

21st Edition

HARRISON'S® PRINCIPLES OF INTERNAL MEDICINE

LOSCALZO

FAUCI

KASPER

HAUSER

LONGO

JAMESON

VOLUME 1

Mc
Graw
Hill



21st Edition

HARRISON'S®

PRINCIPLES OF

**INTERNAL
MEDICINE**

Robert Lindsay, Blossom Samuels

- 412 Paget's Disease and Other Dysplasias of Bone 3209
Rajesh K. Jain, Tamara J. Vokes

SECTION 5 Disorders of Intermediary Metabolism

- 413 Heritable Disorders of Connective Tissue 3217
Joan C. Marini, Fransiska Malfait
- 414 Hemochromatosis 3230
Lawrie W. Powell, David M. Frazer
- 415 Wilson's Disease 3235
Stephen G. Kaler
- 416 The Porphyrias 3237
Robert J. Desnick, Manisha Balwani
- 417 Disorders of Purine and Pyrimidine Metabolism 3248
John N. Mecchella, Christopher M. Burns
- 418 Lysosomal Storage Diseases 3254
Robert J. Hopkin, Gregory A. Grabowski
- 419 Glycogen Storage Diseases and Other Inherited Disorders of Carbohydrate Metabolism 3261
Priya S. Kishnani
- 420 Inherited Disorders of Amino Acid Metabolism in Adults 3268
Nicola Longo
- 421 Inherited Defects of Membrane Transport 3274
Nicola Longo

PART 13 Neurologic Disorders

SECTION 1 Diagnosis of Neurologic Disorders

- 422 Approach to the Patient with Neurologic Disease 3277
Daniel H. Lowenstein, S. Andrew Josephson, Stephen L. Hauser
- 423 Neuroimaging in Neurologic Disorders 3282
William P. Dillon
- 424 Pathobiology of Neurologic Diseases 3293
Stephen L. Hauser, Arnold R. Kriegstein, Stanley B. Prusiner

SECTION 2 Diseases of the Central Nervous System

- 425 Seizures and Epilepsy 3305
Vikram R. Rao, Daniel H. Lowenstein
- 426 Introduction to Cerebrovascular Diseases 3324
Wade S. Smith, S. Claiborne Johnston, J. Claude Hemphill, III
- 427 Ischemic Stroke 3335
Wade S. Smith, S. Claiborne Johnston, J. Claude Hemphill, III
- 428 Intracranial Hemorrhage 3348
Wade S. Smith, J. Claude Hemphill, III, S. Claiborne Johnston
- 429 Subarachnoid Hemorrhage 3353
J. Claude Hemphill, III, Wade S. Smith, Daryl R. Gress
- 430 Migraine and Other Primary Headache Disorders 3357
Peter J. Goadsby
- 431 Alzheimer's Disease 3370
Gil D. Rabinovici, William W. Seeley, Bruce L. Miller
- 432 Frontotemporal Dementia 3378
William W. Seeley, Bruce L. Miller
- 433 Vascular Dementia 3381
Steven M. Greenberg, William W. Seeley
- 434 Dementia with Lewy Bodies 3385

Irene Litvan, William W. Seeley, Bruce L. Miller

- 435 Parkinson's Disease 3386
C. Warren Olanow, Anthony H.V. Schapira
- 436 Tremor, Chorea, and Other Movement Disorders 3400
C. Warren Olanow, Christine Klein
- 437 Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases 3410
Robert H. Brown, Jr.
- 438 Prion Diseases 3416
Stanley B. Prusiner, Michael Geschwind
- 439 Ataxic Disorders 3422
Roger N. Rosenberg
- 440 Disorders of the Autonomic Nervous System 3427
Richard J. Barohn, John W. Engstrom
- 441 Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders 3436
Vanja C. Douglas, Stephen L. Hauser
- 442 Diseases of the Spinal Cord 3445
Stephen L. Hauser
- 443 Concussion and Other Traumatic Brain Injuries 3456
Geoffrey T. Manley, Benjamin L. Brett, Michael McCrea
- 444 Multiple Sclerosis 3462
Bruce A. C. Cree, Stephen L. Hauser
- 445 Neuromyelitis Optica 3477
Bruce A. C. Cree, Stephen L. Hauser
-
- ### SECTION 3 Nerve and Muscle Disorders
- 446 Peripheral Neuropathy 3480
Anthony A. Amato, Richard J. Barohn

447 Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies 3501
Stephen L. Hauser, Anthony A. Amato

448 Myasthenia Gravis and Other Diseases of the Neuromuscular Junction 3509
Anthony A. Amato

449 Muscular Dystrophies and Other Muscle Diseases 3516
Anthony A. Amato, Robert H. Brown, Jr.
-
- ### SECTION 4 Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
- 450 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome 3532
Elizabeth R. Unger, Jn-Mann S. Lin, Jeanne Bertolli
-
- ### SECTION 5 Psychiatric and Addiction Disorders
- 451 Biology of Psychiatric Disorders 3534
Robert O. Messing, Eric J. Nestler, Matthew W. State

452 Psychiatric Disorders 3540
Victor I. Reus

453 Alcohol and Alcohol Use Disorders 3556
Marc A. Schuckit

454 Nicotine Addiction 3563
David M. Burns

455 Marijuana and Marijuana Use Disorders 3567
Nora D. Volkow, Aidan Hampson, Ruben Baler

456 Opioid-Related Disorders 3569
Thomas R. Kosten, Colin N. Haile

457 Cocaine, Other Psychostimulants, and Hallucinogens 3573
Karran A. Phillips, Wilson M. Compton

Section 1 Diagnosis of Neurologic Disorders

422

Approach to the Patient with Neurologic Disease

Daniel H. Lowenstein, S. Andrew Josephson, Stephen L. Hauser



Neurologic diseases are common and costly. According to estimates by the World Health Organization, neurologic disorders affect more than 1 billion people worldwide, constitute 12% of the global burden of disease, and cause 14% of global deaths (Table 422-1). These numbers are only expected to increase as the world's population ages. Because therapies now exist for many neurologic disorders, a skillful approach to diagnosis is essential. Errors commonly result from an overreliance on costly neuroimaging procedures and laboratory tests, which, while useful, do not substitute for an adequate history and examination. The proper approach begins with the patient and focuses the clinical problem first in anatomic and then in pathophysiological terms; only then should a specific neurologic diagnosis be entertained. This method ensures that technology is judiciously applied, a correct diagnosis is established in an efficient manner, and treatment is promptly initiated.

THE NEUROLOGIC METHOD

■ DEFINE THE ANATOMY

The first priority is to identify the region of the nervous system that is likely to be responsible for the symptoms. Can the disorder be mapped to one specific location, is it multifocal, or is a diffuse process present? Are the symptoms restricted to the nervous system, or do they arise in the context of a systemic illness? Is the problem in the central nervous system (CNS), the peripheral nervous system (PNS), or both? In the CNS, is the cerebral cortex, basal ganglia, brainstem, cerebellum, or spinal cord responsible? Are the pain-sensitive meninges involved? In the PNS, could the disorder be located in peripheral nerves and, if so, are motor or sensory nerves primarily affected, or is a lesion in the neuromuscular junction or muscle more likely?

TABLE 422-1 Global Disability-Adjusted Life-Years (DALYs) and Number of Annual Deaths for Selected Neurologic Disorders in 2019

DISORDER	DALYs	DEATHS
Low-back and neck pain	85,766,442	—
Cerebrovascular diseases	143,232,184	6,552,725
Meningitis and encephalitis	21,120,604	326,117
Migraine	42,077,666	—
Epilepsy	13,077,624	114,010
Dementia	25,276,989	1,623,256
Parkinson's disease	6,292,616	362,907
% of total DALYs or deaths for all causes that are neurologic	13.7%	16.1%
% change of DALYs or deaths for neurologic disorders between 2015 and 2019	41.0%	0.0%

Source: Data from Global Burden of Disease Study 2019 (GBD 2019) Data Resources <http://ghdx.healthdata.org/gbd-2019> and GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396:1204, 2020.

The first clues to defining the anatomic area of involvement appear in the history, and the examination is then directed to confirm or rule out these impressions and to clarify uncertainties. A more detailed examination of a particular region of the CNS or PNS is often indicated. For example, the examination of a patient who presents with a history of ascending paresthesias and weakness should be directed toward deciding, among other things, if the lesion is in the spinal cord or peripheral nerves. Focal back pain, a spinal cord sensory level, and incontinence suggest a spinal cord origin, whereas a stocking-glove pattern of sensory loss suggests peripheral nerve disease; areflexia usually indicates peripheral neuropathy but may also be present with so-called spinal shock in acute spinal cord disorders.

Deciding “where the lesion is” accomplishes the task of limiting the possible etiologies to a manageable, finite number. In addition, this strategy safeguards against making serious errors. Symptoms of recurrent vertigo, diplopia, and nystagmus should not trigger “multiple sclerosis” as an answer (etiology) but “brainstem” or “pons” (location); then a diagnosis of brainstem arteriovenous malformation will not be missed for lack of consideration. Similarly, the combination of optic neuritis and spastic ataxic paraparesis suggests optic nerve and spinal cord disease; multiple sclerosis (MS), CNS syphilis, and vitamin B₁₂ deficiency are treatable disorders that can produce this syndrome. Once the question, “Where is the lesion?” is answered, then the question “What is the lesion?” can be addressed.

■ IDENTIFY THE PATHOPHYSIOLOGY

Clues to the pathophysiology of the disease process may also be present in the history. Primary neuronal (gray matter) disorders often present as early cognitive disturbances, movement disorders, or seizures, whereas white matter involvement produces “long tract” disorders of motor, sensory, visual, and cerebellar pathways. Progressive and symmetric symptoms often have a metabolic or degenerative origin; in such cases lesions are usually not sharply circumscribed. Thus, a patient with paraparesis and a clear spinal cord sensory level is unlikely to have vitamin B₁₂ deficiency as the explanation. A Lhermitte symptom (electric shock-like sensations evoked by neck flexion) is due to ectopic impulse generation in white matter pathways and occurs with demyelination in the cervical spinal cord; among many possible causes, this symptom may indicate MS in a young adult or compressive cervical spondylosis in an older person. Symptoms that worsen after exposure to heat or exercise may indicate conduction block in demyelinated axons, as occurs in MS. A patient with recurrent episodes of diplopia and dysarthria associated with exercise or fatigue may have a disorder of neuromuscular transmission such as myasthenia gravis. Slowly advancing visual scotoma with luminous edges, termed *fortification spectra*, indicates spreading cortical depression, typically with migraine.

THE NEUROLOGIC HISTORY

Attention to the description of the symptoms experienced by the patient and substantiated by family members and others often permits an accurate localization and determination of the probable cause, even before the neurologic examination is performed. The history also helps focus the neurologic examination that follows. Each complaint should be pursued as far as possible to identify the location of the lesion, the likely underlying pathophysiology, and potential etiologies. For example, a patient complains of weakness of the right arm. What are the associated features? Does the patient have difficulty with brushing hair or reaching upward (proximal) or fastening buttons or opening a plastic bottle (distal)? Negative associations may also be crucial. A right-handed patient with a right hemiparesis without a language deficit likely has a lesion (internal capsule, brainstem, or spinal cord) different from that of a patient with a right hemiparesis and aphasia (left hemisphere). Other pertinent features of the history include the following:

1. *Temporal course of the illness.* It is important to determine the precise time of appearance and rate of progression of the symptoms

experienced by the patient. The rapid onset of a neurologic complaint, occurring within seconds or minutes, usually indicates a vascular event, a seizure, or migraine. The onset of sensory symptoms located in one extremity that spread over a few seconds to adjacent portions of that extremity and then to the other regions of the body suggests a seizure. A similar but slower temporal march of symptoms accompanied by headache, nausea, or visual disturbance suggests migraine. Less well-localized symptoms that are maximum at onset and persist for seconds, minutes, or much less commonly hours, point to the possibility of transient ischemic attack (TIA). The presence of “positive” sensory symptoms (e.g., tingling or sensations that are difficult to describe) or involuntary motor movements suggests a seizure; in contrast, transient loss of function (negative symptoms) suggests a TIA. A stuttering onset where symptoms appear, stabilize, and then progress over hours or days also suggests cerebrovascular disease; an additional history of transient remission or regression indicates that the process is more likely due to ischemia rather than hemorrhage. A gradual evolution of symptoms over hours or days suggests a toxic, metabolic, infectious, or inflammatory process. Progressing symptoms associated with the systemic manifestations of fever, stiff neck, and altered level of consciousness imply an infectious process. Relapsing and remitting symptoms involving different levels of the nervous system suggest MS or other inflammatory processes. Slowly progressive symptoms without remissions are characteristic of neurodegenerative disorders, chronic infections, gradual intoxications, and neoplasms.

2. *Patients' descriptions of the complaint.* The same words often mean different things to different patients. “Dizziness” may imply impending syncope, a sense of disequilibrium, or true spinning vertigo. “Numbness” may mean a complete loss of feeling, a positive sensation such as tingling, or even weakness. “Blurred vision” may be used to describe unilateral visual loss, as in transient monocular blindness, or diplopia. The interpretation of the true meaning of the words used by patients to describe symptoms obviously becomes even more complex when there are differences in primary languages and cultures.
3. *Corroboration of the history by others.* It is almost always helpful to obtain additional information from family, friends, or other observers to corroborate or expand the patient's description. Memory loss, aphasia, loss of insight, intoxication, and other factors may impair the patient's capacity to communicate normally with the examiner or prevent openness about factors that have contributed to the illness. Episodes of loss of consciousness necessitate that details be sought from observers to ascertain precisely what has happened during the event.
4. *Family history.* Many neurologic disorders have an underlying genetic component. The presence of a Mendelian disorder, such as Huntington's disease or Charcot-Marie-Tooth neuropathy, is often obvious if family data are available. More detailed questions about family history are often necessary in polygenic disorders such as MS, migraine, and many types of epilepsy. It is important to elicit family history about all illnesses, in addition to neurologic and psychiatric disorders. A familial propensity to hypertension or heart disease is relevant in a patient who presents with a stroke. Numerous inherited neurologic diseases are associated with multisystem manifestations that may provide clues to the correct diagnosis (e.g., neurofibromatosis, Wilson's disease, mitochondrial disorders).

