causes of excessive daytime sleepiness must be excluded. Phototherapy is effective and consists of use of bright lights during night-shift work and restriction of light exposure in the morning after night-shift work. Stimulants such as caffeine or modafinil during evening work hours may decrease sleepiness and enhance alertness. Scheduled napping before or during night-shift work also decreases nocturnal sleepiness.

Jet Lag

Jet lag, a misalignment between the timing of circadian rhythm with the external physical environment, develops after rapid eastward or westward air travel across multiple time zones.

Symptoms typically are general malaise, daytime sleepiness, difficulty sleeping, impaired performance, and gastrointestinal complaints. Symptoms usually last for several days and resolve after the traveler adapts to the new time zone. Adjusting to eastward travel is usually more difficult than adjusting to westward travel. Eastward travel can cause difficulty falling asleep and difficulty awakening the next day. Westward travel is associated with early-evening sleepiness and increased wakefulness during the early-morning hours.

Treatment consists of changing the sleep-wake schedule immediately to the time of the destination on the day of arrival. Maintaining good sleep hygiene and eating meals according to local times can be useful. Approximate timed exposure to bright lights in evening exposure for westward travel and morning light exposure for eastward travel is beneficial. Melatonin at bedtime on arrival may be helpful when its use is repeated for up to 4 nights. Short-term use of short-acting hypnotics may also be helpful.

- Circadian rhythm sleep disorders are caused by a recurrent or persistent misalignment between a desired sleep schedule and the circadian sleep-wake rhythm.
- In delayed sleep-phase disorder (DSPD), the major nocturnal sleep occurs later than the conventional or socially acceptable bedtime. Patients who have DSPD are night owls.
- In advanced sleep-phase disorder (ASPD) there is a stable shift in the major sleep period to an earlier time relative to desired or conventional bedtimes.
- Nonentrained sleep-wake disorder is characterized by a steady daily delay of 1 or 2 hours in which the intrinsic circadian pacemaker is not entrained to a physical and social 24-hour cycle.
- Shift-work sleep disorder (SWSD) is characterized by complaints of insomnia, nonrestorative sleep, or excessive sleepiness that occurs in relation to work hours that are scheduled during the usual sleep time.
- Jet lag, a misalignment between the timing of circadian rhythm with the external physical environment, develops after rapid eastward or westward air travel across multiple times zones.
- For the treatment of jet lag, melatonin at bedtime on arrival may be helpful when its use is repeated for up to 4 nights.

Insomnia

Definition and Classification

Patients with insomnia have impaired daytime function due to difficulty initiating sleep, difficulty maintaining sleep, waking up too early, chronically nonrestorative sleep, or poor quality of sleep. The sleep difficulties occur despite adequate opportunity and circumstances for sleep. Insomnia of short duration usually last less than 3 months. Chronic insomnia or insomnia with a longer duration, typically lasts more than 1 to 3 months.

Insomnia is one of the most common medical complaints, and its prevalence increases with age. Patients typically complain of difficulty falling asleep or staying asleep. Impaired daytime function includes fatigue or malaise, poor attention or concentration, reduced motivation, social dysfunction, mood disturbance, daytime sleepiness, increased errors or accidents, tension headache, gastrointestinal symptoms, and anxiety about sleep loss. The International Classification of Sleep Disorders-2 categorizes insomnia into multiple types (Box 87.1).

Acute Insomnia

Acute insomnia is related to an identifiable stressor and tends to resolve when the stressor is removed or when the person adapts to it. Various stressors include changes in the background noise or sleeping environment, consumption of caffeine, nicotine- or alcohol-containing products, stressful life events, medical illness or injuries, and medications or withdrawal of medications.

Other types of insomnia with short duration include circadian rhythm sleep disorders, jet lag, SWSD, and high-altitude insomnia.

Box 87.1 • Insomnia Types, International Classification of Sleep Disorders-2

- Adjustment insomnia or acute insomnia
- Psychophysiologic insomnia
- Paradoxic insomnia
- Idiopathic insomnia
- Insomnia due to mental disorder
- Inadequate sleep hygiene
- Behavioral insomnia of childhood
- Insomnia due to drug or substance
- Insomnia due to medical condition
- Insomnia not due to substance or known physiologic conditions, unspecified
- Physiologic (organic) insomnia, unspecified

Psychophysiologic Insomnia

This condition is also called primary insomnia, chronic insomnia, learned insomnia, or condition insomnia. Patients have difficulty relaxing with associated racing thoughts while trying to fall asleep. Frustration and anxiety increase from the inability to fall asleep. Patients may focus on the perceived negative impact of the lack of sleep on their ability to perform the next day. Patients usually sleep better in a different environment than in their own bedroom.

Paradoxic Insomnia

Paradoxic insomnia is also called sleep-state misperception, subjective insomnia, pseudoinsomnia, and sleep hypochondriasis. Patients misperceive or underestimate the amount of time asleep and complain of insomnia. Polysomnography shows no evidence of sleep disturbance or shortened duration and electroencephalographic sleep stages are normal.

Idiopathic Insomnia

Idiopathic insomnia develops in early childhood and is usually a lifelong condition. Patients have lifelong difficulty initiating and maintaining sleep and thus have poor daytime function. The cause is unknown.

Insomnia Due to Mental Disorders

Chronic insomnia and psychiatric disorders frequently coexist. Associated psychiatric disorders include depression, anxiety, posttraumatic stress disorder, nocturnal panic attacks, drug or alcohol abuse, and psychotic disorders.

Inadequate Sleep Hygiene

Patients have a pattern of activities that are not conducive to sleep. Such activities include consumption of caffeine, nicotine, or stimulants, frequent daytime naps, irregular sleep-wake cycle, stimulating activities before bedtime, uncomfortable sleep environment, and using the bedroom for activities other than sleep.

Behavioral Insomnia of Childhood

Behavioral insomnia of childhood is most common in children aged 0 to 5 years, but it may persist into middle childhood and beyond. It includes the sleep-onset association subtype and the limit-setting subtype. In sleep-onset association, the infant or child has learned to fall asleep under only certain conditions such as bed rocking or being in the parents' bedroom.

The limit-setting subtype is common in children of preschool age or older. It is characterized by active resistance, verbal protests, and repeated demands at bedtime.

Insomnia Associated With Another Condition

Many conditions may result in insomnia, including certain medical disorders and use of certain medications (Box 87.2).

Box 87.2 • Conditions and Medications That May Result in Insomnia

- Comorbid medical conditions
  - Arthritis/other rheumatologic disease
  - Pulmonary disease (eg, COPD)
  - Congestive heart failure
  - Parkinson disease/Alzheimer disease
  - Hyperthyroidism
  - Cancer
  - Urologic disease
  - Pain
  - Endocrine disorders
  - Gastrointestinal diseases
- Medication or supplement
  - Central nervous system stimulants
  - Respiratory stimulants (eg, β-agonists)
  - Appetite suppressants
  - Calcium channel blockers
  - Select antidepressants
  - Glucocorticoids
  - Rebound insomnia from discontinuation of certain medications

Abbreviation: COPD, chronic obstructive pulmonary disease.

In addition, certain primary neurologic diseases may result in insomnia such as Parkinson disease and Alzheimer disease.

Chronic insomnia can be due to underlying sleep disorders, such as restless legs syndrome, periodic limb movement disorder, sleep apnea, and circadian rhythm sleep disorders.

Agyrpnia Excitata

Agyrpnia excitata is a syndrome characterized by the inability to sleep associated with a generalized motor and autonomic over-activation. Oneiric stupor episodes are a feature of agyrpnia excitata. During these episodes, patients perform simple automatic gestures mimicking daily-life activities. Agyrpnia excitata comprises 3 different conditions: fatal familial insomnia, delirium tremens, and Morvan syndrome. Fatal familial insomnia is a hereditary prion disease characterized by loss of sleep, oneiric stupor with autonomic or motor hyperactivity, pyramidal signs, myoclonus, dysarthria or dysphagia, and ataxia. Genetic analysis discloses a mutation at codon 178 of the prion-protein gene (*PRNP*). Fatal familial insomnia can be transmitted to experimental animals. Sporadic fatal familial insomnia cases are rare but can occur without *PRNP* mutation. Profound thalamic hypometabolism or atrophy is documented with positron emission tomography. During polysomnography, lack of sleep spindles and loss of delta sleep are noted. Creutzfeldt-Jakob disease can present with sleep-wake disturbances similar to those reported in fatal familial insomnia.

Patients with Morvan syndrome present with widespread neurologic symptoms involving the peripheral nervous system (neuromyotonia), autonomic system, and the central nervous system. Severe insomnia and autonomic and central nervous system hyperexcitability occur. Many patients have anti–voltage-gated potassium channel antibodies. Some cases are paraneoplastic due to underlying thymoma, lung cancer, testicular cancer, and lymphoma. Plasma exchange and tumor resection are effective.

Treatment

Patients with insomnia should receive therapy for any medical condition, psychiatric illness, substance abuse, or underlying sleep disorders that may be precipitating or exacerbating the insomnia. All patients should receive counseling about sleep hygiene such as maintaining a regular sleep schedule, trying not to force sleep, avoiding caffeine or alcohol, adjusting the bedroom environment, avoiding daytime naps, exercising regularly, and resolving concerns or worries before bedtime.

Behavior therapies include stimulus control, relaxation, sleep restriction therapy, cognitive therapy, and cognitive behavior therapy. Behavior therapy can be used alone or in combination with medications.

Pharmacologic therapy for insomnia includes benzodiazepines, nonbenzodiazepine sedatives, and melatonin agonist (see also Chapter 84, "Neuropharmacology of Sleep"). Risks of pharmacologic therapy include adverse effects and physical and psychologic addiction with long-term use. Over-the-counter herbal products, supplements, and alcoholic beverages have been used as sleeping aids; however, these agents (eg, valerian, melatonin, alcohol) are not regulated by the US Food and Drug Administration.

- Agyrpnia excitata is a syndrome characterized by the inability to sleep associated with a generalized motor and autonomic over-activation.
- Agyrpnia excitata comprises 3 different conditions: fatal familial insomnia, delirium tremens, and Morvan syndrome.
- Patients with insomnia should receive therapy for any medical condition, psychiatric illness, substance abuse, or underlying sleep disorders that may be precipitating or exacerbating the insomnia. Behavior therapy can be used alone or in combination with medications. Pharmacologic therapy for insomnia includes benzodiazepines, nonbenzodiazepine sedatives, and melatonin agonist.

Parasomnias

Parasomnias are abnormal states of behavior and experience in which basic instincts are inappropriately unleashed during sleep, these experiential or physical phenomena are often undesirable, and nondeliberate. They occur during the transition from wakefulness into sleep or during arousals from sleep. Parasomnias are subdivided into several groups: arousal disorders or intrusion of wakefulness into non–rapid-eye-movement (NREM) sleep, parasomnias usually associated with REM sleep, and other parasomnias (Box 87.3).

NREM Sleep Parasomnia: Confusional Arousals

Confusional arousals are more common in children (up to 20%) than adults (2%–5%). The episodes may be precipitated by forced awakening, anxiety, fever, endocrine factors, sleep deprivation such as circadian rhythm sleep disorders, and the use of central nervous system depressants or alcohol.

Confusional arousals (or sleep drunkenness) usually take place in the first part of the night during deep sleep or slow-wave sleep. Patients are partially awake and appear confused without recollection of the event. The event usually lasts a few minutes but can persist for as long as 1 hour.

Box 87.3 • Overview of Parasomnias

- NREM parasomnia
  - Confusional arousals
  - Sleepwalking
  - Sleep terrors
  - Sleep-related eating disorder
  - Bruxism (teeth grinding)
  - Sleep talking
- REM parasomnia
  - Nightmares
  - Recurrent isolated sleep paralysis
  - REM sleep behavior disorder
  - Catathrenia (sleep groaning)
- Other
  - Sleep enuresis
  - Exploding-head syndrome
  - Sleep-related hallucinations
  - Hypnic jerks

Abbreviations: NREM, non–rapid-eye-movement; REM, rapid eye movement.

Polysomnography shows arousals from slow-wave sleep most commonly during the first third of the night. During a spell, electroencephalography may show brief episodes of delta activity, stage I theta patterns, repeated microsleeps, or diffuse or poorly reactive alpha rhythm.

The course is benign, and nonpharmacotherapy includes sleep hygiene, limiting exposures to central nervous system depressants and alcohol, and managing coexistent sleep disorders.

NREM Sleep Parasomnia: Sleepwalking

Sleepwalking, or somnambulism, is common in children between the ages of 4 and 8 years. Sleepwalking is a dissociated state consisting of motor activation or arousal during slow-wave sleep. Somnambulism is common in patients with Tourette syndrome or migraine headaches. A sleep walking episode often lasts from 1 to 5 minutes. It involves a series of complex behaviors that occur within the first third of the sleep period during slow-wave sleep. These events can range from simple to complex, such as walking, moving objects, urinating, walking through a window, and driving a car. Precipitating factors include the use of medication such as lithium, hypnotics, and antihistamines, and consumption of alcohol and other medications can increase the arousals.

Polysomnography typically shows that sleepwalking begins during slow-wave sleep, most commonly toward the end of the first or second episode of slow-wave sleep. Electroencephalographic results are normal. Sleepwalking is treated by avoiding the precipitating factors and establishing a safe living environment. If behaviors are potentially injurious, benzodiazepines or tricyclics antidepressants can be prescribed. A behavioral technique called anticipatory or scheduled awakening has been successful in children.

NREM Sleep Parasomnia: Sleep Terrors

Sleep terrors, or parvor nocturnus, begin with incomplete arousals from slow-wave sleep and are associated with activation of the autonomic nervous system and reports of frightening imagery. The estimated prevalence is approximately 5% in children and 1% to 2% in adults. Predisposing factors include forced awakening from slow-wave sleep, febrile illness, sleep deprivation, emotional stress, and use of central nervous system depressants or alcohol.

Patients may show signs of extreme fear, abruptly scream, have incoherent vocalizations, or have variable motor activity associated with sympathetic activity including tachycardia, tachypnea, and sweating. The spells may be dangerous and self-injurious. These episodes usually last between 30 seconds and 3 minutes.

Children with sleep terrors tend to outgrow them. Adults with sleep terrors should be thoroughly assessed for comorbid psychiatric disorders. Treatment is usually reassurance and avoiding precipitating factors. A low-dose short-acting benzodiazepine or tricyclic antidepressant may be required when the episodes are frequent and disruptive.

NREM Parasomnia: Sleep-Related Eating Disorder

Sleep-related eating disorder is considered a parasomnia, and night eating syndrome (NES) is an eating disorder; however, the distinction between them is controversial. Zolpidem can induce sleep-related eating disorder in susceptible persons.

Sleep-related eating disorders are recurrent episodes of eating during sleep without being aware of the activity. The food or items consumed may be high in calories, inedible, or toxic. This disorder is more common in women and mostly occurs in the third decade of life. Some patients have unexplained weight gain and lack of appetite in the morning. Sleep-related eating disorder may be idiopathic or occur in patients with a history of other sleep disorders such as sleepwalking, periodic limb movement disorder, restless legs syndrome, and sleep-related breathing disorders.

Treatment usually involves treating the underlying sleep disorder, if present. Medications that have been reported for treatment include topiramate, dopaminergic medications, clonazepam, and lithium.

REM Parasomnia: Nightmares

Nightmares are long, complicated, frightening dreams that can wake a person from REM sleep. Memory of the nightmare is generally detailed and vivid, unlike sleep terrors. Nightmares are often associated with emotions of fear and anxiety. The peak age for nightmares is between 6 and 10 years, but they can also occur in adults. Predisposing factors include personality traits, daytime stress, medications, and an underlying psychiatric disorder.

Polysomnography may show an abrupt awakening from REM sleep that typically lasts 10 minutes and is associated with increased blood pressure and sweating during the attack. Nightmares can also occur in NREM sleep, especially in stage N2 after traumatic events.

Treatment is usually reassurance. Imagery rehearsal has been successful in reducing nightmare frequency. For severe or refractory cases, the short-term use of a REM-suppressing agent such as tricyclic antidepressant or selective serotonin reuptake inhibitor may be helpful.

REM Parasomnia: Recurrent Isolated Sleep Paralysis

Recurrent isolated sleep paralysis is a period of inability to perform a voluntary movement at sleep onset (hypnagogic) or on awakening (hypnopompic). Movements of the skeletal muscles of the limbs, trunk, and head are not possible, whereas ocular and respiratory movements remain intact. These episodes can last a few minutes and resolve spontaneously or after stimulation.

Precipitating factors include sleep deprivation and disturbances of the sleep-wake cycle. Differential diagnosis includes cataplexy, atonic epileptic seizures, hypokalemic paralysis, and psychotic states with immobility. Recurrent isolated sleep paralysis can be controlled with L-tryptophan.

REM Parasomnia: REM Sleep-Behavior Disorder

In REM sleep-behavior disorder (RBD), episodes of dream-enacting behaviors are associated with loss of muscle atonia during REM sleep. The estimated prevalence in the general population is 0.5%. Ninety percent of patients are men, and the highest incidence is after age 50 years. Approximately 60% of RBD cases are idiopathic, and the remaining cases are associated with underlying neurologic disorders such as neurodegenerative disorders with dementia (synucleinopathies such as multiple system atrophy or diffuse Lewy-body disease), stroke, multiple sclerosis, and brainstem neoplasm. RBD usually presents in the sixth or seventh decade of life. It may be the first manifestation of the underlying disorder and may precede the clinical manifestations of the underlying neurologic disease by more than a decade.

Spells can consist of talking, yelling, screaming, punching, leaping, or running that correlates with the reported dream imagery. Episodes can be associated with injury to the patient or bed partner and may require medical attention. Spells typically occur in the latter half of the night when REM sleep is more common. Eyes closed during the episode, rapid awakening, and dream recall are the norm. The transient, or acute, form of RBD may occur in the setting of toxic or metabolic disorders, most commonly including withdrawal from use of alcohol and abrupt withdrawal of use of sedative hypnotic agents accompanied by REM rebound.

Positron emission tomography and single-photon emission computed tomography have shown both reduction in striatal dopamine transporters and reduced density of striatal dopaminergic terminals in patients with idiopathic RBD.

Polysomnography shows augmented muscle tone during REM sleep exceeding the normal REM sleep–related-electromyographic twitches (Figure 87.2).

Treatment of RBD usually consists of either clonazepam or melatonin. However, imipramine, carbamazepine, temazepam, levodopa, or pramipexole may also be used. Environmental safety must be emphasized for every patient.

REM Parasomnia: Catathrenia (Sleep-Related Groaning)

Episodes of catathrenia typically involve a prolonged loud groaning sound during expiration. Catathrenia typically occurs during REM sleep but can also occur during non-REM stages. Catathrenia is different from somniloquy (sleep talking). Patients are usually unaware of the problem. Reassurance is typically the treatment of choice because drugs and continuous positive airway pressure produce inconsistent results.

Other Parasomnia: Sleep Enuresis

Sleep enuresis is characterized by recurrent or involuntary urination during sleep. Bedwetting becomes pathologic when it occurs twice weekly or more during sleep in patients who are at least 5 years old. Primary enuresis refers to the inability to obtain urinary control from infancy, and secondary enuresis has periods of remaining dry during sleep for at least 6 months in duration. Patients with primary enuresis may have a neurologic impairment or deficient release of vasopressin.

Treatment generally includes reassurance and positive reinforcement in children. An enuresis alarm or pharmacologic intervention with desmopressin is useful. Patients should avoid drinking fluids during the evening, and behavioral conditioning treatments may be effective.

Other Parasomnia: Sleep Talking

Sleep talking, or somniloquy, consists of speaking words or sounds during sleep without any awareness of the event.

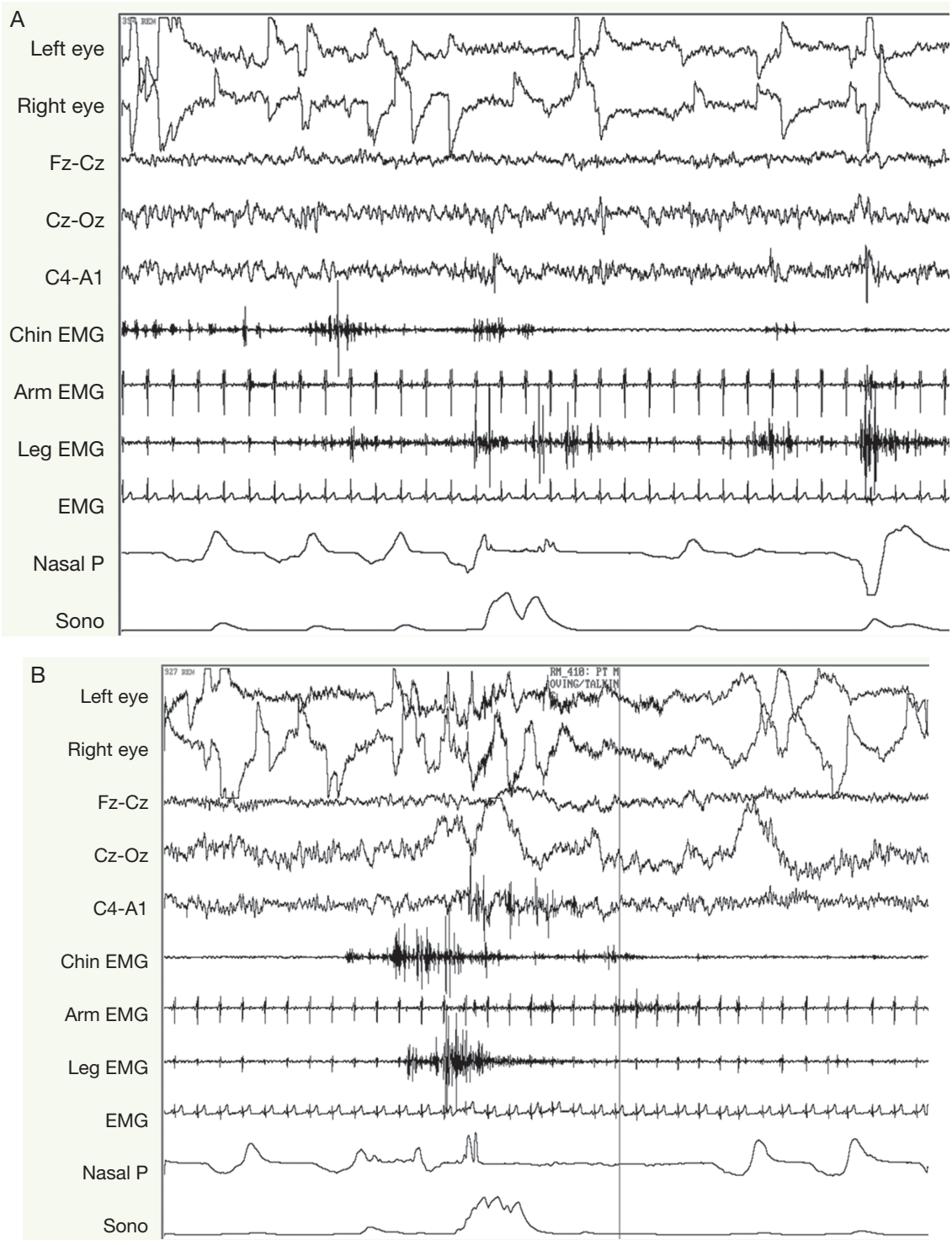

Figure 87.2 *Rapid-Eye-Movement (REM) Sleep Without Atonia.*
A, Increased muscle tone in chin, arm, and anterior tibialis electromyographic (EMG) leads. Some of the periods of loss of muscle atonia were associated with video evidence of excessive movements (punching in the air, kicking) and talking, laughing, and screaming (B), which made the diagnosis of REM sleep behavior disorder possible. Muscle artifact is also present in the eye and electromyographic channels (30-second epochs). Nasal P indicates nasal airflow; Sono, snore microphone.
(Adapted from Young TJ, Tippmann-Peikert M. Neurology of sleep disorders. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 719–52. Used with permission of Mayo Foundation for Medical Education and Research.)