5. *Medical illnesses.* Many neurologic diseases occur in the context of systemic disorders. Diabetes mellitus, hypertension, and abnormalities of blood lipids predispose to cerebrovascular disease. A solitary mass lesion in the brain may be an abscess in a patient with valvular heart disease, a primary hemorrhage in a patient with a coagulopathy, a lymphoma or toxoplasmosis in a patient with AIDS, or a metastasis in a patient with underlying cancer. Patients with malignancy may also present with a neurologic paraneoplastic syndrome ([Chap. 94](#)) or complications from chemotherapy or radiotherapy. Marfan's syndrome and related collagen disorders predispose to dissection of the cranial arteries and aneurysmal subarachnoid hemorrhage; the latter may also occur with polycystic kidney disease

and fibromuscular dysplasia. Various neurologic disorders occur with dyshyroid states or other endocrinopathies. It is especially important to look for the presence of systemic diseases in patients with peripheral neuropathy. Most patients with coma in a hospital setting have a metabolic, toxic, or infectious cause.

6. *Drug use and abuse and toxin exposure.* It is essential to inquire about the history of drug use, both prescribed and illicit. Sedatives, antidepressants, and other psychoactive medications are frequently associated with acute confusional states, especially in the elderly. Aminoglycoside antibiotics may exacerbate symptoms of weakness in patients with disorders of neuromuscular transmission, such as myasthenia gravis, and may cause dizziness secondary to ototoxicity. Vincristine and other antineoplastic drugs can cause peripheral neuropathy, and immunosuppressive agents such as cyclosporine can produce encephalopathy. Excessive vitamin ingestion can lead to disease; examples include vitamin A and intracranial hypertension (“pseudotumor cerebri”) or pyridoxine and peripheral neuropathy. Many patients are unaware that over-the-counter sleeping pills, cold preparations, and diet pills are actually drugs. Alcohol, the most prevalent neurotoxin, is often not recognized as such by patients, and other drugs of abuse such as cocaine, methamphetamine, and heroin can cause a wide range of neurologic abnormalities. A history of environmental or industrial exposure to neurotoxins may provide an essential clue; consultation with the patient's coworkers or employer may be required.
7. *Formulating an impression of the patient.* Use the opportunity while taking the history to form an impression of the patient. Is the information forthcoming, or does it take a circuitous course? Is there evidence of anxiety, depression, or hypochondriasis? Are there any clues to problems with language, memory, insight, comportment, or behavior? The neurologic assessment begins as soon as the patient comes into the room and the first introduction is made.

THE NEUROLOGIC EXAMINATION

The neurologic examination is challenging and complex; it has many components and includes a number of skills that can be mastered only through repeated use of the same techniques on a large number of individuals with and without neurologic disease. Mastery of the complete neurologic examination is usually important only for physicians in neurology and associated specialties. However, knowledge of the basics of the examination, especially those components that are effective in screening for neurologic dysfunction, is essential for all clinicians, especially generalists.

There is no single, universally accepted sequence of the examination that must be followed, but most clinicians begin with assessment of mental status followed by the cranial nerves (CN), motor system, reflexes, sensory system, coordination, and gait. Whether the examination is basic or comprehensive, it is essential that it is performed in an orderly and systematic fashion to avoid errors and serious omissions. Thus, the best way to learn and gain expertise in the examination is to choose one's own approach and practice it frequently and do it in the same exact sequence each time.

The detailed description that follows describes the more commonly used parts of the neurologic examination, with a particular emphasis on the components that are considered most helpful for the assessment of common neurologic problems. Each section also includes a brief description of the minimal examination necessary to adequately screen for abnormalities in a patient who has no symptoms suggesting neurologic dysfunction. A screening examination done in this way can be completed in 3–5 min. *Video demonstrations of the neurologic screening examination (V6) and the detailed neurologic examination (V7) can be found in the Harrison's Video Collection included in this textbook.*

Several additional points about the examination are worth noting. First, in recording observations, it is important to describe what is found rather than to apply a poorly defined medical term (e.g., “patient groans to sternal rub” rather than “obtunded”). Second, subtle CNS abnormalities are best detected by carefully comparing a patient's performance on tasks that require simultaneous activation of both cerebral

hemispheres (e.g., eliciting a pronator drift of an outstretched arm with the eyes closed; extinction on one side of bilaterally applied light touch, also with eyes closed; or decreased arm swing or a slight asymmetry when walking). Third, if the patient's complaint is brought on by some activity, reproduce the activity in the office. If the complaint is of dizziness when the head is turned in one direction, have the patient do this and also look for associated signs on examination (e.g., nystagmus or dysmetria). If pain occurs after walking two blocks, have the patient leave the office and walk this distance and immediately return, and repeat the relevant parts of the examination. Finally, the use of tests that are individually tailored to the patient's problem can be of value in assessing changes over time. Tests of walking a 7.5-m (25-ft) distance (normal, 5–6 s; note assistance, if any), repetitive finger or toe tapping (normal, 20–25 taps in 5 s), or handwriting are examples.

■ MENTAL STATUS EXAMINATION

- The bare minimum: During the interview, look for difficulties with communication and determine whether the patient has recall and insight into recent and past events.*

The mental status examination is underway as soon as the physician begins observing and speaking with the patient. If the history raises any concern for abnormalities of higher cortical function or if cognitive problems are observed during the interview, then detailed testing of the mental status is indicated. The patient's ability to understand the language used for the examination, cultural background, educational experience, sensory or motor problems, or comorbid conditions must be factored into the applicability of the tests and interpretation of results.

The Mini-Mental State Examination (MMSE) is a standardized screening examination of cognitive function that is extremely easy to administer and takes <10 min to complete (Chap. 29). Using age-adjusted values for defining normal performance, the test is ~85% sensitive and 85% specific for making the diagnosis of dementia that is moderate or severe, especially in educated patients. When there is sufficient time available in the outpatient setting, the MMSE is one of the best methods for documenting the current mental status of the patient, and this is especially useful as a baseline assessment to which future scores of the MMSE can be compared.

Individual elements of the mental status examination can be subdivided into level of consciousness, orientation, speech and language, memory, fund of information, insight and judgment, abstract thought, and calculations.

Level of consciousness is the patient's relative state of awareness of the self and the environment, and ranges from fully awake to comatose. When the patient is not fully awake, the examiner should describe the responses to the minimum stimulus necessary to elicit a reaction, ranging from verbal commands to a brief, painful stimulus such as a squeeze of the trapezius muscle. Responses that are directed toward the stimulus and signify some degree of intact cerebral function (e.g., opening the eyes and looking at the examiner or reaching to push away a painful stimulus) must be distinguished from reflex responses of a spinal origin (e.g., triple flexion response—flexion at the ankle, knee, and hip in response to a painful stimulus to the foot).

Orientation is tested by asking the person to state his or her name, location, and time (day of the week and date); time is usually the first to be affected in a variety of conditions.

Speech is assessed by observing articulation, rate, rhythm, and prosody (i.e., the changes in pitch and accentuation of syllables and words).

Language is assessed by observing the content of the patient's verbal and written output, response to spoken commands, and ability to read. A typical testing sequence is to ask the patient to name successively more detailed components of clothing, a watch, or a pen; repeat the phrase "No ifs, ands, or buts"; follow a three-step, verbal command; write a sentence; and read and respond to a written command.

Memory should be analyzed according to three main time scales: (1) immediate memory is assessed by saying a list of three items and having the patient repeat the list immediately; (2) short-term memory is tested by asking the patient to recall the same three items 5 and 15 min

later; and (3) long-term memory is evaluated by determining how well the patient is able to provide a coherent chronologic history of his or her illness or personal events.

Fund of information is assessed by asking questions about major historic or current events, with special attention to educational level and life experiences.

Abnormalities of *insight and judgment* are usually detected during the patient interview; a more detailed assessment can be elicited by asking the patient to describe how he or she would respond to situations having a variety of potential outcomes (e.g., "What would you do if you found a wallet on the sidewalk?").

Abstract thought can be tested by asking the patient to describe similarities between various objects or concepts (e.g., apple and orange, desk and chair, poetry and sculpture) or to list items having the same attributes (e.g., a list of four-legged animals).

Calculation ability is assessed by having the patient carry out a computation that is appropriate to the patient's age and education (e.g., serial subtraction of 7 from 100 or 3 from 20; or word problems involving simple arithmetic).

■ CRANIAL NERVE EXAMINATION

- The bare minimum: Check the fundi, visual fields, pupil size and reactivity, extraocular movements, and facial movements.*

The CNs are best examined in numerical order, except for grouping together CN III, IV, and VI because of their similar function.

CN I (Olfactory) Testing is often omitted unless there is suspicion for inferior frontal lobe disease (e.g., meningioma). With eyes closed, ask the patient to sniff a mild stimulus such as toothpaste or coffee and identify the odorant.

CN II (Optic) Check visual acuity (with eyeglasses or contact lens correction) using a Snellen chart or similar tool. Test the visual fields by confrontation, i.e., by comparing the patient's visual fields to your own. As a screening test, it is usually sufficient to examine the visual fields of both eyes simultaneously; individual eye fields should be tested if there is any reason to suspect a problem of vision by the history or other elements of the examination, or if the screening test reveals an abnormality. Face the patient at a distance of ~0.6–1.0 m (2–3 ft) and place your hands at the periphery of your visual fields in the plane that is equidistant between you and the patient. Instruct the patient to look directly at the center of your face and to indicate when and where he or she sees one of your fingers moving. Beginning with the two inferior quadrants and then the two superior quadrants, move your index finger of the right hand, left hand, or both hands simultaneously and observe whether the patient detects the movements. A single small-amplitude movement of the finger is sufficient for a normal response. Focal perimetry and tangent screen examinations should be used to map out visual field defects fully or to search for subtle abnormalities. Optic fundi should be examined with an ophthalmoscope, and the color, size, and degree of swelling or elevation of the optic disc noted, as well as the color and texture of the retina. The retinal vessels should be checked for size, regularity, arteriovenous nicking at crossing points, hemorrhage, and exudates.

CN III, IV, VI (Oculomotor, Trochlear, Abducens) Describe the size and shape of the pupils and reaction to light and accommodation (i.e., as the eyes converge while following your finger as it moves toward the bridge of the nose). To check extraocular movements, ask the patient to keep his or her head still while tracking the movement of the tip of your finger. Move the target slowly in the horizontal and vertical planes; observe any paresis, nystagmus, or abnormalities of smooth pursuit (saccades, oculomotor ataxia, etc.). If necessary, the relative position of the two eyes, both in primary and multidirectional gaze, can be assessed by comparing the reflections of a bright light off both pupils. However, in practice it is typically more useful to determine whether the patient describes diplopia in any direction of gaze; true diplopia should almost always resolve with one eye closed. Horizontal nystagmus is best assessed at 45° and not at extreme lateral

gaze (which is uncomfortable for the patient); the target must often be held at the lateral position for at least a few seconds to detect an abnormality.

CN V (Trigeminal) Examine sensation within the three territories of the branches of the trigeminal nerve (ophthalmic, maxillary, and mandibular) on each side of the face. As with other parts of the sensory examination, testing of two sensory modalities derived from different anatomic pathways (e.g., light touch and temperature) is sufficient for a screening examination. Testing of other modalities, the corneal reflex, and the motor component of CN V (jaw clench—masseter muscle) is indicated when suggested by the history.

CN VII (Facial) Look for facial asymmetry at rest and with spontaneous movements. Test eyebrow elevation, forehead wrinkling, eye closure, smiling, and cheek puff. Look in particular for differences in the lower versus upper facial muscles; weakness of the lower two-thirds of the face with preservation of the upper third suggests an upper motor neuron lesion, whereas weakness of an entire side suggests a lower motor neuron lesion.

CN VIII (Vestibulocochlear) Check the patient's ability to hear a finger rub or whispered voice with each ear. Further testing for air versus mastoid bone conduction (Rinne) and lateralization of a 512-Hz tuning fork placed at the center of the forehead (Weber) should be done if an abnormality is detected by history or examination. Any suspected problem should be followed up with formal audiometry. **For further discussion of assessing vestibular nerve function in the setting of dizziness, coma, or hearing loss, see Chaps. 22, 28, and 34, respectively.**

CN IX, X (Glossopharyngeal, Vagus) Observe the position and symmetry of the palate and uvula at rest and with phonation ("aah"). The pharyngeal ("gag") reflex is evaluated by stimulating the posterior pharyngeal wall on each side with a sterile, blunt object (e.g., tongue blade), but the reflex may be absent in normal individuals.

CN XI (Spinal Accessory) Check shoulder shrug (trapezius muscle) and head rotation to each side (sternocleidomastoid) against resistance.

CN XII (Hypoglossal) Inspect the tongue for atrophy or fasciculations, position with protrusion, and strength when extended against the inner surface of the cheeks on each side.

MOTOR EXAMINATION

- *The bare minimum: Look for muscle atrophy and check extremity tone. Assess upper extremity strength by checking for pronator drift and strength of wrist or finger extensors. Assess lower extremity strength by checking strength of the toe extensors.*

The motor examination includes observations of muscle appearance, tone, and strength. Although gait is in part a test of motor function, it is usually evaluated separately at the end of the examination.

Appearance Inspect and palpate muscle groups under good light and with the patient in a comfortable and symmetric position. Check for muscle fasciculations, tenderness, and atrophy or hypertrophy. Involuntary movements may be present at rest (e.g., tics, myoclonus, choreoathetosis, pill-rolling tremor of Parkinson's disease), during maintained posture (essential tremor), or with voluntary movements (intention tremor of cerebellar disease or familial tremor).

Tone Muscle tone is tested by measuring the resistance to passive movement of a relaxed limb. Patients often have difficulty relaxing during this procedure, so it is useful to distract the patient to minimize active movements. In the upper limbs, tone is assessed by rapid pronation and supination of the forearm and flexion and extension at the wrist. In the lower limbs, while the patient is supine the examiner's hands are placed behind the knees and rapidly raised; with normal tone, the ankles drag along the table surface for a variable distance before rising, whereas increased tone results in an immediate lift of the heel off the surface. Decreased tone is most commonly due to lower

motor neuron or peripheral nerve disorders. Increased tone may be evident as spasticity (resistance determined by the angle and velocity of motion; corticospinal tract disease), rigidity (similar resistance in all angles of motion; extrapyramidal disease), or paratonia (fluctuating changes in resistance; frontal lobe pathways; or normal difficulty in relaxing). Cogwheel rigidity, in which passive motion elicits jerky interruptions in resistance, is seen in parkinsonism.

Strength Testing for pronator drift is an extremely useful method for screening upper limb weakness. The patient is asked to hold both arms fully extended and parallel to the ground with eyes closed. This position should be maintained for ~10 s; any flexion at the elbow or fingers or pronation of the forearm, especially if asymmetric, is a sign of potential weakness. Patients with shoulder pain or a limited range of motion may have an apparent pronator drift that is not due to true weakness. Muscle strength is further assessed by having the patient exert maximal effort for the particular muscle or muscle group being tested. It is important to isolate the muscles as much as possible, i.e., hold the limb so that only the muscles of interest are active. It is also helpful to palpate accessible muscles as they contract. Grading muscle strength and evaluating the patient's effort is an art that takes time and practice. Muscle strength is traditionally graded using the following scale:

0 = no movement
1 = flicker or trace of contraction but no associated movement at a joint
2 = movement with gravity eliminated
3 = movement against gravity but not against resistance
4 = movement against a mild degree of resistance
4+ = movement against moderate resistance
5 = full power

However, in many cases, it is more practical to use the following terms:

Paralysis = no movement

Severe weakness = movement with gravity eliminated

Moderate weakness = movement against gravity but not against mild resistance

Mild weakness = movement against moderate resistance
Full strength

Noting the pattern of weakness is as important as assessing the magnitude of weakness. Unilateral or bilateral weakness of the upper limb extensors and lower limb flexors ("pyramidal weakness") suggests a lesion of the pyramidal tract, bilateral proximal weakness suggests myopathy, and bilateral distal weakness suggests peripheral neuropathy.

REFLEX EXAMINATION

- *The bare minimum: Check the biceps, patellar, and Achilles reflexes.*

Muscle Stretch Reflexes Those that are typically assessed include the biceps (C5, C6), brachioradialis (C5, C6), triceps (C6, C7), and sometimes finger flexor (C8, T1) reflexes in the upper limbs and the patellar or quadriceps (L3, L4) and Achilles (S1, S2) reflexes in the lower limbs. The patient should be relaxed and the muscle positioned midway between full contraction and extension. Reflexes may be enhanced by asking the patient to voluntarily contract other, distant muscle groups (Jendrassik maneuver). For example, upper limb reflexes may be reinforced by voluntary teeth-clenching, and the Achilles reflex by hooking the flexed fingers of the two hands together and attempting to pull them apart. For each reflex tested, the two sides should be tested sequentially, and it is important to determine the smallest stimulus required to elicit a reflex rather than the maximum response. Reflexes are graded according to the following scale:

0 = absent
1 = present but diminished
2 = normoactive
3 = exaggerated
4 = clonus

Cutaneous Reflexes The plantar reflex is elicited by stroking, with a noxious stimulus such as a tongue blade, the lateral surface of the sole of the foot beginning near the heel and moving across the ball of the foot to the great toe. The normal reflex consists of plantar flexion of the toes. With upper motor neuron lesions above the S1 level of the spinal cord, a paradoxical extension of the toe is observed, associated with fanning and extension of the other toes (termed an *extensor plantar response*, or *Babinski sign*). However, despite its popularity, the reliability and validity of the Babinski sign for identifying upper motor neuron weakness is limited—it is far more useful to rely on tests of tone, strength, stretch reflexes, and coordination. Superficial abdominal reflexes are elicited by gently stroking the abdominal surface near the umbilicus in a diagonal fashion with a sharp object (e.g., the wooden end of a cotton-tipped swab) and observing the movement of the umbilicus. Normally, the umbilicus will pull toward the stimulated quadrant. With upper motor neuron lesions, these reflexes are absent. They are most helpful when there is preservation of the upper (spinal cord level T9) but not lower (T12) abdominal reflexes, indicating a spinal lesion between T9 and T12, or when the response is asymmetric. Other useful cutaneous reflexes include the cremasteric (ipsilateral elevation of the testicle following stroking of the medial thigh; mediated by L1 and L2) and anal (contraction of the anal sphincter when the perianal skin is scratched; mediated by S2, S3, S4) reflexes. It is particularly important to test for these reflexes in any patient with suspected injury to the spinal cord or lumbosacral roots.

Primitive Reflexes With disease of the frontal lobe pathways, several primitive reflexes not normally present in the adult may appear. The suck response is elicited by lightly touching with a tongue blade the center of the lips, and the root response the corner of the lips; the patient will move the lips to suck or root in the direction of the stimulus. The grasp reflex is elicited by touching the palm between the thumb and index finger with the examiner's fingers; a positive response is a forced grasp of the examiner's hand. In many instances, stroking the back of the hand will lead to its release. The palmonental response is contraction of the mentalis muscle (chin) ipsilateral to a scratch stimulus diagonally applied to the palm.

■ SENSORY EXAMINATION

- *The bare minimum: Ask whether the patient can feel light touch and the temperature of a cool object in each distal extremity. Check double simultaneous stimulation using light touch on the hands. Perform the Romberg maneuver.*

Evaluating sensation is usually the most unreliable part of the examination because it is subjective and is difficult to quantify. In the compliant and discerning patient, the sensory examination can be extremely helpful for the precise localization of a lesion. With patients who are uncooperative or lack an understanding of the tests, it may be useless. The examination should be focused on the suspected lesion. For example, in spinal cord, spinal root, or peripheral nerve abnormalities, all major sensory modalities should be tested while looking for a pattern consistent with a spinal level and dermatomal or nerve distribution. In patients with lesions at or above the brainstem, screening the primary sensory modalities in the distal extremities along with tests of “cortical” sensation is usually sufficient.

The five primary sensory modalities—light touch, pain, temperature, vibration, and joint position—are tested in each limb. Light touch is assessed by stimulating the skin with single, very gentle touches of the examiner's finger or a wisp of cotton. Pain is tested using a new pin, and temperature is assessed using a metal object (e.g., tuning fork) that has been immersed in cold and warm water. Vibration is tested using a 128-Hz tuning fork applied to the distal phalanx of the great toe or index finger just below the nail bed. By placing a finger on the opposite side of the joint being tested, the examiner compares the patient's threshold of vibration perception with his or her own. For joint position testing, the examiner grasps the digit or limb laterally and distal to the joint being assessed; small 1- to 2-mm excursions can usually be sensed. The Romberg maneuver is primarily a test of proprioception. The patient is asked to stand with the feet as close together as necessary

to maintain balance while the eyes are open, and the eyes are then closed. A loss of balance with the eyes closed is an abnormal response.

“Cortical” sensation is mediated by the parietal lobes and represents an integration of the primary sensory modalities; testing cortical sensation is only meaningful when primary sensation is intact. Double simultaneous stimulation is especially useful as a screening test for cortical function; with the patient's eyes closed, the examiner lightly touches one or both hands and asks the patient to identify the stimuli. With a parietal lobe lesion, the patient may be unable to identify the stimulus on the contralateral side when both hands are touched. Other modalities relying on the parietal cortex include the discrimination of two closely placed stimuli as separate (two-point discrimination), identification of an object by touch and manipulation alone (stereognosis), and the identification of numbers or letters written on the skin surface (graphesthesia).

■ COORDINATION EXAMINATION

- *The bare minimum: Observe the patient at rest and during spontaneous movements. Test rapid alternating movements of the hands and feet and finger to nose.*

Coordination refers to the orchestration and fluidity of movements. Even simple acts require cooperation of agonist and antagonist muscles, maintenance of posture, and complex servomechanisms to control the rate and range of movements. Part of this integration relies on normal function of the cerebellar and basal ganglia systems. However, coordination also requires intact muscle strength and kinesthetic and proprioceptive information. Thus, if the examination has disclosed abnormalities of the motor or sensory systems, the patient's coordination should be assessed with these limitations in mind.

Rapid alternating movements in the upper limbs are tested separately on each side by having the patient make a fist, partially extend the index finger, and then tap the index finger on the distal thumb as quickly as possible. In the lower limb, the patient rapidly taps the foot against the floor or the examiner's hand. If these rapid alternating movements are imprecise or vary in amplitude or rhythm, a cerebellar lesion is suspected; if however they are slow compared with the other side, a lesion of the pyramidal tract is most likely. Finger-to-nose testing is primarily a test of cerebellar function; the patient is asked to touch his or her index finger repetitively to the nose and then to the examiner's outstretched finger, which moves with each repetition. A similar test in the lower extremity is to have the patient raise the leg and touch the examiner's finger with the great toe. Another coordination test in the lower limbs is the heel-knee-shin maneuver; in the supine position the patient is asked to slide the heel of each foot from the knee down the shin of the other leg. For all these movements, the accuracy, speed, and rhythm are noted.

■ GAIT EXAMINATION

- *The bare minimum: Observe the patient while walking normally, on the heels and toes, and along a straight line.*

Watching the patient walk is the most important part of the neurologic examination. Normal gait requires that multiple systems—including strength, sensation, and coordination—function in a highly integrated fashion. Unexpected abnormalities may be detected that prompt the examiner to return in more detail to other aspects of the examination. The patient should be observed while walking and turning normally, walking on the heels, walking on the toes, and walking heel-to-toe along a straight line. The examination may reveal decreased arm swing on one side (corticospinal tract disease), a stooped posture and short-stepped gait (parkinsonism), a broad-based unstable gait (ataxia), scissoring (spasticity), or a high-stepped, slapping gait (posterior column or peripheral nerve disease), or the patient may appear to be stuck in place (apraxia with frontal lobe disease).

NEUROLOGIC DIAGNOSIS

The clinical data obtained from the history and examination are interpreted to arrive at an anatomic localization that best explains the clinical findings (Table 422-2), to narrow the list of diagnostic possibilities,

TABLE 422-2 Findings Helpful for Localizations within the Nervous System

	SIGNS
Cerebrum	Abnormal mental status or cognitive impairment Seizures Unilateral weakness ^a and sensory abnormalities including head and limbs Visual field abnormalities Movement abnormalities (e.g., diffuse incoordination, tremor, chorea)
Brainstem	Isolated cranial nerve abnormalities (single or multiple) "Crossed" weakness ^a and sensory abnormalities of head and limbs, e.g., weakness of right face and left arm and leg
Spinal cord	Back pain or tenderness Weakness ^a and sensory abnormalities sparing the head Mixed upper and lower motor neuron findings Sensory level Sphincter dysfunction
Spinal roots	Radiating limb pain Weakness ^b or sensory abnormalities following root distribution (see Figs. 25-2 and 25-3) Loss of reflexes
Peripheral nerve	Mid or distal limb pain Weakness ^b or sensory abnormalities following nerve distribution (see Figs. 25-2 and 25-3) "Stocking or glove" distribution of sensory loss Loss of reflexes
Neuromuscular junction	Bilateral weakness including face (ptosis, diplopia, dysphagia) and proximal limbs Increasing weakness with exertion Sparing of sensation
Muscle	Bilateral proximal or distal weakness Sparing of sensation

^aWeakness along with other abnormalities having an "upper motor neuron" pattern, i.e., spasticity, weakness of extensors > flexors in the upper extremity and flexors > extensors in the lower extremity, and hyperreflexia.

^bWeakness along with other abnormalities having a "lower motor neuron" pattern, i.e., flaccidity and hyporeflexia.

and to select the laboratory tests most likely to be informative. The laboratory assessment may include (1) serum electrolytes; complete blood count; and renal, hepatic, endocrine, and immune studies; (2) cerebrospinal fluid examination; (3) focused neuroimaging studies (Chap. 423); or (4) electrophysiologic studies. The anatomic localization, mode of onset and course of illness, other medical data, and laboratory findings are then integrated to establish an etiologic diagnosis.

The neurologic examination may be normal even in patients with a serious neurologic disease, such as seizures, chronic meningitis, or a TIA. A comatose patient may arrive with no available history, and in such cases, the approach is as described in Chap. 28. In other patients, an inadequate history may be overcome by a succession of examinations from which the course of the illness can be inferred. In perplexing cases it is useful to remember that uncommon presentations of common diseases are more likely than rare etiologies. Thus, even in tertiary care settings, multiple strokes are usually due to emboli and not vasculitis, and dementia with myoclonus is usually Alzheimer's disease and not a prion disorder or a paraneoplastic illness. Finally, the most important task of a primary care physician faced with a patient who has a new neurologic complaint is to assess the urgency of referral to a specialist. Here, the imperative is to rapidly identify patients likely to have nervous system infections, acute strokes, and spinal cord compression or other treatable mass lesions and arrange for immediate care.

A

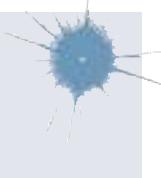
The editors acknowledge the contributions of Joseph B. Martin to earlier editions of this chapter.

FURTHER READING

- B P et al: *Localization in Clinical Neurology*, 7th ed. Philadelphia, Lippincott William & Wilkins, 2016.
- C WW, B RJ: *DeJong's The Neurological Examination*, 8th ed. Philadelphia, Lippincott William & Wilkins, 2019.
- GBD 2019 D I C : Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 396:1204, 2020.
- O'B M: *Aids to the Examination of the Peripheral Nervous System*, 5th ed. Edinburgh, WB Saunders, 2010.

423 Neuroimaging in Neurologic Disorders

William P. Dillon



Numerous noninvasive imaging options are available to clinicians evaluating patients with neurologic disorders. These include computed tomography (CT) and magnetic resonance (MR) imaging (MRI), plus their variations, including: CT angiography (CTA); perfusion CT (pCT); dual-energy CT; MR angiography (MRA); MR vessel wall imaging; functional MRI (fMRI); MR spectroscopy (MRS); MR neurography (MRN); diffusion-weighted MR imaging (DWI); diffusion tensor MR imaging (DTI); susceptibility-weighted MR imaging (SWI); arterial spin label imaging (ASL); and perfusion MRI (pMRI). Furthermore, a number of interventional neuroradiologic techniques have matured including catheter embolization, stent retrieval thrombectomy, aneurysm coiling and stenting, as well as numerous techniques for spine disorders, including CT myelography, fluoroscopy and CT-guided spine interventional procedures for pain and oncology, including radiofrequency and cold ablation and image-guided blood patches. Multidetector CTA (MDCTA) and gadolinium-enhanced MRA techniques have reduced the need for catheter-based angiography, which is now reserved for patients in whom small-vessel detail is essential for diagnosis or for whom concurrent interventional therapy is planned (Table 423-1).

In general, MRI is more sensitive than CT for the detection of lesions affecting the peripheral and central nervous system (CNS). Diffusion MR, a sequence sensitive to the microscopic motion of water, is the most sensitive technique for detecting acute ischemic stroke of the brain or spinal cord, and is also useful in the detection and characterization of encephalitis, abscess, Creutzfeldt-Jacob disease, cerebral tumors, and acute demyelinating lesions. CT, however, is acquired more quickly, making it a pragmatic choice for uncooperative patients, or those with suspected acute stroke, hemorrhage, and acute intracranial or spinal trauma. CT is also more sensitive than MRI for visualizing fine osseous detail and thus is appropriate for the initial imaging evaluation of conductive hearing loss, and lesions affecting the osseous skull and spine. MR may, however, add important diagnostic information regarding bone marrow infiltrative processes that can be difficult to detect on CT.