Precipitating factors include sleep deprivation, emotional stress, febrile illness, and sleep disorders. There is no specific treatment; however, appropriate sleep hygiene and treatment of any underlying sleep disorder can be tried.

Other Parasomnia: Exploding Head Syndrome

Patients report waking up because of a sensation of a loud explosion (sound in their head) that typically occurs just as the patient is falling asleep. The sensation of bursting head explosions is often exacerbated by sleep deprivation and stress.

Treatment is usually reassuring the patient that these events are benign, although treatment with clomipramine is effective.

Other Parasomnia: Sleep-Related Hallucinations

Sleep-related hallucinations occur at sleep onset or on awakening. They usually are visual but can also include auditory, tactile, or comedic sensations. Events are typically brief but can last for a few minutes and can range from simple to complex images and sensations of falling or flying. Sleep-related hallucinations are precipitated by cigarette smoking, sleep deprivation, sedative hypnotics, and certain antidepressants.

Other Parasomnia: Hypnic Jerks (Sleep Starts)

Hypnic jerks typically occur at sleep onset and consist of sudden and brief contractions of the legs and sometimes the arms and head. The jerks occur spontaneously or are due to a stimulus. Hypnic jerks are prevalent and occur in 60% to 70% of the population. Predisposing factors include sleep deprivation, stimulant consumption, stress, and excessive exercise before bedtime.

The differential diagnosis includes myoclonic seizures, fragmentary myoclonus, periodic limb movements of sleep, and startle disease. When episodes are chronic or frequent, they may cause insomnia, awakenings, chronic anxiety, and fear of falling asleep.

The electroencephalographic findings are normal and do not show any cortical potentials related to the twitches. During polysomnography, electroencephalography shows stage N1 sleep drowsiness associated with a vertex sharp wave occurring at the time of the jerk. The electromyographic channel may show brief (<250 milliseconds) high-amplitude potentials. Treatment usually involves reassurance.

- Sleepwalking, or somnambulism, is common in children between the ages of 4 and 8 years. It involves a series of complex behaviors that occur within the first third of the sleep period during slow-wave sleep.
- Sleep terrors, or parvor nocturnus, begin with incomplete arousals from slow-wave sleep and are associated with activation of the autonomic nervous system and reports of frightening imagery.
- Children with sleep terrors tend to outgrow them.
- Nightmares are long, complicated, frightening dreams that can wake a person from REM sleep. Memory of the nightmare is generally detailed and vivid, unlike sleep terrors.
- In REM sleep behavior disorder (RBD), are episodes of dream-enacting behaviors are associated with loss of muscle atonia during REM sleep.
- Approximately 60% of RBD cases are idiopathic, and the remaining cases are associated with underlying neurologic disorders such as neurodegenerative disorders with dementia (synucleinopathies such as multiple system atrophy or diffuse Lewy-body disease), stroke, multiple sclerosis, and brainstem neoplasm.

88 Sleep Disorders in Infants and Children

MARA CVEJIC, DO

Introduction

The prevalence of sleep disorders in children is high; some surveys suggest that roughly 12% of children will report nightly sleep problems and 76% occasional sleep issues. Certain populations are at a much higher risk, such as children with Down syndrome, neuromuscular disease, craniofacial abnormalities, intracranial tumors, epilepsy, and developmental delay.

Children are markedly affected by disturbed sleep architecture or sleep-disordered breathing; several studies have shown a direct association of cognitive deficits and shortened life span. Total sleep time directly correlates with high academic achievement and enjoyment, infrequent illness, and decreased absenteeism. The physiologic explanation behind this correlation continues to elude current understanding of the neuropsychologic changes that occur in children with sleep problems, although there is some theory that they may relate in part to increased cerebral blood flow volume as a physiologic adapted measure to compensate for chronic hypoxemia.

Children may have sleep disorders that are also prevalent in adults, such as narcolepsy, sleep apnea, and restless legs syndrome. These disorders are reviewed in the other chapters of this section.

Normal Sleep Behavior Leading to Referral

Many children are referred for normal sleep phenomena, and it is important to keep in mind that children can have a complex variety of sleep behaviors that are not pathologic (Table 88.1).

- Twelve percent of children will report nightly sleep problems. Certain populations are at a much higher risk, such as children with Down syndrome, neuromuscular disease, craniofacial abnormalities, intracranial tumors, epilepsy, and developmental delay.

Epilepsy and Sleep

Overview

Sleep is generally considered an activating state for seizure activity, especially for children. In the evaluation of children with paroxysmal sleep activity, it can be difficult to distinguish epileptic causes from nonepileptic causes. On polysomnography, identifying respiratory abnormalities that lead to abnormal movements or seizure activity is important.

Children with epilepsy have a high rate of sleep-disordered breathing, estimated at more than 40%. Antiepileptic medications tend to cause weight gain, increasing the risk of obstructive sleep apnea. In addition, benzodiazepines and barbiturates increase relaxation of the upper airway musculature. Both central and obstructive sleep apnea are more frequent; however, it is unclear whether central sleep apnea leads to seizures or vice versa. Children with epilepsy are also at higher risk for periodic limb movement syndrome and sleep pattern disturbance.

Specific Syndromes

Benign epilepsy of childhood is characterized by centrotemporal spikes with epileptiform activity that increases significantly during sleep and drowsiness.

Landau-Kleffner syndrome is a disorder of language and behavioral regression and epileptiform activity.

Abbreviations: EEG, electroencephalography; MPS, mucopolysaccharidoses

Table 88.1 • Normal Sleep Behavior Leading to Sleep Referral

Sleep Behavior	Description
Benign sleep myoclonus of infancy	Myoclonus, diffuse or focal, in an otherwise healthy infant with normal EEG
Sleep starts	Brief myoclonic jerks at transition of wakefulness and sleep
Somniloquy (sleep talking)	Sleep talking occurs most commonly during NREM sleep. It is distinguished from seizures by nonstereotypical speech and no abnormal movements
Nocturnal psychogenic nonepileptic seizures	Episodes of bizarre nonrhythmic movements arising out of wakefulness even though they appear during sleep without an EEG accompaniment
Sandifer syndrome	Nocturnal arousal with posturing and stiffening, sometimes with paroxysmal movements. Often due to gastroesophageal reflux at ages 2 months to 5 years
Sleep paralysis	Episodes of paralysis that occur during transitions of sleep, accompanied by vivid visual and auditory hallucinations. These can be normal but also occur in epilepsy
Jactatio capitus (head banging)	Headbanging, along with body rocking, that occurs in wakefulness or during sleep. Typically, these behaviors occur in autistic children, or children with significant intellectual disability
Nightmares	Unpleasant and frightening dreams, typically in childhood, occurring in the early hours of the morning during REM sleep. The child can typically recall the dream and is fully alert on awakening
Confusional arousals	Confusion on awakening during NREM sleep
Somnabulism (sleep walking)	A parasomnia occurring during stage 3 NREM sleep, often occurring in children or adolescents
Pavor nocturnus (night terrors)	A parasomnia of NREM sleep. Toddlers will arise from deep sleep, usually with horrific screams and a look of panic and terror and are often inconsolable

Abbreviations: EEG, electroencephalography; NREM, non–rapid-eye-movement; REM, rapid-eye-movement.

It occurs in children 3 to 7 years old who are otherwise normally developed. Children acquire the inability to recognize or localize familiar noises or sounds (auditory verbal agnosia). Both expressive and receptive aphasia can be severe. Landau-Kleffner syndrome is commonly associated with an electroenceophalographic (EEG) abnormality distinct for its appearance of continuous spike-and-wave activity in non–rapid-eye-movement sleep but absent in rapid-eye-movement sleep and in the awake state (electrical status epilepticus in slow-wave sleep). Treatment often requires corticosteroids, antiepileptics, and, on occasion, corticotropin.

The seizures of frontal lobe epilepsy are more likely to occur during sleep, and they are often complex, bizarre, violent, and associated with choking or motor activity. Most cases are a result of focal cortical dysplasia located deep within the frontal cortex, undetectable by EEG. Nocturnal frontal lobe epilepsy occurs almost consistently in sleep and shows a familial pattern of inheritance. Currently, the autosomal dominant form has been linked to the gene involving nicotinic acetylcholine receptor subunits (*CHRNA4/CHRNB2*). Unfortunately, only 30% to 35% show epileptiform activity on EEG.

Seizure types are classified as paroxysmal arousals, nocturnal paroxysmal dystonia, or episodic nocturnal wandering. Paroxysmal arousals are short, about 10 to 20 seconds, and occur out of non–rapid-eye-movement sleep, with what appears to be arousal, quickly followed by vocalizations and stereotyped dystonic posturing. Nocturnal paroxysmal dystonia can be 1 to 2 minutes long and is accompanied by complex movements such as kicking, bicycling, flailing limbs, or tonic-clonic seizures. Only about 20% of affected patients with frontal lobe epilepsy have detectable epileptiform activity. Episodic nocturnal wandering initially seems very similar to a paroxysmal arousal but leads to agitated behavior and ambulation. Unfortunately, it is the most difficult to detect on EEG; only about 1 of 50 patients having discernible EEG changes or abnormal imaging.

- Landau-Kleffner syndrome is a disorder of language and behavioral regression and epileptiform activity.
- Landau-Kleffner syndrome is commonly associated with an electroenceophalographic (EEG) abnormality distinct for its appearance of continuous spike-and-wave activity in non–rapid-eye-movement sleep but absent in rapid-eye-movement sleep and in the awake state (electrical status epilepticus in slow-wave sleep).

Neuromuscular Disease and Sleep

Overview

Childhood neuromuscular disease encompasses a large group of congenital and inherited diseases that, although categorized under the broad term of nerve-muscle disease,

are distinctly different from adult disorders and require unique management by multiple childhood subspecialists. Spinal muscular atrophy, muscular dystrophy, mitochondrial and congenital myopathies, myasthenia gravis, hereditary sensory and motor neuropathies, and multiple metabolic diseases are congenital disorders that influence muscle and tone. Prevalence of sleep-disordered breathing is more than 40% in pediatric patients with neuromuscular disease, 10 times higher than that in their general peer group.

Sleep-disordered breathing in children with neuromuscular disease can be due to anatomical anomalies, such as craniofacial deformities, or an underlying disturbance in physiologic function of neuromuscular control. Typically, hypoventilation during sleep is the first manifestation of respiratory muscle weakness before daytime symptoms occur. Lung function tends to follow a restrictive pattern of disease; vital capacity is often less than 60% predicted. Sleep-disordered breathing defines a larger group of breathing patterns: central apnea, obstructive sleep apnea, mixed apnea (central and obstructive), paradoxic breathing, and hypopnea. These patterns of breathing can, in turn, lead to restless sleep, hypoxemia, and carbon dioxide retention. Progression of these problems also leads to autonomic nervous system dysfunction during the daytime and to the cognitive impairment that frequently occurs in children with sleep-disordered breathing.