COMPUTED TOMOGRAPHY

TECHNIQUE

The CT image is a cross-sectional representation of anatomy created by a computer-generated analysis of the attenuation of x-ray beams passed through a section of the body. As the x-ray beam, collimated to the desired slice width, rotates around the patient, it passes through selected regions in the body. X-rays that are not attenuated by body structures are detected by sensitive x-ray detectors aligned 180° from

TABLE 423-1 Guidelines for the Use of CT, Ultrasound, and MRI

CONDITION	RECOMMENDED TECHNIQUE
Hemorrhage	
Acute parenchymal	CT, MR
Subacute/chronic	MRI
Subarachnoid hemorrhage	CT, CTA, lumbar puncture → angiography
Chronic subarachnoid blood	Angiography > CTA, MRA
Aneurysm	MR with SWI
Ischemic infarction	
Hemorrhagic infarction	CT or MRI
Bland infarction	MRI with diffusion > CT, CTA, angiography
Carotid or vertebral dissection	MRI/MRA
Vertebral basilar insufficiency	CTA, MRI/MRA
Carotid stenosis	CTA, MRA > US
Suspected mass lesion	
Neoplasm, primary or metastatic	MRI + contrast
Infection/abscess	MRI + contrast
Immunosuppressed with focal findings	MRI + contrast
Vascular malformation	MRI ± angiography
White matter disorders	MRI
Demyelinating disease	MRI ± contrast
Dementia	MRI > CT
Trauma	
Acute trauma	CT
Shear injury/chronic hemorrhage	MRI + susceptibility-weighted imaging
Headache/migraine	CT/MRI
Seizure	
First time, no focal neurologic deficits	MRI > CT
With neurologic deficit, or immunocompromised or cancer	CT, followed by MR
Partial complex/refractory	MRI
Cranial neuropathy	MRI with contrast
Meningeal disease	MRI with contrast
Spine	
Low-back pain	
No neurologic deficits	MRI or CT after >6 weeks
With focal deficits	MRI > CT
Spinal stenosis	MRI or CT
Cervical spondylosis	MRI, CT, CT myelography
Infection	MRI + contrast, CT
Myelopathy	MRI + contrast
Arteriovenous malformation	MRI + contrast, angiography

Abbreviations: CT, computed tomography; CTA, CT angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.

the x-ray tube. A computer calculates a “back projection” image from the 360° x-ray attenuation profile. Greater x-ray attenuation (e.g., as caused by bone), results in areas of high “density” (whiter) on the scan, whereas soft-tissue structures that have poor attenuation of x-rays, such as organs and air-filled cavities, are lower (blacker) in density. The resolution of an image depends on the radiation dose, the detector size, collimation (slice thickness), the field of view, and the matrix size of the display. A modern CT scanner is capable of obtaining sections as thin as 0.5–1 mm with 0.4-mm in-plane resolution at a speed of 0.3 s per rotation; complete studies of the brain can be completed in 1–10 s.

Multidetector CT (MDCT) is now standard. Single or multiple (from 4 to 320) solid-state detectors positioned opposite to the x-ray source result in multiple slices per revolution of the beam around the patient. In helical mode, the table moves continuously through the rotating x-ray beam, generating a continuous “helix” of information that can

be reformatted into various slice thicknesses and planes. Advantages of MDCT include shorter scan times and thus reduced patient and organ motion, and the ability to acquire images dynamically during the infusion of intravenous (IV) contrast, the basis of CTA and CT perfusion (Figs. 423-1B and C). CTA is displayed in three dimensions to yield angiogram-like images (Figs. 423-1C, 423-2E and F, and see Fig. 420-3).

IV iodinated contrast is used to identify vascular structures and to detect defects in the blood-brain barrier (BBB) that are caused by tumors, infarcts, and infections. In the normal CNS, only vessels and structures lacking a BBB (e.g., the pituitary gland, choroid plexus, and dura) enhance after contrast administration. While helpful in characterizing mass lesions as well as essential for the acquisition of CTA studies, the decision to use contrast material should always be considered carefully as it carries a small risk of allergic reaction and adds additional expense.

■ INDICATIONS

CT is the primary study of choice in the evaluation of an acute change in mental status, focal neurologic findings, acute trauma to the brain and spine, suspected subarachnoid hemorrhage, and conductive hearing loss (Table 423-1). CT often is complementary to MR in the evaluation of the skull base, orbit, and osseous structures of the spine. In the spine, CT is useful in evaluating patients with osseous spinal stenosis and spondylosis, but MRI is often preferred in those with neurologic deficits. CT is often acquired following intrathecal contrast injection to evaluate for spinal and intracranial cerebrospinal fluid (CSF) fistula, as well as the spinal subarachnoid space (*CT myelography*) in failed back surgery syndromes.

■ COMPLICATIONS

CT is safe, fast, and reliable. Radiation exposure depends on the dose used but is normally 2–5 mSv (millisievert) for a routine brain CT study. For all patients, especially children, it is important to use as low a radiation dose as possible for diagnostic purposes. Where feasible, MR or ultrasound is preferred. With the advent of MDCT, CTA, and CT perfusion, the benefit must be weighed against the increased radiation doses associated with these techniques. Advances in postprocessing software now permit acceptable diagnostic CT scans at 30–40% lower radiation doses.

The most frequent complications are those associated with use of IV contrast agents. While two broad categories of contrast media, ionic and nonionic, are in use, ionic agents have been largely replaced by safer nonionic compounds.

Contrast nephropathy is rare. It may result from hemodynamic changes, renal tubular obstruction and cell damage, or immunologic reactions to contrast agents. A rise in serum creatinine of at least 44 µmol/L (0.5 mg/dL) within 48 h of contrast administration is often used as a definition of contrast nephropathy, although there is no accepted definition and other causes of acute renal failure must be excluded. The prognosis is usually favorable, with serum creatinine levels returning to baseline within 1–2 weeks. Risk factors for contrast nephropathy include age (>80 years), preexisting renal disease (serum creatinine exceeding 2 mg/dL), solitary kidney, diabetes mellitus, dehydration, paraproteinemia, concurrent use of nephrotoxic medication or chemotherapeutic agents, and high contrast dose. Patients with diabetes and those with mild renal failure should be well hydrated prior to the administration of contrast agents; careful consideration should be given to alternative imaging techniques such as MRI, noncontrast CT, or ultrasound (US). Nonionic, low-osmolar media produce fewer abnormalities in renal blood flow and less endothelial cell damage but should still be used carefully in patients at risk for allergic reaction. Estimated glomerular filtration rate (eGFR) is a more reliable indicator of renal function compared to creatinine alone because it takes into account age and sex. In one study, 15% of outpatients with a normal serum creatinine had an estimated creatinine clearance of ≤ 50 mL/min per 1.73 m^2 (normal is ≥ 90 mL/min per 1.73 m^2). The exact eGFR threshold, below which withholding IV contrast should be considered, is controversial. The risk of contrast nephropathy is minimal in

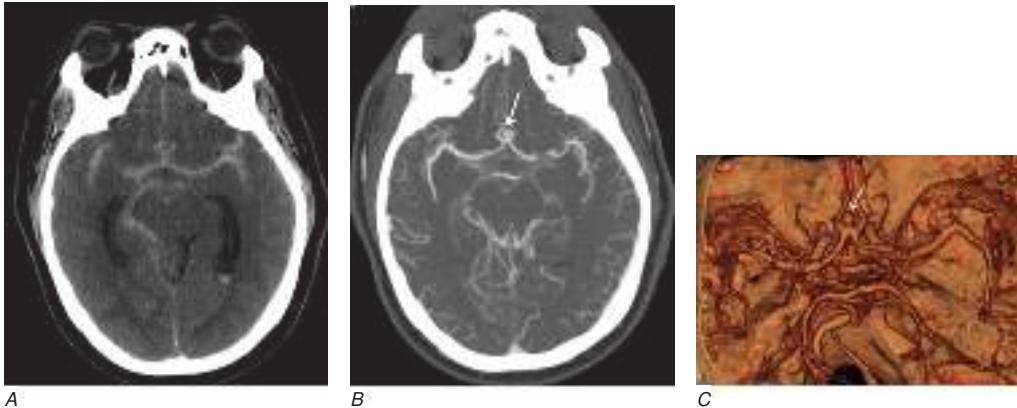


FIGURE 423-1 Computed tomography (CT) angiography (CTA) of ruptured anterior cerebral artery aneurysm in a patient presenting with acute headache. *A*, Noncontrast CT demonstrates subarachnoid and intraventricular hemorrhage and mild obstructive hydrocephalus. *B*, Axial maximum-intensity projection from CTA demonstrates enlargement of the anterior cerebral artery (arrow). *C*, Three-dimensional surface reconstruction using a workstation confirms the anterior cerebral aneurysm and demonstrates its orientation and relationship to nearby vessels (arrow). CTA image is produced by 0.5- to 1-mm helical CT scans performed during a rapid bolus infusion of IV contrast medium.

patients with eGFR >30 mL/min per 1.73 m²; however, the majority of these patients will have only a temporary rise in creatinine. The risk of dialysis after receiving contrast significantly increases in patients with eGFR <30 mL/min per 1.73 m². At the current time, there is very little evidence that IV iodinated contrast material is an independent risk factor for acute kidney injury in patients with eGFR ≥30 mL/min per 1.73 m². The American College of Radiology suggests, if a threshold for risk is used at all, an eGFR of 30 mL/min per 1.73 m² seems to have the greatest level of evidence.

If contrast must be administered to a patient with an eGFR <30 mL/min per 1.73 m², the patient should be well hydrated, and a reduction in the dose of contrast should be considered. Use of other agents such as bicarbonate and acetylcysteine may reduce the incidence of contrast nephropathy.

Below are suggested guidelines for creatinine testing prior to contrast administration. If serum creatinine is not available, creatinine testing should be performed IF the patient has ANY of the following risk factors:

- Age >60 years
- History of “kidney disease” as an adult, including tumor and transplant
- Family history of kidney failure
- Diabetes mellitus treated with insulin or other prescribed medications
- Hypertension
- Paraproteinemia syndromes or diseases (e.g., myeloma)
- Collagen vascular disease (e.g., systemic lupus erythematosus [SLE], scleroderma, rheumatoid arthritis)
- Solid-organ transplant recipient

If creatinine testing is required, a creatinine level within the prior 6 weeks is sufficient in most clinical settings.

Allergy Immediate reactions following IV contrast media occur through several mechanisms. The most severe reactions are related to allergic hypersensitivity (anaphylaxis) and range from mild hives to bronchospasm and death. The pathogenesis of allergic hypersensitivity reactions is thought to include the release of mediators such as histamine, antibody-antigen reactions, and complement activation. Severe allergic reactions occur in ~0.04% of patients receiving nonionic media, sixfold lower than with ionic media. Risk factors include a history of prior contrast reaction (fivefold increased likelihood), food and/or drug allergies, and atopy (asthma and hay fever). The predictive value of specific allergies, such as those to shellfish, once thought important, actually is now recognized to be unreliable. Nonetheless, in patients with a history worrisome for potential allergic reaction, a non-contrast CT or MRI procedure should be considered as an alternative to contrast administration. If iodinated contrast is absolutely required,

a nonionic agent should be used in conjunction with pretreatment with glucocorticoids and antihistamines (Table 423-2); however, pretreatment does not guarantee safety. Patients with allergic reactions to iodinated contrast material do not usually react to gadolinium-based MR contrast material, although such reactions can occur. It would be wise to pretreat patients with a prior allergic history to MR contrast administration in a similar fashion. Subacute (>1 h after injection) reactions are frequent and probably related to T cell-mediated immune reactions. These are typically urticarial but can occasionally be more severe. Drug provocation and skin testing may be required to determine both the culprit agent involved and a safe alternative.

Other side effects of CT contrast include a sensation of warmth throughout the body and a metallic taste during IV administration. Extravasation of contrast media, although rare, can be painful and lead to compartment syndrome. When this occurs, immediate consultation with plastic surgery is indicated. Patients with significant cardiac disease may be at increased risk for contrast reactions, and in these patients, limits to the volume and osmolality of the contrast media should be considered. Patients who may undergo systemic radioactive iodine therapy for thyroid disease or cancer should not receive iodinated contrast media, if possible, because this will decrease the uptake of the radioisotope into the tumor or thyroid (see the *American College of Radiology Manual on Contrast Media*, 2021; https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf).

MAGNETIC RESONANCE IMAGING

■ TECHNIQUE

MRI is a complex interaction between hydrogen protons in biologic tissues, a static magnetic field (the magnet), and energy in the form of radiofrequency (RF) waves of a specific frequency introduced by coils placed next to the body part of interest. Images are made by computerized processing of resonance information received from protons (typically hydrogen) in the body. Field strength of the magnet is directly related to signal-to-noise ratio. While 1.5 Tesla (T) and 3-T magnets are now widely available and have distinct advantages in the brain and musculoskeletal systems, even higher field magnets (7-T) and positron emission tomography (PET)-MR machines promise increased resolution and anatomic-functional information on a variety of disorders. Spatial localization is achieved by magnetic gradients surrounding the main magnet, which impart slight changes in magnetic field throughout the imaging volume. RF pulses transiently excite the energy state of the hydrogen protons in the body. RF is administered at a frequency specific for the field strength of the magnet. The subsequent return to equilibrium energy state (*relaxation*) of the hydrogen protons results in a release of RF energy (the *echo*), which is detected by the coils that