Assessment of Patients With Neuromuscular Disease for Potential Sleep Disorders

When evaluating a child with neuromuscular disease, historical features (Box 88.1), examination, and additional testing may be useful for determining whether the child has an associated sleep disorder. Pulmonary function tests remain a useful tool for deciding on further testing and treatment. They are a daytime predictor of respiratory function. Central respiratory control can be tested with measurement of mouth pressure in the first 0.1 second of inspiration after an occlusion and is generally normal. Lung compliance tends to be decreased in children with neuromuscular disease compared to that in children with normal lung volumes, but when it is adjusted for a patient's lung volume, it is normal as a result of microatelectasis.

One study of children with neuromuscular disease assessed spirometry results, lung volume, and arterial blood gases and correlated the results with polysomnography results to assess for sleep-disordered breathing. In that study, the forced expiratory volume in the first second of expiration was a sensitive but not specific predictor of sleep hypoventilation, whereas a $Paco_2$ value of 45 mm Hg or more was a sensitive and more specific test. The authors suggested that arterial blood gas testing should be performed once the forced expiratory volume in the first second of expiration decreases to less than 40% of the predicted value, and polysomnography should be considered when the $Paco_2$ value is 45 mm Hg or more, particularly if the base excess is 4 mmol/L or more. The strongest predictor of the onset of sleep-disordered breathing was an inspiratory vital capacity of less than 60%, and an inspiratory vital capacity of less than 40% was the strongest predictor for nocturnal hypercapnic hypoventilation.

Box 88.1 • Historical Features to Assess in Children With Neuromuscular Disease

- Snoring: habitual, if defined as 3 nights/week
- Allergic rhinitis: significant predictor of habitual snoring
- Restless legs
- Nocturnal sweating, nausea, morning headaches, fatigue, poor school performance
- Breathlessness with minimal activity
- Claustrophobia or feeling that air in room is somehow bad
- Dyspnea: difficulty speaking for more than a short time, speaking full sentences, or raising voice
- Inability to lie flat during sleep or while awake, need to sleep sitting up (orthopnea)
- Sleep disruption: trouble falling asleep and staying asleep
- Failure to thrive, weight loss
- Anxiety about going to sleep

- Prevalence of sleep-disordered breathing is more than 40% in pediatric patients with neuromuscular disease, 10 times higher than that in their general peer group.
- Sleep-disordered breathing in children with neuromuscular disease can be due to anatomical anomalies, such as craniofacial deformities, or an underlying disturbance in physiologic function of neuromuscular control.

Neurologic Conditions Associated With Sleep Disorders

Smith-Magenis Syndrome

Smith-Magenis syndrome is a congenital disorder characterized by a severely disrupted sleep-wake pattern caused by an inverted pattern of melatonin secretion. It is associated with a deletion of genes on chromosome 17p11.2 or a mutation in the *RAI1* gene.

Facial features are distinctive with multiple dysmorphisms, such as brachycephaly, down-slanting palpebral fissures, a flat midface, and a down-turned mouth. During infancy, parents might report that the child is very friendly

and easygoing, often an excellent sleeper. By age 1 to 2 years, complaints of frequent night awakenings and daytime naps indicate a shortened sleep cycle. By childhood, aggressive behaviors and temper tantrums can progress to self-injurious behaviors; these typically prompt parents to seek medical attention despite global developmental delay early on in the disorder.

Polysomnography is often difficult because of the temperament of the patients; however, actigraphy can be enlightening about their sleep-wake cycles. β_1-Adrenergic blocking agents such as acebutolol can be given in the morning hours to suppress melatonin levels, allowing them to increase again during the nighttime hours.

Autism Spectrum Disorder and Developmental Delay

Autism spectrum disorder and developmental delay affect many children who have pervasive developmental delay. The incidence of sleep disorders in this population is high, almost 90% depending on the disorder being studied. Angelman syndrome, Prader-Willi syndrome, and Williams syndrome are all genetic disorders that have sleep disturbance as a diagnostic criterion.

Children with Angelman syndrome, otherwise known as the happy puppet syndrome, have problems with sleep maintenance and nocturnal seizures. The syndrome is often distinguishable on examination by balance problems, wide-based gait, puppet-like hand movements, and cheery disposition.

Prader-Willi syndrome is a disorder of hyperphagia, obesity, hypogonadism, and mental retardation. Affected children often have excessive daytime sleepiness, and studies suggest that more than 50% have obstructive sleep apnea. Rapid-eye-movement abnormalities have also been found in children with Prader-Willi syndrome (severely shortened rapid-eye-movement latency), and associations with narcolepsy have been made.

Autism is linked to sleep-onset insomnia, sleep-maintenance insomnia, and nocturnal seizures. Autism has become a very widely recognized group of disorders, often leading to parental-initiated referral with many misperceptions and media-guided bias. Children have stereotyped and repetitive behaviors such as hand flapping, wringing, and echolalia. They have impaired social interaction, speech delay, and a wide range of IQs that can vary from highly functional to severely mentally retarded. Children with autism have shortened sleep times in 24 hours, less time spent in bed at night, and shorter naps than children with developmental delay without autism and healthy, normally developing children.

Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a group of disorders such as Hurler syndrome (MPS I), Hunter syndrome (MPS II), and Sanfilippo syndrome (MPS III). These are a group of inherited lysosomal storage diseases, all leading to a different genetic expression depending on the glycosaminoglycan that accumulates in the body, causing symptomatic disease (see Chapter 74, "Lysosomal Storage Disorders"). All of these mucopolysaccharidoses lead to deposition of glycosaminoglycan in body tissue, causing tongue hypertrophy and enlarged adenoidal and laryngeal mucosa. Obstructive sleep apnea has been found in up to 95% of children with MPS, put at risk despite adenotonsillectomy, because the adenoids will regrow in most children. In addition, vocal chord abnormalities and kyphoscoliosis predispose them to further obstructive symptoms.

Sanfilippo syndrome, or MPS III, manifests almost immediately after birth with severe insomnia. Deposition of glycosaminoglycan heparin sulfate affects the brain from a very early age, leading to seizures and aggressive and destructive behaviors. Children with Sanfilippo syndrome are different from those with other types of MPS in that they have chaotic sleep patterns, with insomnia so severe that it becomes disruptive to the whole family.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder in children is characterized by overstimulation, hyperactivity, impulsivity, and difficulty maintaining attention for significant periods. Problems with sleep are linked both directly and indirectly to children with this disorder. Often, stimulant medication used for treatment can disrupt sleeping habits. More recently, several studies have shown that the disorder is a risk factor for restless legs syndrome.

Rett Syndrome

Rett syndrome is a developmental disorder of girls that results in regression of milestones at age 1 to 2 years. They have a high prevalence of sleep disorders; 80% to 95% of parents report issues to physicians. Interestingly, their sleep issues are age- and mutation-related, and most problems improve with age and almost all sleep problems are linked to certain deletion types. Mutation in the MECP2 or methyl-CpG binding protein 2 leads to abnormal protein function. This protein is needed for proper brain development, acting as one of the many biochemical crossing-guards that can either increase gene expression or tell other genes when to turn off and stop producing their own unique proteins.

A typical course of Rett syndrome in a young girl begins with normal development. The child will be walking and beginning to talk, and over time parents notice hand flapping or wringing movements, and the child will lose speech ability. Hypotonia, toe walking, and autistic-like features are common. Microcephaly, eventual loss of purposeful hand function, and seizures that are difficult to control are the hallmark of this neurodegenerative disease.

Children with Rett syndrome have a pathognomonic breathing disorder while awake with periods of hyperventilation followed by apneas, but surprisingly do not have much sleep-disordered breathing at night. The sleep disturbances in Rett syndrome are most frequently nighttime laughter, nocturnal seizures, teeth grinding, nighttime screaming, and frequent daytime napping.

Down Syndrome

Down syndrome due to trisomy 21 is characterized by distinct facial features—upslanting palpebral fissures, epicanthal folds, single palmar crease on the hand, small ears, and craniofacial abnormalities (see also Volume 1, Chapter 30, "Chromosal Syndromes"). Patients are at increased risk for cardiac anomalies, gastrointestinal abnormalities, leukemia, and other medical issues. Most notably, their craniofacial structures—maxillary hypoplasia, a large posteriorly placed tongue, small nose, and absent frontal and sphenoid sinuses—form a relatively crowded oropharyngeal airway. In addition, they typically have obesity, hypotonia, tracheal abnormalities, and gastroesophageal reflux disease, all predisposing them to upper airway resistance and obstructive sleep apnea. Obstructive sleep apnea is so common in Down syndrome that several experts recommend performing polysomnography after the age of 3 years in all children with this diagnosis.

Adenotonsillectomy is first-line treatment but is often followed by residual or recurrent obstructive sleep apnea. Continuous positive airway pressure or biphasic positive airway pressure is used, similar to use in other children; however, rates of failure are higher because of intolerance for facial masks. If desensitization therapy does not work, maxillary midface advancement, tongue-base reduction, and mandibular distraction can be offered.

Chiari Malformation

Chiari malformation, a caudal herniation of the cerebellar tonsils more than 5 mm below the foramen magnum, can result in sleep-disordered breathing. Both cervicomedullary compression from herniation and cervical syrinx formation can cause bulbar weakness. Oropharyngeal dysfunction from cranial nerve weakness can cause lingual atrophy, absent gag reflex, soft-palate weakness, and bilateral abductor vocal cord paralysis. Both central and obstructive sleep patterns occur.

Obstructive hydrocephalus and mechanical compression can be treated surgically, but immature development of the respiratory center in the brainstem and ischemic or hemorrhagic changes are beyond the help of modern medicine. Magnetic resonance imaging of the craniocervical junction in flexion and extension can aid in treatment guidance by providing dynamic imaging. Often, there is controversy surrounding the level at which to treat Chiari malformations, and polysomnography can help guide a surgeon on whether the malformation is symptomatic, and hence requires posterior fossa decompression.

- Autism is linked to sleep-onset insomnia, sleep-maintenance insomnia, and nocturnal seizures.
- The sleep disturbances in Rett syndrome are most frequently nighttime laughter, nocturnal seizures, teeth grinding, nighttime screaming, and frequent daytime napping.
- Obstructive sleep apnea is so common in Down syndrome that several experts recommend performing polysomnography after the age of 3 years in all children with this diagnosis.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

XIV.1. A 17-year-old boy is brought in by his parents for evaluation of a several-month history of episodic hypersomnia (sleeping 20 hours daily) lasting several weeks. The episodes were punctuated by brief waking periods with a prodigious appetite; between episodes he had a spontaneous return to normal. Which of the following is the most likely diagnosis?
a. Narcolepsy
b. Agyrpnia excitata
c. Kleine-Levin syndrome
d. Idiopathic hypersomnia
e. Normal adolescent sleep behavior

XIV.2. Which of the following statements regarding restless legs syndrome (RLS) is most correct?
a. It is frequently associated with periodic limb movements of sleep
b. Dopamine-agonist therapy should not be used until all other pharmacologic options have been exhausted
c. Augmentation, or gradual improvement of nocturnal symptoms, often occurs in chronic RLS
d. Correction of iron deficiency plays no role in the management of RLS
e. The prevalence of RLS is low (1%–2% of the population)

XIV.3. Which of the following parasomnias is associated with rapid-eye-movement sleep?
a. Pavor nocturnus
b. Somnambulism
c. Bruxism
d. Confusional arousals
e. Recurrent isolated sleep paralysis

XIV.4. Progressive synucleinopathies such as idiopathic Parkinson disease are most likely to develop in patients who have which one of the following parasomnias?
a. Nocturnal enuresis
b. Sleep talking
c. Catathrenia
d. Rapid-eye-movement sleep behavior disorder
e. Exploding head syndrome

XIV.5. Which of the following pediatric disorders is associated with disordered daytime breathing but not sleep-disordered breathing?
a. Congenital myasthenic syndromes
b. Rett syndrome
c. Trisomy 21 (Down syndrome)
d. Spinal muscular atrophy
e. Chiari malformation