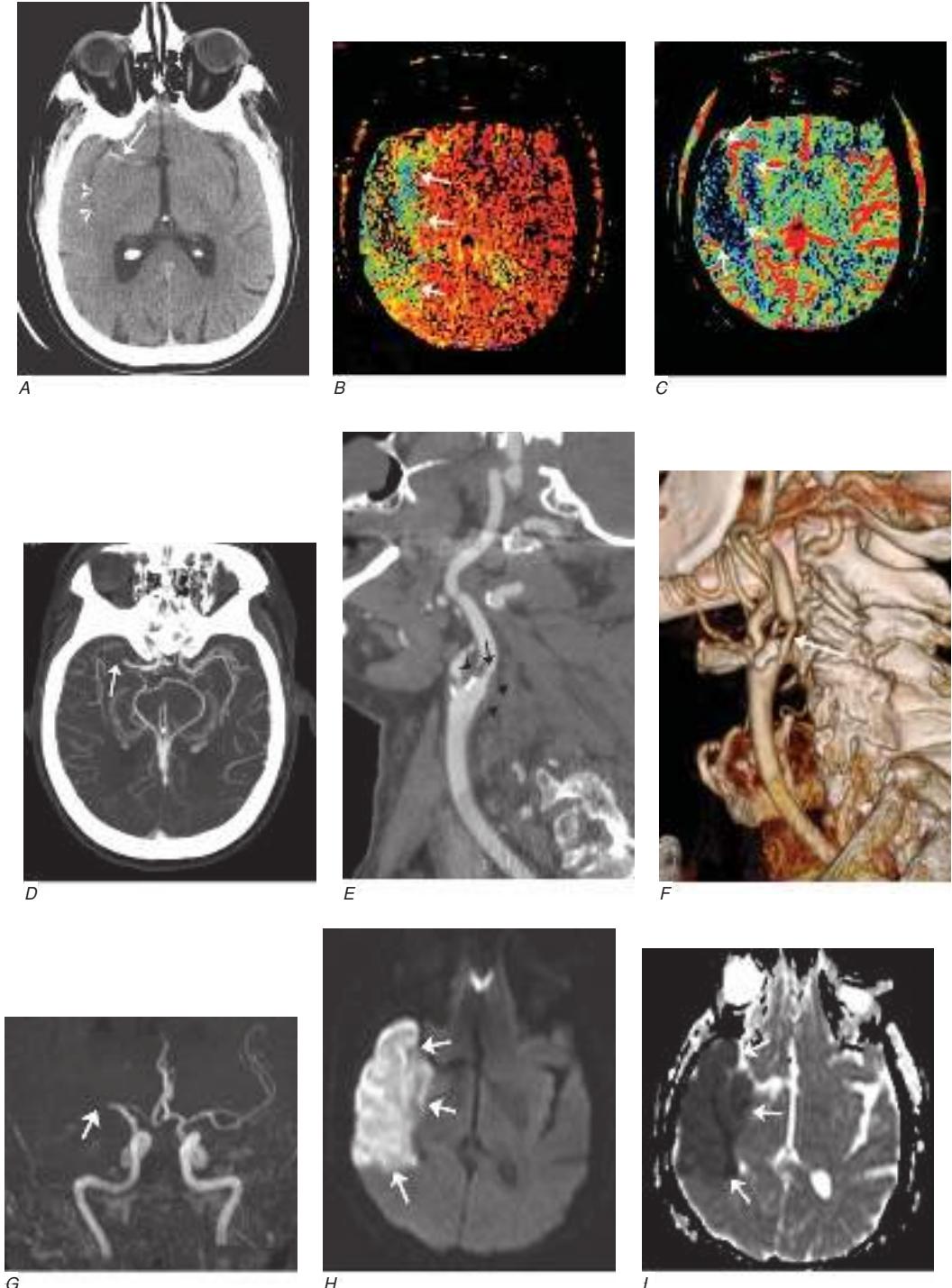


FIGURE 423-2 Acute left hemiparesis due to right middle cerebral artery occlusion. *A*, Axial noncontrast computed tomography (CT) scan demonstrates high density within the right middle cerebral artery (arrow) associated with subtle low density involving the right putamen (arrowheads). *B*, Mean transit time CT perfusion parametric map indicating prolonged mean transit time involving the right middle cerebral territory (arrows). *C*, Cerebral blood volume (CBV) map shows reduced CBV involving an area within the defect shown in *B*, indicating a high likelihood of infarction (arrows). *D*, Axial maximum-intensity projection from a CT angiography (CTA) study through the circle of Willis demonstrates an abrupt occlusion of the proximal right middle cerebral artery (arrow). *E*, Sagittal reformation through the right internal carotid artery demonstrates a low-density lipid-laden plaque (arrowheads) narrowing the lumen (black arrow). *F*, Three-dimensional surface-rendered CTA image demonstrates calcification and narrowing of the right internal carotid artery (arrow), consistent with atherosclerotic disease. *G*, Coronal maximum-intensity projection from magnetic resonance angiography shows right middle cerebral artery (MCA) occlusion (arrow). *H* and *I*, Axial diffusion-weighted image (*H*) and apparent diffusion-coefficient image (*I*) document the presence of a right middle cerebral artery infarct.

TABLE 423-2 Guidelines for Premedication of Patients with Prior Contrast Allergy

12 h prior to examination:

Prednisone, 50 mg PO or methylprednisolone, 32 mg PO

2 h prior to examination:

Prednisone, 50 mg PO or methylprednisolone, 32 mg PO and cimetidine, 300 mg PO or ranitidine, 150 mg PO

Immediately prior to examination:

Benadryl, 50 mg IV (alternatively, can be given PO 2 h prior to exam)

delivered the Rf pulses. Fourier analysis is used to transform the echo into the information used to form an MR image. The MR image thus consists of a map of the distribution of hydrogen protons, with signal intensity imparted by both density of hydrogen protons and differences in the relaxation times (see below) of hydrogen protons on different molecules. Although clinical MRI currently makes use of the ubiquitous hydrogen proton, sodium and carbon imaging and spectroscopy are also possible but have yet to be integrated into mainstream practice.

T1 and T2 Relaxation Times The rate of return to equilibrium of perturbed protons is called the *relaxation rate*. The relaxation rate varies among normal and pathologic tissues. The relaxation rate of a hydrogen proton in a tissue is influenced by local interactions with surrounding molecules and atomic neighbors. Two relaxation rates, T1 and T2, influence the signal intensity of the image. The T1 relaxation time is the time, measured in milliseconds, for 63% of the hydrogen protons to return to their normal equilibrium state, whereas the T2 relaxation is the time for 63% of the protons to become dephased owing to interactions among nearby protons. The intensity and image contrast of the signal within various tissues can be modulated by altering acquisition parameters such as the interval between Rf pulses (TR) and the time between the Rf pulse and the signal reception (TE). T1-weighted (T1W) images are produced by keeping the TR and TE relatively short, whereas using longer TR and TE times produces T2-weighted (T2W) images. Fat and subacute hemorrhage have relatively shorter T1 relaxation rates and thus higher signal intensity than brain on T1W images. Structures containing more water, such as CSF and edema, have long T1 and T2 relaxation rates, resulting in relatively lower signal intensity on T1W images and higher signal intensity on T2W images (Table 423-3). Gray matter contains 10–15% more water than white matter, which accounts for much of the intrinsic contrast between the two on MRI (Fig. 423-4A). T2W images are more sensitive than T1W images to edema, demyelination, infarction, and chronic hemorrhage, whereas T1W imaging is more sensitive to subacute hemorrhage and fat-containing structures.

Many different MR pulse sequences exist, and each can be obtained in various planes (Figs. 423-2, 423-3, and 423-4). The selection of a proper protocol that will best answer a clinical question depends on an accurate clinical history and indication for the examination. Fluid-attenuated inversion recovery (FLAIR) is a very useful pulse sequence that produces T2W images in which the normally high signal intensity of CSF is suppressed (Fig. 423-4B). FLAIR images are more sensitive than standard spin echo images for water-containing

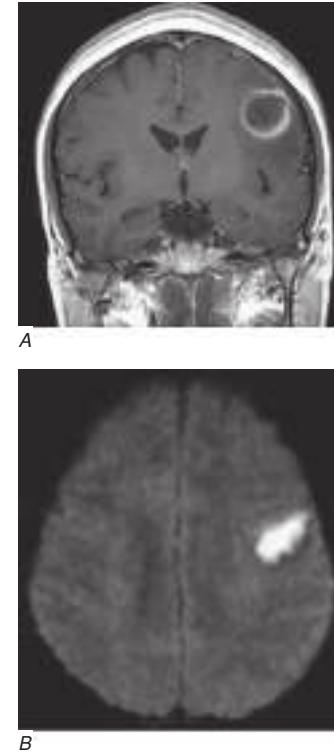


FIGURE 423-3 Cerebral abscess in a patient with fever and a right hemiparesis. A. Coronal postcontrast T1-weighted image demonstrates a ring-enhancing mass in the left frontal lobe. B. Axial diffusion-weighted image demonstrates restricted diffusion (high signal intensity) within the lesion, which in this setting is highly suggestive of cerebral abscess.

lesions or edema, especially those close to CSF-filled cisterns and sulci. Diffusion-weighted imaging is also routinely obtained in most brain protocols. This sequence interrogates the microscopic motion of water, which is restricted in areas of infarction, abscess, and some tumors. SWI is a gradient echo sequence that is very sensitive to alterations in local magnetic field generated by blood, calcium, and air. SWI is also now routinely obtained and helps detect microhemorrhages, such as is typical of amyloid angiopathy, hypertension, hemorrhagic metastases, traumatic brain injury, and thrombotic states (Fig. 423-5C). MR images can be generated in any plane without changing the patient's position. Each sequence, however, is currently obtained separately and takes 1–10 min on average to complete. Three-dimensional volumetric imaging is also possible with MRI, resulting in a volume of data that can be reformatted in any orientation to highlight certain disease processes. Perfusion techniques such as arterial spin labeling also provide quantitative imaging information regarding cerebral blood flow.

MR Contrast Material The heavy-metal element gadolinium forms the basis of all currently approved IV MR contrast agents. Gadolinium reduces the T1 and T2 relaxation times of nearby water protons in the presence of a magnetic field, resulting in a high signal on T1W images and a low signal on T2W images (the latter requires a sufficient local concentration, usually in the form of an IV bolus). Unlike iodinated contrast agents, the effect of MR contrast agents depends on the presence of local hydrogen protons on which it must act to achieve the desired effect. There are nine different gadolinium agents approved in the United States for use with MRI. These differ according to the attached chelated moiety, which also affects the strength of chelation of the otherwise toxic gadolinium element. The chelating carrier molecule for gadolinium can be classified by whether it is macrocyclic or has linear geometry and whether it is ionic or nonionic. Macrocylic ligands (Group 2 agents) are considered more stable as the gadolinium

TABLE 423-3 Some Common Intensities on T1- and T2-Weighted MRI Sequences

IMAGE	TR	TE	SIGNAL INTENSITY			
			CSF	FAT	BRAIN	EDEMA
T1W	Short	Short	Low	High	Low	Low
T2W	Long	Long	High	High	Medium	High
FLAIR(T2)	Long	Long	Low	High	Medium	High

Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; TE, interval between radiofrequency pulse and signal reception; TR, interval between radiofrequency pulses; T1W and T2W, T1- and T2-weighted.

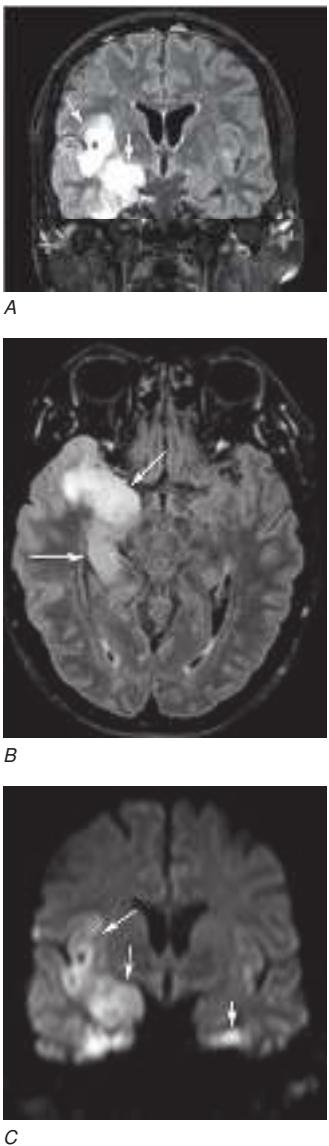


FIGURE 423-4 Herpes simplex encephalitis in a patient presenting with altered mental status and fever. *A.* and *B.* Coronal (*A*) and axial (*B*) T2-weighted fluid-attenuated inversion recovery images demonstrate expansion and high signal intensity involving the right medial temporal lobe and insular cortex (arrows). *C.* Coronal diffusion-weighted image demonstrates high signal intensity indicating restricted diffusion involving the right medial temporal lobe and hippocampus (arrows) as well as subtle involvement of the left inferior temporal lobe (arrowhead). This is most consistent with neuronal death and can be seen in acute infarction as well as encephalitis and other inflammatory conditions. The suspected diagnosis of herpes simplex encephalitis was confirmed by cerebrospinal fluid polymerase chain reaction analysis.

ion is “caged” in the cavity of the ligand, and thus the rate of dissociation of gadolinium is slower compared to linear ligands (Group 1 agents). Most agents are excreted by the renal system.

BRAIN ACCUMULATION OF GADOLINIUM It recently has become evident that gadolinium accumulates in the dentate nuclei and globus pallidus of the brain after serial administration of some linear Group 1 gadolinium agents. This has not been demonstrated for Group 2 macrocyclic agents. Gadolinium deposition in the brain appears to be dose dependent and occurs in patients with no clinical evidence of kidney or liver disease. To date, there have been no reports to suggest these

deposits are associated with histologic changes that would suggest neurotoxicity, even among agents with the highest rates of deposition.

ALLERGIC HYPERSENSITIVITY Gadolinium-DTPA (diethylenetriaminepentaacetic acid) does not normally cross the intact BBB immediately but will enhance lesions lacking a BBB (Fig. 423-3*A*) as well as areas of the brain that normally are devoid of the BBB (pituitary, dura, choroid plexus). However, gadolinium contrast slowly crosses an intact BBB over time and especially in the setting of reduced renal clearance or inflamed meninges. The agents are generally well tolerated; overall adverse events after injection range from 0.07–2.4%. True allergic reactions are rare (0.004–0.7%) but have been reported. Severe life-threatening reactions are exceedingly rare; in one report, only 55 reactions out of 20 million doses occurred. However, the adverse reaction rate in patients with a prior history of reaction to gadolinium is eight times higher than normal. Other risk factors include atopy or asthma (3.7%). There is no cross reactivity between different classes of contrast media; a prior reaction to gadolinium-based contrast does not predict a future reaction to iodinated contrast medium, or vice versa, more than any other unrelated allergy. Gadolinium contrast material can be administered safely to children as well as adults, although these agents are generally avoided in those aged <6 months.

NEPHROTOXICITY Contrast-induced renal failure does not occur with gadolinium agents. A rare complication, nephrogenic systemic fibrosis (NSF), has occurred in patients with severe renal insufficiency who have been exposed to linear (Group 1 and 3) gadolinium contrast agents. The onset of NSF has been reported between 5 and 75 days following exposure; histologic features include thickened collagen bundles with surrounding clefts, mucin deposition, and increased numbers of fibrocytes and elastic fibers in skin. In addition to dermatologic symptoms, other manifestations include widespread fibrosis of the skeletal muscle, bone, lungs, pleura, pericardium, myocardium, kidney, muscle, bone, testes, and dura. The American College of Radiology recommends that a glomerular filtration rate (GFR) assessment be obtained within 6 weeks prior to elective gadolinium-based MR contrast agent administration in patients with:

1. A history of renal disease (including solitary kidney, renal transplant, renal tumor)
2. Age >60 years
3. History of hypertension
4. History of diabetes
5. History of severe hepatic disease, liver transplantation, or pending liver transplantation; for these patients, it is recommended that the patient's GFR assessment be nearly contemporaneous with the MR examination.