XIV.6. Which of the following disorders is associated with electrical status epilepticus in slow-wave sleep?
a. Benign epilepsy with centrotemporal spikes
b. Autosomal dominant nocturnal frontal lobe epilepsy
c. Smith-Magenis syndrome
d. Childhood absence epilepsy
e. Landau-Kleffner syndrome

XIV.7. Which of the following statements about the multiple sleep latency test (MSLT) is most correct?
a. To maximize sensitivity, it should be performed only after 1 or 2 nights of sleep deprivation (around 4 hours per night)
b. It may be unnecessary to perform an MSLT if a cause for excessive daytime sleepiness is discovered on routine polysomnography
c. Commonly prescribed medications are unlikely to affect the results of the MSLT
d. Six sequential naps are performed in a complete MSLT
e. Sleep-onset rapid-eye-movement period noted on one nap of the MSLT is highly specific for narcolepsy

XIV.8. Which of the following recordings is unnecessary during routine polysomnography?
a. Nasal and oral airflow
b. Surface electromyogram
c. Electrocardiogram
d. Blood pressure
e. Electroencephalogram

XIV.9. Which of the following statements regarding the pharmacology of sleep-promoting agents is most correct?
a. Ramelteon acts as a melatonin-receptor agonist
b. Diphenhydramine acts as a histamine-receptor agonist
c. Zolpidem acts as a γ-aminobutyric acid–receptor antagonist
d. γ-Hydroxybutyric acid acts as a γ-aminobutyric acid–receptor antagonist
e. Mirtazapine acts as a histamine-receptor agonist

XIV.10. Which of the following statements regarding the pharmacology of alertness-promoting agents is most correct?
a. Modafinil inhibits dopamine release in the basal forebrain
b. Methylphenidate blocks dopamine transporters
c. Amphetamines inhibit norepinephrine release
d. Caffeine acts as an adenosine agonist
e. Armodafinil has a mechanism of action distinct from that of modafanil

XIV.11. You evaluate a 50-year-old obese man who has excessive daytime sleepiness. His polysomnogram shows moderate obstructive sleep apnea. Which of the following is the most appropriate first-line therapy?
a. Maxillary advancement
b. Uvulopalatopharyngoplasty

c. Tracheostomy
d. Tongue-base reduction surgery
e. Nocturnal continuous positive airway pressure

XIV.12. Which of the following statements regarding obstructive sleep apnea (OSA) is most correct?
a. Less than 1% of the adult US population has OSA
b. Obesity modestly reduces the risk of developing OSA
c. Patient perception of daytime sleepiness is subjective and therefore is not a useful screen for OSA
d. OSA is associated with a higher risk of vascular events such as myocardial infarction and stroke
e. The diagnosis of OSA can be established solely on the presence of snoring

Answers

XIV.1. Answer c.
Silber MH, Krahn LE, Morgenthaler TI. Sleep medicine in clinical practice. London (UK): Taylor & Francis; c2004. 392 p.

XIV.2. Answer a.
Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 5th ed. Philadelphia (PA): Saunders/Elsevier; c2011. 1723 p.

XIV.3. Answer e.
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XIV.4. Answer d.
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XIV.5. Answer b.
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XIV.6. Answer e.
Sheldon SH, Ferber R, Kryger MH. Principles and practice of pediatric sleep medicine. Philadelphia (PA): Saunders; c2005. 356 p.

XIV.7. Answer b.
Avidan AY, Barkoukis TJ, editors. Review of sleep medicine. 3rd ed. Philadelphia (PA): Elsevier/Saunders; c2012. 770 p.

XIV.8. Answer d.
Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester (IL): American Academy of Sleep Medicine; c2007. 59 p.

XIV.9. Answer a.
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XIV.10. Answer b.
Avidan AY, Barkoukis TJ, editors. Review of sleep medicine. 3rd ed. Philadelphia (PA): Elsevier/Saunders; c2012. 770 p.

XIV.11. Answer e.
Silber MH, Krahn LE, Morgenthaler TI. Sleep medicine in clinical practice. London (UK): Taylor & Francis; c2004. 392 p.

XIV.12. Answer d.
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Section
XV

Neurology in Practice

Lyell K. Jones Jr, MD, *editor*

89 Neuroethics

JIMMY R. FULGHAM, MD

Introduction

Medical ethics is the system of morally defined values and principles applied to the practice of medicine. Medical ethics has been central to the practice of medicine since antiquity. Ethical behavior was clearly a cornerstone of the behavior expected of the physician in the Hippocratic oath. Ethical behavior is not only important in the physician's practice, but is the expectation of the individual patient when interacting with a physician, and it is an expectation of society in general. Paramount to the ethical practice of medicine is the maintenance of the doctor-patient relationship. Medical ethics instruction is now required in medical schools and most residency programs. Trainees are taught through didactics and also by observing the behaviors of mentors, other trainees, and attendings. Every interaction is an opportunity to teach medicine, ethical behaviors in doctor-patient interactions, and decisions related to managing patients. The following sections cover concepts and terminology used in discussions of medical ethics.

- Medical ethics is the system of morally defined values and principles applied to the practice of medicine.

Dilemmas

Dilemmas are commonly encountered during medical decisions when there are alternatives that are equally satisfactory or unsatisfactory, and a solution to dilemmas requires the application of the principles encompassed in the following sections.

Beneficence and Nonmaleficence

Beneficence is a central tenet of medical practice: We physicians will act in the patient's interest and do good. Nonmaleficence is a fundamental goal of our treatment of patients: Do no harm. Although all would agree that the ideal medical practice is to act in the patient's best interests and that our actions should do no harm, this is not always possible. The intent of our actions in the practice of medicine is extremely important, and the intent of the acts needs to have an ethical foundation.

Autonomy and Paternalism

Each patient is an autonomous individual, with some exceptions. Patients who can be coerced, because they are incarcerated, because they are children, or because they otherwise lack the cognitive abilities to make informed decisions, are not autonomous. Otherwise, patients should be encouraged to participate in their health care and in the decisions that are made. The physician's role is to inform and educate the patient about the issues, discuss the options, and guide the decision. This is inherently paternalistic and often defines the doctor-patient relationship. Clashes between patients' autonomy and physicians' paternalism toward their patients often occur. It is therefore important to form a relationship with patients and recognize that patients vary in their understanding of medical conditions and that some patients require a more paternalistic approach. In some situations, the physician acts and recommends a treatment plan with no regard for the patient's autonomous ability to make decisions. This attitude—"either my way or nothing"—is not conducive to maintaining the doctor-patient relationship or to delivering medical care.

Abbreviations: HIPAA, Health Insurance Portability and Accountability Act; PAS, physician-assisted suicide.

Veracity and Fidelity

Veracity (truthfulness) and fidelity (to act in good faith) are the traits that our patients expect of us and we expect of ourselves.

Privacy and Confidentiality

An individual is entitled to privacy when interacting with the medical system in regard to family life, child rearing, and other personal choices. There must be a free and open discussion of the patient's medical condition so that appropriate treatments can be prescribed. Therefore, a patient gives up some privacy but retains the right to confidence of the information given to or gained by the physician or medical staff. A breach of confidentiality occurs if medical information is reviewed by someone without a medical need to review that information.

Breaches can also occur in more subtle ways. Discussing a patient's condition in a public area, even if the patient is not identified by name, is a breach of the confidence that the patient has in the physician or in the medical care team. Discussion of a patient's condition alone may be enough to identify the patient. Leaving written information or electronic information available to others in private areas has the potential to break confidence.

Spouses do not necessarily, by stature, have a right to each other's medical information. A patient should be asked whether it is acceptable for the spouse to be present. Likewise, if the patient wants the spouse to have access to medical records or to discuss care with the physician, a release must be signed and kept with the medical record.

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 describes several privacy mandates and governs who can receive protected health information. This act covers most practitioners using HIPAA-mandated electronic codes for billing purposes. It also mandates physical and electronic safeguards to prevent unauthorized access to protected patient information. The privacy rules were implemented in 2003, and the security rules were implemented in 2004. The Department of Health and Human Services has levied fines on large and small practices that have failed to implement privacy and security measures in accordance with the HIPAA mandates.

Despite the recognized right to privacy and confidentiality, it is not an absolute right. Depending on the context of the interaction, a disclosure such as a court-ordered psychiatric evaluation may not be a breach of confidence. If there is a direct threat to a specific individual, that information need not be held in confidence and should be reported to the proper authorities (under the Tarasoff "duty to warn" rule). Likewise, any concern for the public welfare should be reported, and the information gained is not protected by the right to privacy or confidentiality.

- Dilemmas are commonly encountered during medical decisions when there are alternatives that are equally satisfactory or unsatisfactory.
- The Health Insurance Portability and Accountability Act (HIPAA) of 1996 describes several privacy mandates and governs who can receive protected health information.

Specific Issues in Neuroethics

Disclosure

Disclosure involves providing information to the patient and family about procedures and treatments to be rendered. A prime example is informed consent. Specific medical treatments that carry some risk require discussion of the choices and specific recommendations, which would include alternative therapies.

The amount of information that needs to be given to a patient varies according to the clinical situation. When the situation is emergent, such as status epilepticus or a large acute subdural hematoma, little information can be given to the patient and family because urgent intervention is warranted and necessary.

Elective treatments and procedures require that more information be given to the patient and family members. At the outset, the discussion should include to whom the patient wants information given.

For surgery and some medical procedures that carry significant morbidity and possible mortality, disclosure should include the patient's current medical state and how the proposed procedure will affect the prognosis, with a discussion of the risks, benefits, other options, and uncertainties that exist. It should be clearly stated that the recommendation is a professional opinion based on clinical judgment.

Issues that arise when providing informed consent can be divided into physician-related concerns and patient-related concerns. Physicians often discuss treatment recommendations with technical terms that the patient does not understand. The physician can also be concerned that too much information, including discussion of alternatives, may confuse the patient. Patients who have limited knowledge may feel intimidated in a clinical setting in which they have to make a decision. The patient is likely to have some fear and anxiety. For elective procedures, it may be necessary to discuss these issues again later. Allowing time to ask and answer questions is important during this process or at a later date if necessary.

Truth Telling

Truth telling involves veracity (ie, telling the truth) but also fidelity to the patient. This is often associated with

disorders that carry a poor or terminal prognosis. Some feel that a patient may not want to know that a condition is terminal, such as amyotrophic lateral sclerosis or an inoperable glioblastoma. Fidelity to the patient and not wanting to burden the patient may lead to withholding the diagnosis or prognosis. In interviews with patients, however, most want to know their diagnosis and their prognosis, whether good or bad. At times, family members want information withheld. This can usually be resolved through communication with the family members.

If the medical opinion is that giving the diagnosis or prognosis would be harmful to the patient, such information can be withheld, but this would be a rare situation. The patient's religious and cultural background also need to be taken into account. In some cultures, discussion of risks with a patient means that the negative outcome will occur since it has been discussed.

Conflict of Interest

Conflict of interest occurs when an action is performed or made possible by a person's position as a physician, and the motivation for the action is personal gain. There are processes for physicians to disclose any interests that they or their family members may have with industry. Conflicts of interest need not involve industry and can occur in day-to-day dealings with patients. The information gained is not a conflict unless it is acted on for personal gain.

Physician-Assisted Suicide, Active Euthanasia, and Passive Euthanasia

Physician-assisted suicide (PAS) is a major, ongoing ethical issue worldwide. In PAS and active euthanasia, the physician actively participates in the patient's death. PAS involves a physician providing a patient with the means for suicide or the necessary information when the physician knows that the patient intends to use it to commit suicide. In active euthanasia, the physician directly participates in the patient's death. For passive euthanasia, treatments are withheld, but no active treatments are performed with the intent of promoting the patient's death.