The incidence of NSF in patients with severe renal dysfunction (GFR <30) varies from 0.19–4%. Other risk factors for NSF include acute kidney injury, the use of nonmacrocyclic agents, and repeated or high-dose exposure to gadolinium. The American College of Radiology Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to standard or lower doses of Group 2 gadolinium agents (macrocyclic agents) to be sufficiently low or possibly nonexistent such that the assessment of renal function is optional prior to administration. Group 2 agents are strongly preferred in patients at risk for NSF. Renal function, dialysis status, or informed consent are not recommended prior to injection of Group 2 agents, but deference is made to local practice preferences. Patients receiving any Group 1 (linear) or 3 gadolinium-containing agent should be considered at risk of NSF if they are on dialysis (of any form); have severe or end-stage chronic renal disease (eGFR <30 mL/min per 1.73 m²) without dialysis; eGFR of 30–40 mL/min per 1.73 m² without dialysis (as the GFR may fluctuate); or have acute renal insufficiency. The use of gadolinium in young children and infants is discouraged due to the unknown risks and their immature renal systems.

■ COMPLICATIONS AND CONTRAINDICATIONS

From the patient's perspective, an MRI examination can be intimidating, and a higher level of cooperation is required than with CT. The

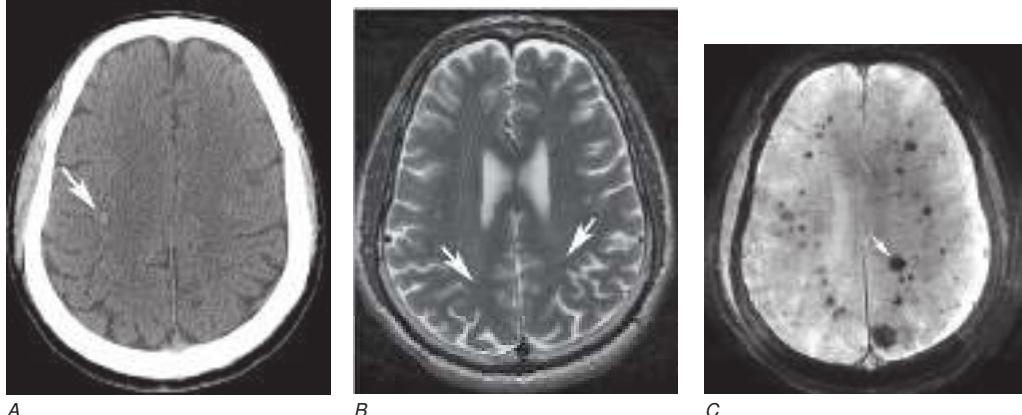


FIGURE 423-5 Susceptibility-weighted imaging in a patient with familial cavernous malformations. *A*, Noncontrast computed tomography scan shows one hyperdense lesion in the right hemisphere (arrow). *B*, T2-weighted fast-spin echo image shows subtle low-intensity lesions (arrows). *C*, Susceptibility-weighted image shows numerous low-intensity lesions consistent with hemosiderin-laden cavernous malformations (arrow).

patient lies on a table that is moved into a long, narrow gap within the magnet. Approximately 5% of the population experiences severe claustrophobia in the MR environment. This can be reduced by mild sedation but remains a problem for some. Movement of the patient during an MR examination may distort all of the images in sequence; therefore, uncooperative patients should either be sedated for the MR study or scanned with CT. Generally, children aged <8 years usually require conscious sedation in order to complete the MR examination without motion degradation.

MRI is considered safe for patients, even at very high field strengths. Serious injuries have been caused, however, by attraction of ferromagnetic objects into the magnet, which act as missiles if brought too close to the magnet. Likewise, ferromagnetic implants, such as aneurysm clips, may torque within the magnet, causing damage to vessels and even death. Metallic foreign bodies in the eye have moved and caused intraocular hemorrhage; screening for ocular metallic fragments is indicated in those with a history of metal work or ocular metallic foreign bodies. Implanted cardiac pacemakers are generally a contraindication to MRI owing to the risk of induced arrhythmias; however, some newer pacemakers have been shown to be safe and if necessary MR may be performed if the pacemaker can be safely turned off during the scan. All health care personnel and patients must be screened and educated thoroughly to prevent such disasters because the magnet is always “on.” [Table 423-4](#) lists common contraindications for MRI.

TABLE 423-4 Common Contraindications to Magnetic Resonance Imaging

Cardiac pacemaker or permanent pacemaker leads
Internal defibrillatory device
Cochlear prostheses
Bone growth stimulators
Spinal cord stimulators
Electronic infusion devices
Intracranial aneurysm clips (some but not all)
Ocular implants (some) or ocular metallic foreign body
McGee stapedectomy piston prosthesis
DuraPhase penile implant
Swan-Ganz catheter
Magnetic stoma plugs
Magnetic dental implants
Magnetic sphincters
Ferromagnetic inferior vena cava filters, coils, stents—safe 6 weeks after implantation
Tattooed eyeliner (contains ferromagnetic material and may irritate eyes)

Note: See also <http://www.mrisafety.com>.

MAGNETIC RESONANCE ANGIOGRAPHY

On routine spin echo MR sequences, moving protons (e.g., flowing blood, CSF) exhibit complex MR signals that range from high- to low-signal intensity relative to background stationary tissue. Fast-flowing blood returns no signal (flow void) on routine T1W or T2W spin echo MR images. Slower-flowing blood, as occurs in veins or distal to arterial stenosis, may appear high in signal. *MR angiography* makes use of pulse sequences called *gradient echo sequences* that increase the signal intensity of moving protons in contrast to suppressed low signal background intensity of stationary tissue. This results in a stack of images, which can be reformatted in any plane to highlight vascular anatomy and relationships.

Several types of MRA techniques exist. *Time-of-flight (TOF) MRA* is normally done without contrast administration and relies on the suppression of nonmoving tissue to provide a low-intensity background for the high signal intensity of flowing blood entering the section. A typical TOF MRA sequence results in a series of contiguous, thin MR sections (0.6–0.9 mm thick), which can be viewed as a stack and manipulated to create an angiographic image data set that can be reformatted and viewed in various planes and angles, much like that seen with conventional angiography ([Fig. 423-2G](#)).

Phase-contrast MRA has a longer acquisition time than TOF MRA, but in addition to providing anatomic information similar to that of TOF imaging, it can be used to reveal the velocity and direction of blood flow in a given vessel.

MRA is also often acquired during infusion of IV gadolinium contrast material. Advantages include faster imaging times (1–2 min vs 10 min), fewer flow-related artifacts, and 4D temporal imaging resulting in arterial and venous phases. Recently, contrast-enhanced MRA has become the standard for assessment of the extracranial vascular structures. This technique entails rapid imaging using coronal three-dimensional TOF sequences during a bolus infusion of gadolinium contrast agent.

MRA has lower spatial resolution compared with conventional film-based angiography, and therefore the detection of small-vessel abnormalities, such as vasculitis and distal vasospasm, is problematic. MRA is also less sensitive to slowly flowing blood and thus may not reliably differentiate complete from near-complete occlusions. Motion, either by the patient or by anatomic structures, may distort the MRA images, creating artifacts. These limitations notwithstanding, MRA has proved useful in evaluation of the extracranial carotid and vertebral circulation as well as of larger-caliber intracranial arteries and dural sinuses. It has also proved useful in the noninvasive detection of intracranial aneurysms and vascular malformations.

Vessel wall MR imaging (VWI) is an MR technique that relies on suppression of all moving protons within vessels and CSF, combined with IV contrast administration ([Fig. 423-6](#)). Unlike MRA, VWI is a high

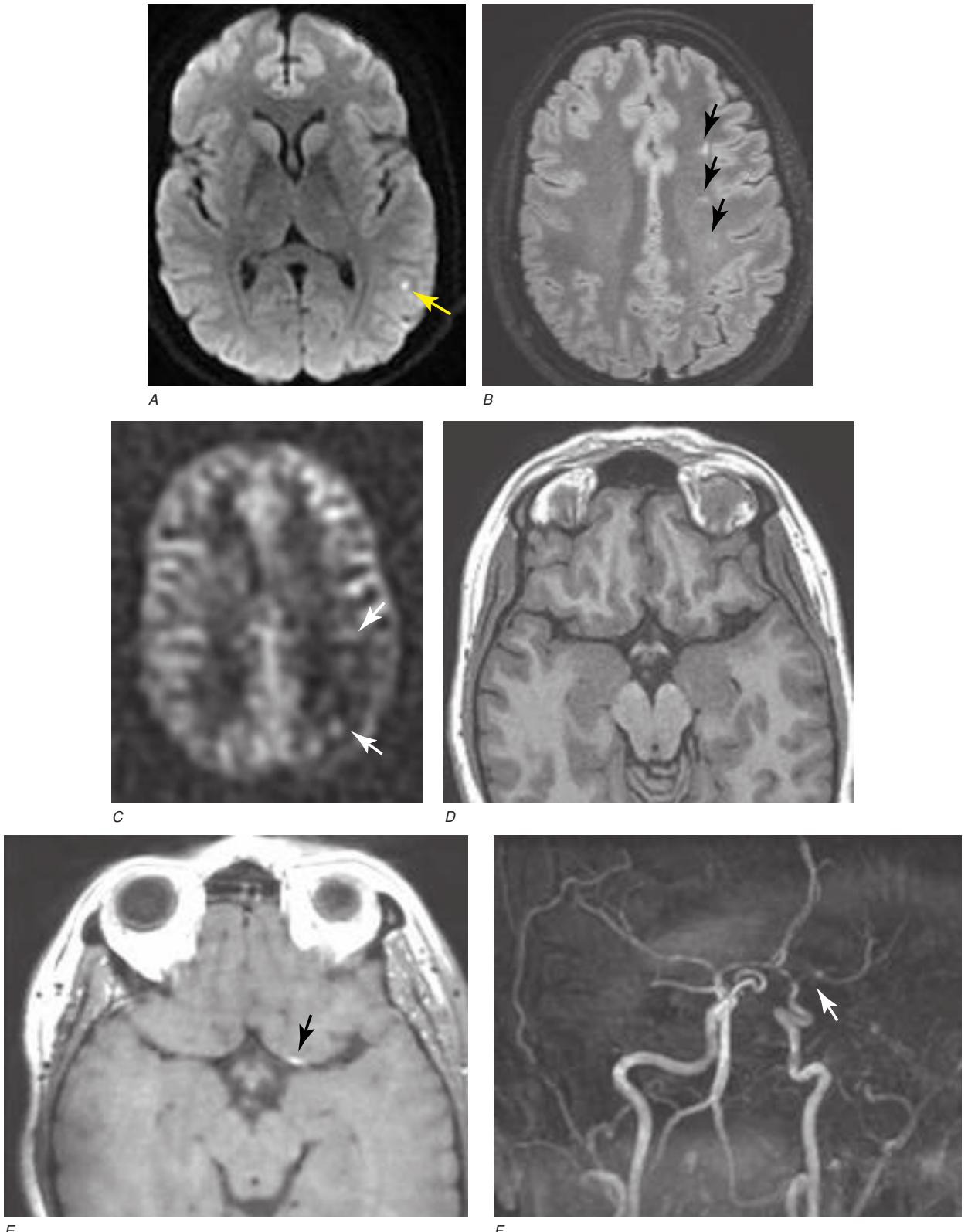


FIGURE 423-6 Arterial spin label and vessel wall imaging in a 25-year-old woman with focal cerebral arteriopathy. The patient had an 8-month history of intermittent weakness of the right side with spasms. Imaging shows evidence of cerebral ischemia. CSF was transiently inflammatory. *A*, Diffusion-weighted image shows focal region of reduced diffusion in left parietal lobe. *B*, T2 FLAIR images show several foci of high signal in left deep subcortical white matter. *C*, Arterial spin label image demonstrates reduced cerebral blood flow in left parietal lobe (arrows). *D*, 3D T1 image without contrast administration. *E*, 3D T1-weighted Cube vessel wall image following gadolinium contrast shows focal enhancement of the left proximal middle cerebral artery (arrow). (*F*), 3D TOFMRA shows focal narrowing of the left supraclinoid internal carotid artery (arrow).

spatial resolution, 3D, T1-weighted technique used to assess pathology of the vessel wall itself. This technique can be used to detect, characterize, and differentiate such pathologies as atherosclerosis, vasculitis (such as primary angiitis of the central nervous system [PACNS]), and vasculopathies such as reversible cerebral vasoconstriction syndrome (RCVS), and has been used to assess the wall of aneurysms.

ECHO PLANAR MRI

Echo planar MRI (EPI) forms the basis of several important MR imaging sequences. EPI uses fast gradients that are switched on and off at high speeds to create the information used to form an image. With EPI, all of the information required for processing an image is accumulated in milliseconds, and the information for the entire brain can be obtained in <1–2 min, depending on the degree of resolution required or desired. Fast MRI reduces patient and organ motion and is the basis of perfusion imaging during contrast infusion and kinematic motion studies. EPI is also the sequence used to obtain diffusion-weighted imaging (DWI) and tractography (DTI), as well as functional MRI (fMRI) and arterial spin-labeled (ASL) perfusion studies (Figs. 423-2H, 423-3, 423-4C, and 423-6; and Fig. 426-13).

Perfusion and diffusion imaging are EPI techniques that are useful in early detection of ischemic injury of the brain and may be useful together to demonstrate infarcted tissue as well as ischemic but potentially viable tissue at risk of infarction (e.g., the ischemic penumbra). DWI assesses microscopic motion of water; water protons that move reduce signal intensity on diffusion-weighted images. Pathology that reduces microscopic water motion results in relatively higher signal.

Infarcted tissue reduces the water motion within cells and in the interstitial tissues, resulting in high signal on DWI. DWI is the most sensitive technique for detection of acute cerebral infarction of <7 days in duration (Fig. 423-2H). It is also quite sensitive for detecting dying or dead brain tissue secondary to encephalitis, as well as abscess and purulent formations (Fig. 423-3B).

Perfusion MRI can be performed by the acquisition of fast EPI during a rapid IV bolus of gadolinium contrast material or by noncontrast arterial spin labeling (ASL) techniques. With contrast perfusion imaging, parametric maps of relative cerebral blood volume, mean transit time (MTT), time to maximum (tMAX), and cerebral blood flow can be derived. Prolonged MTT and tMAX and reduction in cerebral blood volume and cerebral blood flow are typical of infarction. In the setting of reduced blood flow, a prolonged MTT of contrast but normal or elevated cerebral blood volume may indicate tissue supplied by slower collateral flow that is at risk of infarction. Perfusion MRI imaging can also be used in the assessment of brain tumors to differentiate intraaxial primary tumors, whose BBB is relatively intact, from extraaxial tumors or metastases, which demonstrate a relatively more permeable BBB.