Palliative care, the process that treats pain and discomfort in patients with a terminal condition, is defined as passive euthanasia by some. This does have consequences because some countries ban active euthanasia and passive euthanasia.

Issues related to PAS have particular relevance to neurologic practice. Patients with catastrophic cerebral injury or those with a terminal disorder, such as amyotrophic lateral sclerosis, may request that support be withdrawn or that the care plan be changed to palliation only.

Passive euthanasia and palliative care are examples of the principle of double effect—that is, an action is ethical if it is intended to provide relief to the patient. Although unwanted consequences are foreseen, the unwanted consequences are not the intent of the treatment.

End-of-Life Decision-Making

The term *living will* was coined in 1969 and is a clear expression of a patient's autonomy. Over time, the living will has been redefined as an advanced directive, a document that states the patient's wishes at the end of life and can describe treatments and interventions that the patient finds acceptable. If the patient is incapacitated, a person given power of attorney for health care issues acts as a surrogate. The Patient Self-Determination Act was passed into law by Congress in 1990. This act applies to health care institutions and addresses the patient's right to have an advance directive, which must be addressed with the patient (as an inpatient or outpatient).

Do Not Resuscitate

The do-not-resuscitate order has been firmly established as an option in patient care. Often the order is rescinded during a surgical procedure and if the status is changed, a specific order needs to be entered into the record. Currently, resuscitation is the default action, and a do-not-resuscitate order is based on the wishes of the patient or on those of the patient's health care proxy. Ethical issues may arise when counseling patients and their families regarding the likelihood of meaningful recovery after resuscitation. In those situations, advance directives can be very helpful in guiding the medical team and the family according to the patient's wishes.

Tissue and Organ Donation

Neurology is intimately involved in tissue and organ transplant because most organs and tissues are obtained from cadaver donors who have met the criteria for brain death. The criteria for brain death and the declaration of brain death are well established and have been accepted by the American Academy of Neurology and the American Board of Psychiatry and Neurology.

Public concerns about ethics and transplant include worry over preference for organs based on race or socioeconomic status and whether organs can be bought or sold. Most of these concerns can be allayed. Patients should be in contact with the center doing the transplant because those questions are easily answered.

Ethics Committee

Ethics committees are multidisciplinary groups that perform multiple functions. They can review ethical issues related to inpatient and outpatient medical practice. Committees may have a permanent member to address ethics or members who are available to provide input when

needed. This committee is available to address ethical concerns of the staff during the care of patients in their charge. The service should be available 24 hours a day, and a response should be expected within 48 hours. Depending on the conflict, the decision may be that an ethical issue does not exist, and recommendations can be made on how to solve the dilemma. If an ethical issue does exist, committee members often meet with the parties involved to resolve the problem.

- Disclosure involves providing information to the patient and family about procedures and treatments rendered (eg, informed consent).
- Conflict of interest occurs when an action is performed or made possible by a person's position as a physician, and the motivation for the action is personal gain.
- An ethics committee, composed of a multidisciplinary team, addresses ethical concerns of the staff during the care of patients in their charge.

90 Interpersonal and Communication Skills

MARK C. LEE, MD

Introduction

The practice of medicine is fundamentally based on the creation of relationships developed through effective interpersonal and communication skills. These core skills make up the foundation of the practice of medicine and are independent of medical specialty, medical economic systems, or cultural background. Although communication is enhanced by innate ability of physicians to connect with their patients, several useful techniques can be used to maximize the effectiveness. The goal of this chapter is to review the following:

1. Techniques and concepts in effective patient-centered communication
2. Communication skills that physicians can adapt across challenging communication dilemmas
3. Effective communication skills for physicians as members of intraprofessional and interprofessional health care teams

Patient-Centered Communication

The physician-patient relationship is arguably the most honored partnership, exemplified by implicit trust and confidentiality. Competent communication skills are essential to the development and maintenance of this partnership and can improve health care delivery. Patient adherence, outcomes, and satisfaction can be improved while reducing physician malpractice risk.

The essence of patient-centered communication involves 3 primary functions:

1. Building and maintaining a therapeutic relationship
2. Gathering information from the patient
3. Effectively communicating information to the patient

Although multiple frameworks for patient-centered communication have been described in the literature, key concepts are summarized in the SEGUE framework (Table 90.1).

Set the Stage

Setting the stage with the patient involves not only the initial contact but also the advance preparation that the physician does in reviewing pertinent records, data, and results to help anticipate the flow of the patient care visit. Observation of the patient is important for perceiving and resolving any communication barriers. The problems of the chief complaint should be surveyed, and the physician should connect with the patient and set a clear agenda for the episode of care.

Table 90.1 • SEGUE Approach to Patient-Centered Communication

SEGUE Framework	Structured Behaviors
Set the stage	Greet the patient Connect with the patient Set the agenda for the visit
Elicit information	Obtain the pertinent history Give the patient opportunity and time to talk Clarify information
Give information	Explain the rationale for diagnostic tests Counsel the patient about the medical situation Check the patient's understanding
Understand the patient's perspective	Acknowledge the patient's accomplishments Express caring, concern, and empathy
End the encounter	Ask whether the patient would like to discuss anything else Set goals

Adapted from Makoul G. The SEGUE Framework for teaching and assessing communication skills. Patient Educ Couns. 2001 Oct;45(1):23–34. Used with permission.

Elicit Information

Information should be elicited by asking open-ended questions and allowing adequate opportunity and time for patients to express their concerns. Many complaints from patients stem from the perception that physicians are not skilled listeners. Physicians can overcome this barrier by repeating back to the patient what the physician understood from the information provided.

Give Information

When information is given to patients, the content should be explained in a way that is appropriate for the patient's education level while overcoming communication barriers to optimize understanding. It is important to explain the rationale for diagnostic testing and treatment because the patient has an active role in the informed consent and the decision. The assumption that a patient understands is often inaccurate and can easily be verified through communication.

Understand the Patient's Perspective

Understanding the patient's perspective enhances the physician-patient relationship by promulgating mutual trust and respect. Patients with low trust in their physician are less likely to adhere to therapy and follow-up. A healthy relationship can be fostered by demonstrating empathy and caring through eliciting patients' feelings and concerns about their medical condition as well as acknowledging their accomplishments in adhering to therapy or in reaching clinical goals.

End the Encounter

Upon closure of the clinical visit, patients should be given the opportunity to ask any additional questions they would like to discuss. An agreement should be reached on prioritized problems and a plan for therapy and follow-up negotiated.

- Competent communication skills are essential to the development and maintenance of this partnership and can improve health care delivery.
- Information should be elicited by asking open-ended questions and allowing adequate opportunity and time for patients to express their concerns.
- It is important to explain the rationale for diagnostic testing and treatment because the patient has an active role in the informed consent and the decision.

Managing the Difficult Patient Encounter

The difficult patient encounter is a primary source of physician dissatisfaction and can influence physician attitudes in the delivery of care. Physicians often perceive difficult patients as manipulative, demanding, distrustful, and time consuming. Consequently, physicians may become apathetic to follow-up appointments and order more tests, consultations, and prescription drugs. Studies suggest that difficult patients are more likely than not-difficult patients to have an underlying psychiatric condition such as anxiety, somatoform, panic, major depressive, or substance abuse disorders.

Communicating with patients may be challenging for physicians in certain clinical situations. These situations may unintentionally escalate despite the physician's efforts and require additional assistance from security personnel or legal counsel. Physician attitudes and behaviors are important in successfully managing specific challenging communication scenarios (Table 90.2).

Table 90.2 • Tips for Managing Challenging Patient Communication Scenarios

Clinical Communication Scenario	Structured Behaviors
Managing the angry patient	Ascertain the underlying reason for anger Acknowledge the reasons for anger Allow the patient to express anger Validate the patient's feelings without placing blame Do not tolerate hostility or combativeness Redirect the patient by setting mutual patient-centered, productive goals
Breaking bad news	Set the stage Inquire about the patient's own clinical understanding Disclose information in simple terms Ascertain and allow time for the stages of coping: denial, anger, bargaining, depression, and acceptance Reassure the patient that you will be a partner through the illness Answer questions
Disclosing a medical error	Set the stage Disclose the error without excuses Accept the blame when appropriate Allow the patient to express emotions Understand the patient's perspective Propose a patient-centered solution and follow up for error
Managing the manipulative patient	Set the stage Acknowledge the patient's illness and concerns Express a common goal for the patient's healing Abide by your clinical judgment Redirect negativity toward common goals Be a partner with the patient to set realistic expectations

Interprofessional Communication

Effective interprofessional communication is a necessary process between health care delivery teams to ensure quality medical care. This communication encompasses all aspects of care between physicians, physician extenders, pharmacists, and allied health professionals. The Joint Commission has reported that communication failure was the root cause of over 70% of sentinel events, drawing significant national attention to improving this process. Investments in improving health care communication can improve quality, safety, and patient outcomes in addition to patient and family satisfaction and professional job satisfaction.

The fundamentals of effective interprofessional communication require that health care delivery teams understand and respect all participants' roles. Professional opinions should be clearly expressed to team members in a respectful manner to ensure common understanding. The communication environment should foster active listening, feedback, collaborative decisions, and shared accountability.

The SBAR framework (Table 90.3) was created to improve transfers of care in the health care setting through providing a shared communication model between health professionals. This tool comprises 4 prompts (situation, background, assessment, and recommendation) to promote the sharing of relevant and focused information.

Table 90.3 • SBAR Framework

SBAR Framework	Conveyed Information
Situation	What is happening at the present time? *"Mr. J is a 67-year-old man who has new left-sided weakness"*
Background	What are the circumstances leading up to the situation? *"He has a history of transient ischemic attacks and atrial fibrillation but has not been receiving warfarin for 1 week in anticipation of elective knee surgery"*
Assessment	What do I think is the problem? *"I'm concerned that he has had a stroke"*
Recommendation	What should we do to correct the problem? *"We will need to monitor his neurologic status closely and consider further evaluation, including brain imaging"*

The use of SBAR has been shown to significantly enhance team satisfaction and patient quality metrics.

- The Joint Commission has reported that communication failure was the root cause of >70% of sentinel events.

91 Guide to Maintenance of Certification[a]

LYELL K. JONES JR, MD

Introduction

Until relatively recently, *board preparation* meant simply studying for and hoping to pass the board certification examination. Since the final approval of the Maintenance of Certification (MOC) Program by the American Board of Medical Specialties (ABMS) in 2006, board certification has evolved from a 1-step event to a continuous and multifaceted process.

In addition to providing a thorough review of medical knowledge of neurology and related topics, the *Mayo Clinic Neurology Board Review* provides the reader with a guide to the MOC process. Furthermore, this book has been approved for up to 109.25 continuing medical education (CME) credits (32 for volume 1 and 77.25 for volume 2) and additional self-assessment (SA) credits (explained further below), which can be applied to your American Board of Psychiatry and Neurology (ABPN) recertification. These credits are available for purchase separately and can be accessed at https://ce.mayo.edu. This chapter outlines the background and features of MOC as it applies to neurologists and provides guidance on how to navigate what some perceive to be a complex and confusing program.

ABPN certification and MOC requirements are in a constant state of evolution, and the ABPN website (http://www.abpn.com) should be reviewed before and periodically during certification or recertification preparation. In other words, although this chapter provides an overview of MOC, the reader *must* refer directly to the ABPN for detailed, up-to-date requirements.

- This book has been approved for up to 109.25 CME credits and additional SA credits, which can be applied to your ABPN recertification.
- ABPN and MOC requirements are in a constant state of evolution, and the ABPN website (http://www.abpn.com) should be reviewed before and periodically during certification or recertification preparation.