Diffusion tensor imaging (DTI) is derived from diffusion MRI sequences. This technique assesses the direction and integrity of protons flowing within white matter architecture. It has proven valuable in the assessment of subcortical white matter tract anatomy prior to brain tumor surgery, as well as determining normal and abnormal white matter architecture in congenital and acquired pathologies such as traumatic brain injury as well as assessing the integrity of peripheral nerves (Fig. 423-7).

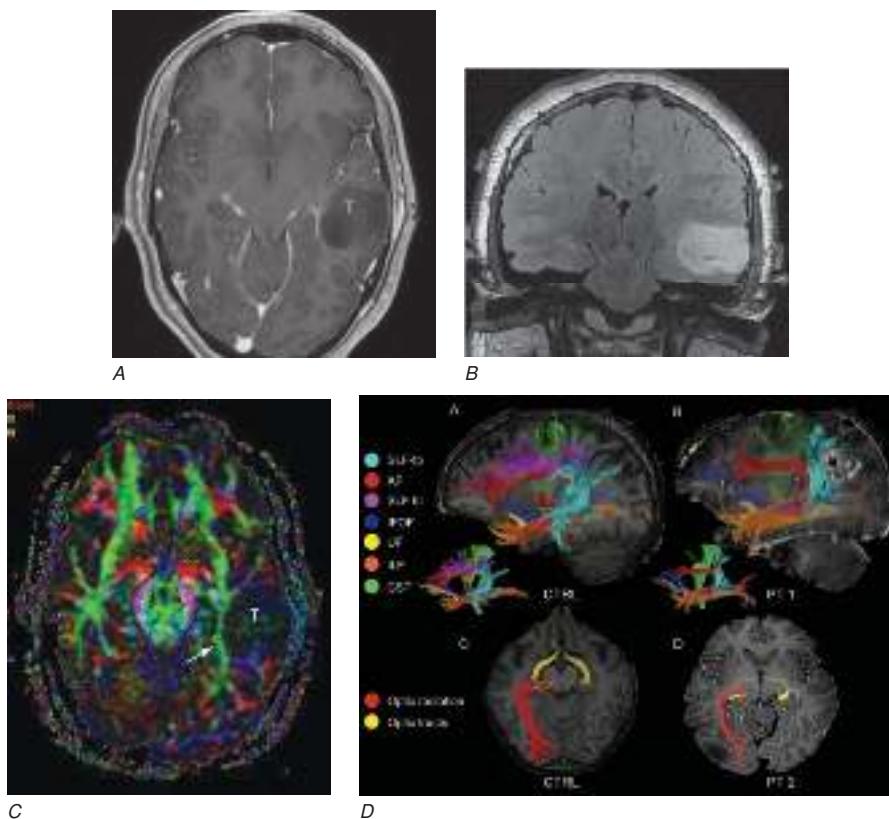


FIGURE 423-7 Diffusion tractography in cerebral glioma. Associative and descending pathways in a healthy subject (A) and in a patient with parietal lobe glioblastoma (B) presenting with a language deficit: the mass causes a disruption of the arcuate-SLF complex, in particular of its anterior portion (SLF III). Also shown are bilateral optic tract and left optic radiation pathways in a healthy subject (C) and in a patient with left occipital grade II oligoastrocytoma (D): the mass causes a disruption of the left optic radiation. *Shown in neurologic orientation, i.e., the left brain appears on the left side of the image.* AF, long segment of the arcuate fascicle; CST, corticospinal tract; IFOF, inferior fronto-occipital fascicle; ILF, inferior longitudinal fascicle; SLF III, superior longitudinal fascicle III or anterior segment of the arcuate fascicle; SLF-tp, temporo-parietal portion of the superior longitudinal fascicle or posterior segment of the arcuate fascicle; T, tumor; UF, uncinate fascicle. (Part D used with permission from Eduardo Caverzasi and Roland Henry.)

fMRI is an EPI technique that localizes regions of activity in the brain following task activation or at rest (so-called resting state fMRI). Neuronal activity elicits a slight increase in the delivery of oxygenated blood flow to a specific region of activated brain. This results in an alteration in the balance of oxyhemoglobin and deoxyhemoglobin, which yields a 2–3% increase in signal intensity within veins and local capillaries. Currently, preoperative somatosensory and auditory cortex localization is possible, and methods to assess motor and language function are in development. This technique has proved useful to neuroscientists interested in interrogating the localization of certain brain functions.

ARTERIAL SPIN LABELING

ASL is a quantitative noninvasive MR technique that measures cerebral blood flow (Fig. 423-6). Blood traversing in the neck is labeled by an MR pulse and then imaged in the brain after a short (2 s) delay. The signal is reflective of blood flow. ASL is an especially important technique for patients in whom the use of contrast agents is contraindicated. ASL has become almost standard in many MR protocols because it is relatively fast to acquire and does not require contrast administration. Increased cerebral flow is more easily identified than slow flow, which can be sometimes difficult to quantify. This technique has also been useful in detecting shunting in arteriovenous malformations and fistulas, as well as increased blood flow in brain tumors, and patients post TIA, post seizure, or post migraine.

MAGNETIC RESONANCE NEUROGRAPHY

MRN is an MR technique that shows promise in detecting increased signal in irritated, inflamed, or infiltrated peripheral nerves. T1W and T2W imaging are obtained with fat-suppressed fast-spin echo imaging or short inversion recovery sequences. Inflamed peripheral nerves will demonstrate high signal on T2W imaging. MRN is indicated in patients with radiculopathy whose conventional MR studies of the spine (cervical or lumbar) are normal, or in those suspected of peripheral nerve entrapment or trauma. This technique is now also being used to assess peripheral nerve damage after trauma or from compressive neuropathies.

POSITRON EMISSION TOMOGRAPHY

PET relies on the detection of positrons emitted during the decay of a radionuclide that has been injected into a patient. The most frequently used moiety is $2-[^{18}\text{F}]\text{fluoro-2-deoxy-}\beta\text{-glucose}$ (FDG), which is an analogue of glucose and is taken up by cells competitively with 2-deoxyglucose. Many other radioisotopes are used in other indications. With FDG, multiple images of glucose uptake activity are formed 45–60 min after IV administration of FDG. Images reveal differences in regional glucose activity among normal and pathologic brain structures. FDG-PET is used primarily for the detection of extracranial metastatic disease; however, a lower activity of FDG in the parietal lobes is associated with Alzheimer's disease, a finding that may simply reflect atrophy that occurs in the later stages of the disease. Combination PET-CT scanners, in which both CT and PET are obtained at one sitting, have largely replaced PET scans alone. MR-PET scanners have also been developed and may prove useful for imaging the brain and other organs without the radiation exposure of CT. More recent PET ligand developments include beta-amyloid and tau PET tracers (Chap. 29). Studies have shown an increased percentage of amyloid deposition in patients with Alzheimer's disease compared with mild cognitive impairment and healthy controls; however, up to 25% of cognitively "normal" patients show abnormalities on amyloid PET imaging (Chap. 431). This may either reflect subclinical disease processes or variation of normal. Tau imaging may be more specific for Alzheimer's disease, and clinical studies are in progress.

MYELOGRAPHY

■ TECHNIQUE

Myelography involves the intrathecal instillation of specially formulated water-soluble iodinated contrast medium into the lumbar

or cervical subarachnoid space. CT scanning is typically performed after myelography to better demonstrate the spinal cord and roots, which appear as filling defects in the opacified subarachnoid space. CT myelography, in which CT is performed after the subarachnoid injection of a small amount of contrast material, has replaced conventional myelography for many indications, thereby reducing exposure to radiation and contrast media. CT is obtained at a slice thickness of ~2.5 mm and reconstructed at 0.625-mm thick slices, which can quickly be reformatted in sagittal and coronal planes, equivalent to traditional myelography projections.

■ INDICATIONS

CT myelography and MRI have largely replaced conventional myelography for the diagnosis of diseases of the spinal canal and cord (Table 423-1). Remaining indications for conventional plain-film myelography include the evaluation of suspected meningeal or arachnoid cysts and the localization of CSF fistulas. Conventional myelography and CT myelography provide the most precise information in patients with failed back syndrome following spinal fusion procedures.

■ CONTRAINDICATIONS

Myelography is relatively safe; however, it should be performed with caution in any patient with elevated intracranial pressure, evidence of a spinal block, or a history of allergic reaction to intrathecal contrast media. In patients with a suspected spinal block, MR is the preferred imaging technique. If myelography is necessary, only a small amount of contrast medium should be instilled below the block in order to minimize the risk of neurologic deterioration. Lumbar puncture (LP) is to be avoided in patients with bleeding disorders, and those with infections of the overlying soft tissues. Anticoagulant therapy should be withheld prior to elective LP to avoid epidural or intradural hemorrhage, unless required in emergent situations (Chap. S9).

■ COMPLICATIONS

Headache is the most frequent complication of myelography and is reported to occur in 5–30% of patients. Nausea and vomiting may also occur rarely. Postural headache (post-LP headache) is generally due to continued epidural leakage of CSF from the dural puncture site. A higher incidence is noted among younger women and with the use of larger gauge cutting-type spinal needles. If significant headache persists for >48 h, placement of an epidural blood patch should be considered. Management of LP headache is discussed in Chap. 16. Vaso-vagal syncope may occur during LP; it is accentuated by the upright position used during conventional lumbar myelography. Adequate hydration before and after myelography will reduce the incidence of this complication.

Hearing loss is a rare complication of myelography. It may result from a direct toxic effect of the contrast medium or from an alteration of the pressure equilibrium between CSF and perilymph in the inner ear. Puncture of the spinal cord is a rare but serious complication of cervical (C1–2) or high LP. The risk of cord puncture is greatest in patients with spinal stenosis, Chiari malformations, or conditions that reduce CSF volume. CT myelography following a lumbar injection and MRI are safer alternatives to cervical puncture. Reactions to intrathecal contrast administration are rare; aseptic meningitis and encephalopathy are reported rare complications. The latter is usually dose related and associated with contrast entering the intracranial subarachnoid space. Seizures rarely occur following myelography, historically reported in 0.1–0.3% of patients. Risk factors include a preexisting seizure disorder and the use of a total iodine dose of >4500 mg. Other reported complications include hyperthermia, hallucinations, depression, and anxiety states. These side effects have been reduced by the development of nonionic, water-soluble contrast agents as well as by head elevation and generous hydration following myelography.

SPINE INTERVENTIONS

■ DISKOGRAPHY

The evaluation of back pain and radiculopathy (Chap. 15) may require diagnostic procedures that attempt either to reproduce the patient's

pain or relieve it, indicating its correct source prior to lumbar fusion. Diskography is now rarely indicated. It is performed by fluoroscopic placement of a 22- to 25-gauge needle into the intervertebral disk and subsequent injection of 1–3 mL of contrast media. The intradiskal pressure is recorded, as is an assessment of the patient's response to the injection of contrast material. Little or no pain is felt during injection of a normal disk, which does not accept much more than 1 mL of contrast material, even at pressures as high as 415–690 kPa (60–100 lb/in²). CT and plain films are obtained following the procedure. Concerns have been raised that diskography may contribute to an accelerated rate of disk degeneration; furthermore, patients who suffer from depression or anxiety are more likely to find diskography painful and in some cases the procedure-associated pain became persistent, lasting a year or longer. Thus, it is rarely used as a reliable biomarker of pain generation.

■ SELECTIVE NERVE ROOT AND EPIDURAL SPINAL INJECTIONS

Percutaneous selective nerve root and epidural administration of glucocorticoid and anesthetic mixtures may be both therapeutic and diagnostic. Typically, 1–2 mL of an equal mixture of a long-acting glucocorticoid such as betamethasone or decadron combined with a long-acting anesthetic such as bupivacaine 0.75% is instilled under CT or fluoroscopic guidance in the intraspinal epidural space or adjacent to an existing nerve root in question as a pain source. This can also be performed into the facet joints, or around the medial nerve branches that supply innervation to the facet joints.

ANGIOGRAPHY

Catheter angiography is indicated for evaluating intracranial small-vessel pathology (such as vasculitis), for assessing vascular malformations and aneurysms, and in endovascular therapeutic procedures (Table 423-1). As noted above, angiography has been replaced for many indications by CT/CTA or MRI/MRA.

Angiography carries the greatest risk of morbidity of all diagnostic imaging procedures, owing to the necessity of inserting a catheter into a blood vessel, directing the catheter to the required location, injecting contrast material to visualize the vessel, and removing the catheter while maintaining hemostasis. Therapeutic transcatheter procedures (see below) have become important options for the treatment of some cerebrovascular diseases. The decision to undertake a diagnostic or therapeutic angiographic procedure requires careful assessment of the goals of the investigation and its attendant risks.

Patients undergoing angiography should be well hydrated before and after the procedure. Because the femoral route is used most commonly, the femoral artery must be compressed after the procedure to prevent a hematoma from developing. The puncture site and distal pulses should be evaluated carefully after the procedure; complications can include thigh hematoma or lower-extremity emboli.

■ COMPLICATIONS

A common femoral arterial puncture provides retrograde access via the aorta to the aortic arch and great vessels. The most feared complication of cerebral angiography is stroke. Thrombus can form on or inside the tip of the catheter, rarely arterial dissection or perforation can occur, and atherosclerotic thrombus or plaque can be dislodged by the catheter or guide wire or by the force of injection and can embolize distally in the cerebral circulation. Risk factors for ischemic complications include limited experience on the part of the angiographer, atherosclerosis, vasospasm, low cardiac output, decreased oxygen-carrying capacity, advanced age, and prior history of migraine. The risk of a neurologic complication varies but is ~4% for transient ischemic attack and stroke, 1% for permanent deficit, and <0.1% for death.

Nonionic contrast material is used exclusively in cerebral angiography. Nonionic contrast injected into the cerebral vasculature can be

neurotoxic if the BBB is breached, either by an underlying disease or by the injection of hyperosmolar contrast agent. Patients with dolichoectasia of the basilar artery can suffer reversible brainstem dysfunction and acute short-term memory loss during angiography, owing to the slow percolation of the contrast material and the consequent prolonged exposure of the brain. Rarely, an intracranial aneurysm ruptures during an angiographic contrast injection, causing subarachnoid hemorrhage, perhaps as a result of injection under high pressure.