Background

Historically, the determination of qualification in medicine has occurred largely at the training level. That is, the determination of a physician's ability to provide the minimum standard of care was made primarily by the successful completion of an approved or otherwise adequate training program (eg, medical school, residency, or fellowship) followed in most cases by passing a board certification examination. In the 1990s, the development of recertification examinations by member boards of the ABMS introduced the measurement of medical knowledge as a requirement for continuing specialty certification. However, ABMS certification generally is not a requisite for the practice of medicine, and the board certification process has not historically included measures of other, important components of quality of care, such as professionalism, patient satisfaction, or clinical outcomes. In 2000, member boards of the ABMS agreed to develop models of continuous professional development, and in 2006 the resulting MOC programs were approved for implementation. Member boards, including the ABPN, incorporated ongoing quality

[a] Portions previously published in Jones LK Jr, Arnold ML, Gleveckas-Martens NG, Narayanaswami P, Brock LA, Dawodu ST, et al. Continuous quality improvement in neuromuscular and electrodiagnostic practice: an educational review of the AANEM Quality Improvement Committee. Muscle & Nerve. 2013 Jun;47(6):943–9. Used with permission.

Abbreviations: ABMS, American Board of Medical Specialties; ABPN, American Board of Psychiatry and Neurology; ACCME, Accreditation Council for Continuing Medical Education; ACGME, Accreditation Council for Graduate Medical Education; CME, continuing medical education; C-MOC, Continuous Maintenance of Certification; MOC, Maintenance of Certification; PIP, Performance in Practice; SA, self-assessment

self-measurement and improvement in practice (ie, Performance in Practice [PIP]) as a required element of continued certification. In contrast to prespecified quality measures, these programs provide practitioners an opportunity to identify areas in their own practice that may be improved after referring to literature or guidelines on specific topics relevant to their practice.

Components of MOC

The goal of the ABPN MOC program as stated on its website (http://www.abpn.com/moc.html), is to "advance the clinical practice of psychiatry and neurology by promoting the highest evidence-based guidelines and standards to ensure excellence in all areas of care and practice improvement." Quality of care is assessed within the 6 core domains of competence identified by the ABMS and the Accreditation Council for Graduate Medical Education (ACGME) in 1999 (Box 91.1).

Four components of MOC are used to assess qualification within the 6 competencies for all applicants: licensure and professional standing, lifelong learning and SA, cognitive expertise, and practice performance assessment.

Licensure and Professional Standing

Neurologists seeking ABPN recertification must hold a valid, unrestricted medical license in at least 1 state or jurisdiction in the United States or its territories or in Canada.

Lifelong Learning and SA

Participation in ongoing educational and SA programs is required for ABPN recertification. This requirement is divided into 2 separate but related components: CME and SA.

Continuing Medical Education

A total of 30 conventional CME credits per year are required for recertification (the credits may be averaged over a 3-year period, so that obtaining 25, 25, and 40 credits in consecutive years is acceptable). The CME must be relevant to neurology or to 1 of its subspecialties and must be Category 1 CME accredited by the Accreditation Council for Continuing Medical Education (ACCME), Category 1-A CME accredited by the American Osteopathic Association, or Category 1 CME accredited by the Royal College of Physicians and Surgeons of Canada. Further, a proportion of these CME credits must be SA credits (discussed below).

Self-assessment

The ABPN requires that, on average, 8 of the 30 annual CME credits must fulfill SA criteria. As of 2014, SA credit activities must have prior approval of the ABPN and must meet the following requirements:

Box 91.1 • The 6 Core Domains of Competence in Medical Practice

Patient care
Medical knowledge
Practice-based learning and improvement
Professionalism
Interpersonal and communication skills
Systems-based practice

1. Cover new knowledge or current best practices in 1 or more of the 6 competency domains
2. Guide focused CME, lifelong learning, or professional development
3. Include recommended literature resources for each question
4. Include comparative performance to peers
5. Include the correct answer
6. Be approved for Category 1 CME credit by an accredited organization

Additionally, beginning in 2014, MOC participants may apply a limited amount of non-CME activity to SA credit (eg, peer-reviewed publications or grant applications). Additional changes will be forthcoming. For example, in 2016, all participants who complete certification or recertification will have to complete an approved patient safety course.

As mentioned in the Introduction section above, readers of the *Mayo Clinic Neurology Board Review* are eligible to purchase CME and SA credits, which may be applied to this requirement.

Cognitive Expertise

The most recognizable component of MOC is the assessment of medical knowledge through the recertification examination. The majority of the content of the *Mayo Clinic Neurology Board Review* (much like most board review products) is designed to prepare the applicant for the medical knowledge assessment included in the certification and recertification examinations. Specific content outlines are available on the ABPN website, and these were reviewed in detail in the development of this book.

Practice Performance Assessment

The first 3 components of MOC are relatively intuitive and have a historical correlate (licensure, CME, and examination). The so-called MOC Part IV, or the practice performance assessment, introduces a new element to MOC and is an area prone to confusion for MOC participants. Commonly called PIP, Part IV consists of 2 components: 1) a clinical module and 2) a feedback module. Both modules are intended to help practicing clinicians review and improve

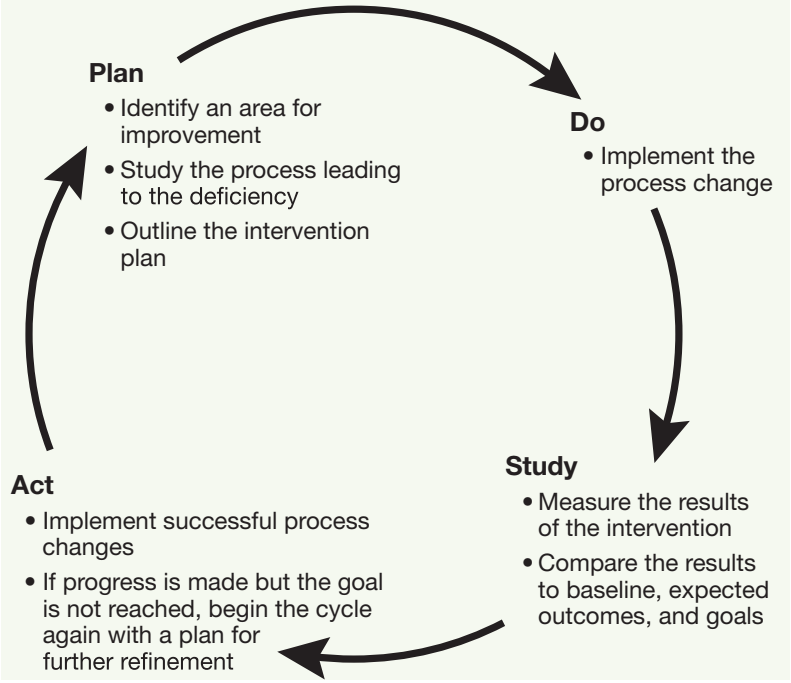

Figure 91.1 *Outline of the Plan-Do-Study-Act Cycle.*
(Adapted from Jones LK Jr, Arnold ML, Gleveckas-Martens NG, Narayanaswami P, Brock LA, Dawodu ST, et al. Continuous quality improvement in neuromuscular and electrodiagnostic practice: an educational review of the AANEM Quality Improvement Committee. Muscle & Nerve. 2013 Jun;47[6]:943–9. Used with permission.)

their practices. The modules are structured to include a measurement, an intervention designed to improve practice quality, and a remeasurement no more than 24 months later.

The clinical module requires the physician to perform a practice review of at least 5 patient charts and compare the findings from that review with established best practices, such as practice guidelines. The clinician should then develop and implement a plan to improve the quality of practice and target those identified elements, ideally using established principles of systematic quality improvement. Key elements of an iterative process of quality improvement are variably described as Plan-Do-Check-Act (PDCA) or Plan-Do-Study-Act (PDSA) (Figure 91.1). A brief case study in clinical quality improvement is provided at the end of this chapter (Box 91.2).

The second component of Part IV is the feedback module. Currently, this requirement calls for the physician to obtain feedback from at least 5 peers or patients, review the results, plan and implement changes in practice to improve the feedback, and remeasure with another sample within 24 months. The structure is similar to the clinical module, but rather than measuring, improving, and remeasuring an element of clinical practice, it is the feedback itself that is the outcome of interest.

As with all the other elements of MOC, Part IV requirements will continue to evolve, and the participant should periodically review the ABPN website for changes to the requirements. The website also provides criteria for the selection of approved Part IV products available to meet its requirements. Several specialty societies and organizations offer ABPN-approved products (eg, NeuroPI modules are offered by the American Academy of Neurology as a membership benefit).

A list of approved products satisfying CME, SA, and clinical and feedback module requirements is available on the ABPN website.

- Four components of MOC are used to assess qualification within the 6 competencies for all applicants: licensure and professional standing, lifelong learning and SA, cognitive expertise, and practice performance assessment.

Two ABPN MOC Programs

A further complexity of the MOC process is the existence of 2 ABPN MOC programs: 1) the 10-year MOC Program for diplomates who received time-limited initial certification before 2012 and 2) the Continuous MOC (C-MOC) Program for diplomates certified in 2012 or later. There are graduated requirements for MOC applicants in the 10-year program, and readers should refer to the ABPN website for those details well in advance of their anticipated recertification year (Figure 91.2). The 10-year program will sunset on December 31, 2021; after that, all diplomates with

Box 91.2 • Case Study in Clinical Quality Improvement

Case Study: A Peripheral Neuropathy Screening Quality Improvement Project

Dr Lee, a member of a 20-physician, academic-affiliated neurology practice, was approached by a primary care colleague. She reported to Dr Lee that she followed a patient with peripheral neuropathy, previously evaluated by another member of the neurology practice, who had not had a serum glucose checked. Dr Lee discussed the case with the neurologist in question, and it quickly became apparent that it had been a simple oversight.

Plan

Noting a possible opportunity for improvement, Dr Lee and his neurology colleague reviewed 100 patient records from within the practice, identified by their office manager as patients who had a coded diagnosis of peripheral neuropathy. Because the purpose of the review was for quality improvement, they were aware that they did not require a review from their institutional review board (IRB) and that the review was protected under the quality improvement provisions of the Health Insurance Portability and Accountability Act (HIPAA, 45 CFR 164.506). In their review, they found that 8/100 (8%) patients with peripheral neuropathy did not have a documented serum glucose or other diabetes screening study. In addition, they noted that several other patients had not had studies commonly performed to review for other recognized causes of neuropathy, and by consensus they determined that 14/100 (14%) of these patients had not been adequately screened for relevant conditions (including diabetes).

Dr Lee identified several interested members of his practice to collaborate on a quality improvement project, with an overall goal of improving laboratory screening of patients with peripheral neuropathy. During a series of meetings over several weeks, the team discussed possible knowledge- and system-based shortfalls leading to missed screening opportunities.

To measure a potential knowledge gap, Dr Lee and his team surveyed the practice regarding which conditions are typically screened when evaluating patients with peripheral neuropathy. They learned there was considerable variability in testing ordered in this clinical scenario. The survey also brought to light some concerns among the group regarding perceived difficulty ordering some tests, specifically that the various laboratory tests commonly performed in this setting required a number of separate ordering steps.

Do

After consulting the medical literature and specialty organization guidelines and practice parameters, Dr Lee and his team developed a list of tests which should be considered in evaluating all patients with newly diagnosed peripheral neuropathy. To address the difficulties in ordering some tests, they discussed with their electronic health record vendor possible means of organizing the needed tests in their electronic ordering platform. Collaboratively, they designed a "peripheral neuropathy" screen that could be accessed from the software's main ordering screen, and it included testing options for all of the relevant conditions. Before it was released, the update was advertised to the practice through posters in office work areas, through electronic communications and through an announcement at the monthly staff meeting. The goal of the project was to reduce the rate of missed screens for common predisposing conditions to 5% of peripheral neuropathy patients or less. The implementation phase of the project was set at 6 months.

Study

After 6 months, Dr Lee and the quality improvement team met again and reviewed 125 charts from patients who had been evaluated for new diagnoses of peripheral neuropathy during the implementation phase of the project. Of these, they determined that 119 (95%) had received adequate predetermined screening for conditions which could predispose the patient to peripheral neuropathy. They performed a satisfaction survey regarding the new ordering process and found it to be generally well received.

Act

Dr Lee and his colleagues believed that the project had achieved its stated goals and left the new process in place following their review. They did agree to meet again in 12 months with a new review of the practice's peripheral neuropathy patients to ensure that the screening process remained effective.

Adapted from Jones LK Jr, Arnold ML, Gleveckas-Martens NG, Narayanaswami P, Brock LA, Dawodu ST, et al. Continuous quality improvement in neuromuscular and electrodiagnostic practice: an educational review of the AANEM Quality Improvement Committee. Muscle & Nerve. 2013 Jun;47(6):943–9. Used with permission.

ABPN 10-Year MOC Component Requirements

All CME, SA, and PIP Requirements Must Be Completed Before the Application

Original Certification or Recertification Year	MOC Application Year	MOC Examination Year	Medical License	Total CME Credits Required	CME from ≥2 SA Activities	PIP Unit Required
2005	2014	2015	Active, full, unrestricted license No restrictions on any license	270	24	1
2006	2015	2016		300	24	1
2007	2016	2017		↓	↓	↓
2008	2017	2018				
2009	2018	2019				
2010	2019	2020				
2011	2020	2021				
2012	See C-MOC program at www.abpn.com/c-moc					

Figure 91.2 *Requirements and Timeline for ABPN Diplomates in the 10-Year MOC Program.*
ABPN indicates American Board of Psychiatry and Neurology; CME, continuing medical education; C-MOC, Continuous Maintenance of Certification; MOC, Maintenance of Certification; PIP, Performance in Practice; SA, self-assessment.
(Adapted from Maintenance of Certification Program. Buffalo Grove [IL]: American Board of Psychiatry and Neurology. [cited 2014 Dec 22] Available from: http://www.abpn.com/dowloads/moc/moc_web_doc.pdf. Used with permission.)

ABPN Continuous MOC (C-MOC)

For Diplomates Certified or Recertified in 2012 or Later

MOC Cycle	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11	Year 12
Examination (Part III)										MOC examination		
License (Part I)	← License maintained and verified continuously →											
SA (Part II)	Deadline			Deadline			Deadline			Deadline		
	24 CME credits from SA activities			24 CME credits from SA activities			24 CME credits from SA activities			24 CME credits from SA activities		
CME (Part II)	Deadline			Deadline			Deadline			Deadline		
	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1	30 Cat 1
	90 CME credits per stage			90 CME credits per stage			90 CME credits per stage			90 CME credits per stage		
PIP (Part IV)	Deadline			Deadline			Deadline			Deadline		
	≥1 PIP			≥1 PIP			≥1 PIP			≥1 PIP		
Annual MOC registration fee	Deadline			Deadline			Deadline			Deadline		
	Annual fee	Annual fee	Annual fee	Annual fee	Annual fee	Annual fee	Annual fee	Annual fee	Annual fee	Annual fee	Annual fee	Annual fee
	3 annual fee payments			3 annual fee payments			3 annual fee payments			3 annual fee payments		
	Milestone			Milestone			Milestone			Milestone		

Figure 91.3 *Requirements and Timeline for Diplomates in the ABPN C-MOC Program.*
ABPN indicates American Board of Psychiatry and Neurology; Cat, Category; CME, continuing medical education; C-MOC, Continuous Maintenance of Certification; MOC, Maintenance of Certification; PIP, Performance in Practice; SA, self-assessment.
(Adapted from Maintenance of Certification Program. Buffalo Grove [IL]: American Board of Psychiatry and Neurology. [cited 2014 Dec 22] Available from: http://www.abpn.com/dowloads/moc/moc_web_doc.pdf. Used with permission.)

time-limited certificates will participate in C-MOC. There is a mechanism for diplomates who want to transition from the 10-year program to the C-MOC program.

Diplomates in the C-MOC program have set requirements to be completed every 3 years, culminating in the recertification examination in year 10 (Figure 91.3). These periodic requirements have already evolved since the inception of MOC and are likely to change further; again, the reader should check with the ABPN for the most up-to-date requirements. Currently in the C-MOC program, every 3 years diplomates are required to complete 90 specialty-relevant CME credits (24 of which must be SA credits) and 1 clinical and feedback module and pay an annual fee.

Planning for Certification and Recertification

As mentioned above, it is very important for holders of time-limited ABPN certificates to review the MOC requirements that apply to them. Even if the recertification date is years away, the applicant will likely have CME, SA, and clinical and feedback module requirements to complete well in advance.

Applications for recertification are generally submitted the year before the expected examination date. To submit the application, the applicant must attest to the completion of all requirements up to that point. Most applicants will not be required to submit evidence or proof of completion of these requirements, but the ABPN ensures compliance by auditing a small percentage of applicants. Therefore, it is critically important for MOC participants to keep careful, up-to-date, and accurate records of all their completed CME, SA, and clinical and feedback module activities. The ABPN offers an online service (ABPN Physician Folios) to keep track of completed requirements, but the use of this service is not currently a requirement, and those records do not automatically populate the recertification application.

As mentioned above, a small percentage of MOC participants are audited at the time of application for the recertification examination to ensure that all requirements have been completed. Anecdotally, the audit process is not particularly onerous. If audited, the applicant will be required to submit documentation of licensure, CME and SA credits, completed clinical and feedback modules, and some supporting paperwork. These can be mailed or submitted electronically, and, depending on how well records have been kept, the process generally takes no more than a few hours to complete.

Preparation for the certification and recertification examinations should be tailored to the applicant's preference. Factors such as currency of medical knowledge, available preparation time, preferred studying techniques, and general anxiety level should be considered in developing the study plan for the examination. Although neurologists should develop their own plans that are best suited to their own preferences, most will feel comfortable beginning to study for the test several months before the examination date.

Questions and Answers

Questions

Multiple Choice (choose the best answer)

XV.1. Which of the following statements about effective patient-centered communication is *false*?
a. Understanding the patient's perspective promotes mutual trust in the physician-patient relationship
b. Physicians should provide justification for the costs of diagnostic testing
c. It is important to explain the rationale for diagnostic testing and treatment
d. Verbally recognizing a patient's accomplishments in reaching clinical goals is an effective means of developing a physician-patient relationship
e. Setting a clear agenda for the episode of care is important early in the clinical encounter

XV.2. When dealing with an angry patient clinical encounter, which of the following structured behaviors is *not* recommended?
a. Allow time for the patient to express anger
b. Ascertain the underlying reason for anger
c. Acknowledge the patient's reasons for anger
d. Prepare by requesting security to assist in the clinical encounter
e. Set mutual, patient-centered, productive goals

XV.3. Which of the following concepts is *not* important in fostering effective interprofessional communication?
a. Understanding and establishing professional hierarchy is encouraged
b. The situation-background-assessment-recommendation (SBAR) process provides a shared communication framework between health professionals
c. Professional opinions should be expressed clearly and in a respectful manner
d. Health care teams should understand and respect all participants' roles
e. The use of the SBAR process has been shown to enhance patient quality metrics

XV.4. A neurologist diverts and directly injects intravenous fentanyl before using the same needle and syringe on his patients. This behavior most directly violates which of the following ethical principles?
a. Autonomy
b. Privacy
c. Disclosure
d. Nonmaleficence
e. Conflict of interest

XV.5. A 92-year-old cognitively normal woman with atrial fibrillation has a severe gastrointestinal hemorrhage during therapeutic anticoagulation. After recovery she declines further anticoagulation for stroke prevention. She lucidly repeats back a good understanding of the risks associated with atrial fibrillation and anticoagulation, the options available to her, and the potential consequences of each choice. Her neurologist strongly recommends restarting anticoagulation, and when she disagrees the neurologist seeks appointment of a guardian to overrule the decision. This behavior violates which of the following ethical principles?
a. Beneficence
b. Autonomy
c. Privacy
d. Nonmaleficence
e. Fidelity

XV.6. An outpatient neurology clinic reviews its electronic medical record system to ensure that it adequately secures patient records from illicit access. Which of the following is primarily responsible for stipulating the related requirements?
a. The Social Security Act
b. The Patient Protection and Affordable Care Act
c. The Emergency Medical Treatment and Active Labor Act
d. The Medicare Modernization Act
e. The Health Insurance Portability and Accountability Act

XV.7. Which of the following is an example of physician-assisted suicide?
a. A neurologist provides morphine and lorazepam to relieve air hunger in a patient with end-stage amyotrophic lateral sclerosis
b. A neurologist writes the order to discontinue ventilation of a patient who has a massive intraparenchymal hemorrhage at the direction of a clearly written advance directive and with the agreement of the surrogate decision maker
c. A neurologist administers sodium thiopental and vecuronium to a patient with end-stage glioblastoma multiforme
d. A neurologist dismisses to residential hospice a patient with multiple melanomatous brain metastases
e. A neurologist declares the time of death of a patient who has a valid do-not-resuscitate order following cardiac arrest

XV.8. Which of the following is a key function in effective patient-centered communication?
a. Building and maintaining a therapeutic relationship
b. Ensuring that you are not late for patient appointments
c. Hiring on-staff medical interpreters
d. Delivering test results in-person only
e. Maintaining a comfortable, organized waiting room

XV.9. In the SEGUE approach to patient-centered communication, which of the following is a key element in closing the clinical encounter?
a. Obtain relevant interim history
b. Ensure a comfortable environment
c. Greet the patient
d. Set goals for the next visit
e. Examine the patient

XV.10. You are asked by a colleague to offer a second opinion on a patient who has been unhappy with his prior care for his chronic daily headache. Before entering the room, your desk staff warns you that the patient is livid because he had to wait in the waiting room for this appointment. Which of the following structured behaviors may be helpful in managing this encounter?
a. Explain that the room is called a waiting room because it is where patients wait
b. Confidentially inform the patient that you render second opinions for this colleague all the time
c. Acknowledge the patient's reasons for being angry
d. Surreptitiously record the encounter in case there is litigation later
e. Keep the visit short by informing the patient that you have only a few minutes

XV.11. You meet with a 67-year-old woman to review her brain biopsy results and inform her that she has an inoperable high-grade glioma. Which of the following stages of coping could you expect to encounter in your subsequent care of this patient?
a. Confusion
b. Paranoia
c. Anger
d. Excitement
e. Indifference

XV.12. Which of the following statements about interprofessional communication is most correct?
a. Less than half of medical errors are related to communication failures
b. Use of structured communication tools in patient handoffs improves patient safety
c. Nurse-to-nurse sign-outs are more important than interdisciplinary communication
d. Asking questions at the end of sign-out offers little advantage and delays care
e. Team members should accept recommendations only from providers at or higher than them in the clinical hierarchy

XV.13. Which of the following is the most important step in preparation for American Board of Psychiatry and Neurology (ABPN) Maintenance of Certification?
a. Review the latest requirements before and during recertification on the ABPN website
b. Retain counsel in case you are audited
c. Begin your review of requirements 2 months before your current certification expires
d. Survey patients or providers who will give you only favorable reviews
e. Ask your colleagues what they put for an answer to question 157

Answers

XV.1. Answer b.
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XV.2. Answer d.
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XV.3. Answer a.
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XV.4. Answer d.
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XV.5. Answer b.
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XV.6. Answer e.
Bernat JL. Ethical issues in neurology. 3rd ed. Philadelphia (PA): Wolters Kluwer Health/Lippincott Williams & Wilkins; c2008. 524 p.

XV.7. Answer c.
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XV.8. Answer a.
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XV.9. Answer d.
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XV.10. Answer c.
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XV.11. Answer c.
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XV.12. Answer b.
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SUGGESTED READING

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