■ SPINAL ANGIOGRAPHY

Spinal angiography is indicated to evaluate the location of vascular malformations and to identify the artery of Adamkiewicz (Chap. 442) prior to aortic aneurysm repair. The procedure is lengthy and requires the use of relatively large volumes of contrast; the incidence of serious complications, including paraparesis, subjective visual blurring, and altered speech, is less than 1%. Gadolinium-enhanced MRA has been used successfully in this setting, as has iodinated contrast CTA, which has promise for replacing diagnostic spinal angiography for some indications.

INTERVENTIONAL NEURORADIOLOGY

This rapidly developing field is providing new therapeutic options for patients with challenging neurovascular problems. Available procedures include detachable coil therapy for aneurysms, particulate or liquid adhesive embolization of arteriovenous malformations, stent retrieval systems for embolectomy in acute stroke, balloon angioplasty and stenting of arterial stenosis or vasospasm, transarterial or transvenous embolization of dural arteriovenous fistulas, balloon occlusion of carotid-cavernous and vertebral fistulas, endovascular treatment of vein-of-Galen malformations, preoperative embolization of tumors, and thrombolysis of acute arterial or venous thrombosis. Many of these disorders place the patient at high risk of cerebral hemorrhage, stroke, or death.

The highest complication rates are found with the therapies designed to treat the highest risk diseases. The advent of electrolytically detachable coils ushered in a new era in the treatment of cerebral aneurysms (Chap. 429). Two randomized trials found reductions of morbidity and mortality at 1 year among those treated for aneurysm with detachable coils compared with neurosurgical clipping. In many centers, coiling has become standard therapy for many proximal circle of Willis aneurysms.

Finally, recent studies of stent retrieval systems used to withdraw emboli have shown improved clinical outcomes in patients presenting with large vessel occlusions and signs of acute stroke (Chap. 427).

■ FURTHER READING

- B S et al: Arterial spin labeling applications in pediatric and adult neurologic disorders. *J Magn Reson Imaging* 2020.
- C JW, M WJ: Gadolinium deposition in the brain: Current updates. *Korean J Radiol* 20:134, 2019.
- M DM et al: Intracranial vessel wall MRI: Principles and expert consensus recommendations of the American Society of Neuroradiology. *AJR Am J Neuroradiol* 38:218, 2017.
- P DM et al: Interventional neuroradiology: A review. *Can J Neurol Sci* 16:1, 2020.
- S C, B K: Adverse reactions during procedures: Hypersensitivity to contrast agents and dyes. *Ann Allergy Asthma Immunol* 124:156, 2020.
- T JD: Diffusion MRI in the brain—theory and concepts. *Prog Nucl Magn Reson Spectrosc* 112-113:1, 2019.
- W RE et al: MR imaging safety events: Analysis and improvement. *Magn Reson Imaging Clin N Am* 28:593, 2020.

Stephen L. Hauser, Arnold R. Kriegstein,
Stanley B. Prusiner



The human nervous system is the organ of consciousness, cognition, ethics, and behavior; as such, it is the most intricate structure known to exist. More than one-third of the 23,000 genes encoded in the human genome are expressed in the nervous system. Each mature brain is composed of 100 billion neurons, several million miles of axons and dendrites, and $>10^{15}$ synapses. Neurons exist within a dense parenchyma of multifunctional glial cells that synthesize myelin, preserve homeostasis, and regulate immune responses. Measured against this background of complexity, the achievements of molecular neuroscience have been extraordinary. Advances have occurred in parallel with the development of new enabling technologies—in bioengineering and computational sciences; imaging; and cell, molecular, and chemical biology—and moving forward it is likely that the pace of new discoveries will only increase. This chapter reviews a number of the most dynamic areas in neuroscience, specifically highlighting advances in immunology and inflammation, neurodegeneration, and stem cell biology. In each of these areas, recent discoveries are providing context for an understanding of the triggers and mechanisms of disease and offering new hope for prevention, treatment, and repair of nervous system injuries. Discussions of the neurogenetics of behavior, advances in addiction science, and diseases caused by network dysfunction can be found in Chap. 451 (Biology of Psychiatric Disorders); and new approaches to rehabilitation via harnessing of neuroplasticity, neurostimulation, and computer-brain interfaces are presented in Chap. 487 (Emerging Neurotherapeutic Technologies).

NEUROIMMUNOLOGY AND NEUROINFLAMMATION

■ OLIGODENDROCYTES AND MYELIN

Myelin is the multilayered insulating substance that surrounds axons and speeds impulse conduction by permitting action potentials to jump between naked regions of axons (nodes of Ranvier) and across myelinated segments. Oligodendrocytes contact axons at paranodes, where sodium and potassium channels essential for saltatory conduction are clustered. Molecular interactions between the myelin membrane and axon are required to maintain the stability, function, and normal life span of both structures. The process of myelination is directed both by axon-derived cues as well as the physical properties of the axon-membrane curvature. Importantly, ongoing neuronal activity influences both the differentiation of oligodendrocytes as well as the extent of myelination, a process referred to as *adaptive myelination*. A single oligodendrocyte usually ensheathes multiple axons in the central nervous system (CNS), whereas in the peripheral nervous system (PNS), each Schwann cell typically myelinates a single axon. Myelin is a lipid-rich material formed by a spiraling process of the membrane of the myelinating cell around the axon, creating multiple membrane bilayers that are tightly apposed (compact myelin) by charged protein interactions. A number of clinically important neurologic disorders are caused by inherited mutations in myelin proteins (Chap. 446), and constituents of myelin also have a propensity to be targeted as autoantigens in autoimmune demyelinating disorders (Chap. 447).

Premyelinating oligodendrocyte precursor cells (OPCs) are highly motile cells that migrate extensively during development and in the adult brain following injuries to the myelin sheath. OPCs migrate along the inner (or abluminal) surface of endothelial cells, a process regulated by *Wnt* pathway signaling and upregulation of the chemokine receptor Cxcr4 that drives their attachment and retention to the vasculature. In the normal adult brain, large numbers of OPCs are widely distributed. Following demyelination, remyelination is largely dependent on OPCs

that differentiate into myelin-producing oligodendrocytes and produce characteristic thinly remyelinated fibers. In some situations, a second population of regenerating oligodendrocytes derived from neural stem cells can mediate more effective remyelination, with thicker lamellae and greater functional preservation of axons. A recent C^{14} labeling study from human multiple sclerosis (MS) lesions indicated that a third population of nonmitotic preexisting oligodendrocytes may represent an additional source of remyelinating cells.

Both acquired demyelinating disorders, such as MS, and inherited ones, such as Pelizaeus-Merzbacher disease (duplication or deletion of CNS proteolipid protein) and adrenoleukodystrophy (mutations in the *ABCD1* gene responsible for transport of very long chain fatty acids into the peroxisome for degradation), are associated with progressive axonal loss. It is now increasingly recognized that oligodendrocyte dysfunction can contribute to neuronal and axonal loss in a wide variety of CNS disorders including Alzheimer's disease (AD; Chap. 431), amyotrophic lateral sclerosis (ALS; Chap. 437), traumatic brain injury (Chap. 443), and stroke (Chap. 426), among other conditions.

Loss of oligodendrocyte support can produce axonal damage through a variety of mechanisms, including reductions in the supply of glucose and other essential nutrients; an increased axonal workload; impaired glutamate and calcium buffering; mitochondrial damage; loss of neurotrophins; enhanced susceptibility to reactive oxygen species including nitric oxide; as well as failure to maintain normal synapses.

A number of molecules have been identified that regulate oligodendrocyte differentiation and myelination, including LINGO-1, hyaluronan, chondroitin sulfate proteoglycan, the *Wnt* pathway, Notch (and its receptor Jagged), fibrinogen, and the M1 muscarinic receptor Chrm1, all of which are inhibitory. Other targets are the retinoic acid receptor RXR α , vitamin D, and thyroid hormone, all of which promote oligodendrocyte maturation. All are also potential targets for myelin repair therapies. In the preclinical model of autoimmune demyelination, experimental allergic encephalomyelitis (EAE; Fig. 424-1), oligodendrocyte-specific knockout of *Chrm1* improved remyelination, protected axons, and restored function, directly demonstrating that remyelination can be neuroprotective following injury. A pivotal trial of a monoclonal antibody against LINGO-1 in patients with acute optic neuritis failed to improve clinical outcomes, a disappointing result given that the antibody appeared to have promising clinical effects in an earlier phase 2 trial. More recently, in a preliminary trial of chronic optic neuritis, a promising result was reported with clemastine, an anti-histamine and M1 muscarinic receptor antagonist, raising hope that clinically effective remyelination might be achievable even in a chronic demyelinating condition.

■ MICROGLIA AND MACROPHAGES

These represent the major cell types in the nervous system responsible for antigen presentation and innate immunity. Brain microglia migrate from the yolk sac early in embryogenesis before the blood-brain barrier is formed, and are believed to maintain their cell numbers through cell division within the nervous system and not via repopulation from the circulation. In mice, most microglia require signaling through colony-stimulating factor 1 receptor (Csflr), via its natural ligands Csflr and IL-34, for survival. Depletion of microglia by administration of a selective inhibitor of Csflr (PLX5622) was followed by rapid repopulation, which led to identification of a second population of ramified microglial precursor cells that do not require Csflr signaling. Single-cell transcriptome sequencing approaches are now producing evidence for substantial microglial cell diversity in the CNS.

Microglia play critical roles in sculpting neuronal populations during development and across the life span, through secretion of brain-derived neurotrophic factor (BDNF) and other trophic factors that promote neuronal survival, and also via production of reactive oxygen species (ROS) and other molecules that mediate cell death. Microglia regulate development and maintenance of neural circuits through pruning of excitatory synapses and control of dendritic spine densities (Fig. 424-2). Mice depleted of microglia during development exhibit a variety of cognitive, learning, and behavioral deficits, including abnormal social behaviors. These processes are dependent on

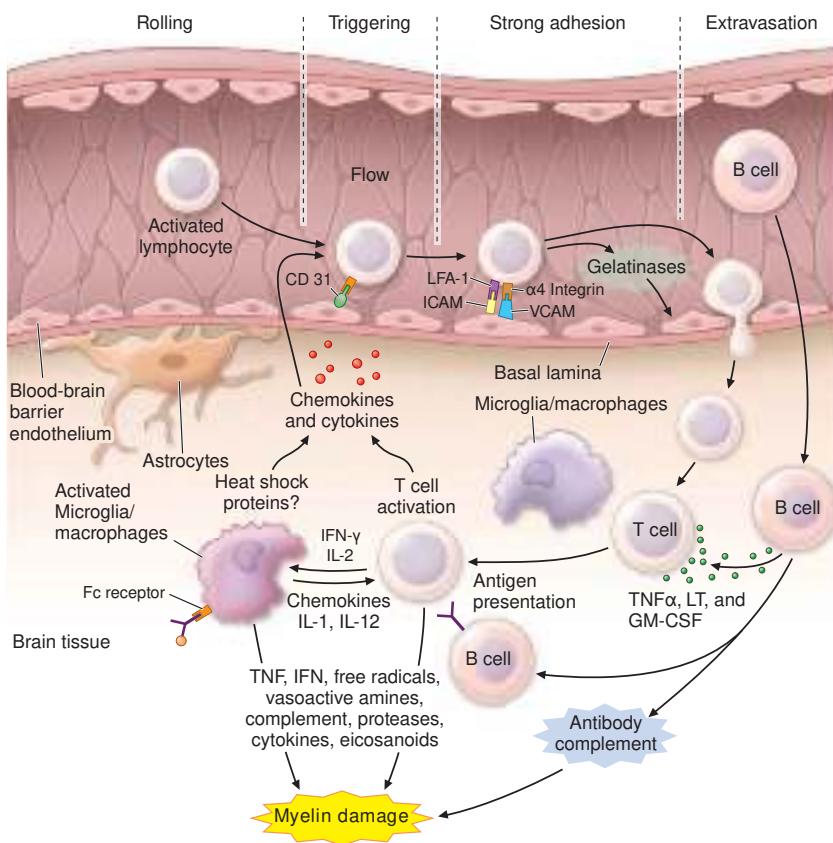


FIGURE 424-1 A model for experimental allergic encephalomyelitis (EAE). Crucial steps for disease initiation and progression include peripheral activation of preexisting autoreactive T cells; homing to the central nervous system (CNS) and extravasation across the blood-brain barrier; reactivation of T cells by exposed autoantigens; secretion of cytokines; activation of microglia and astrocytes and recruitment of a secondary inflammatory wave; and immune-mediated myelin destruction. ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; LFA-1, leukocyte function-associated antigen-1; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

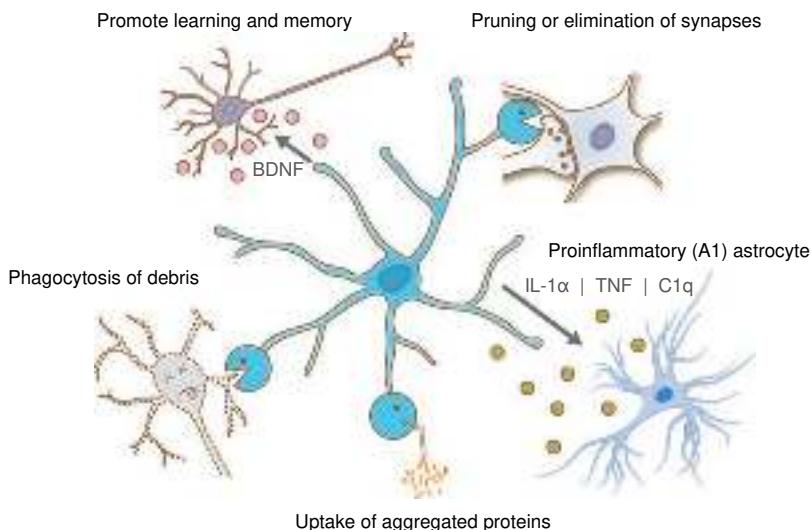


FIGURE 424-2 The multifunctional microglial cell. Microglia have diverse functions that can support healthy development and maintain homeostasis, or contribute to tissue damage in pathologic conditions. Homeostatic functions include promotion of learning and memory through secretion of soluble proteins such as brain derived neurotrophic factor (BDNF); participation in normal synaptic pruning; and clearing cellular debris and protein aggregates via phagocytosis. However, in pathologic states activated microglia also contribute to tissue damage, by targeting normal healthy neurons and synapses; by promoting formation of β -amyloid or other misfolded proteins deposited in neurodegenerative diseases; and secreting cytokines (such as IL-1 α , TNF, and the complement component C1q) incriminated in induction of neurotoxic A1 astrogliosis. In addition, microglia have diverse functions in adaptive immunity, including roles in antigen presentation and immune regulation (Fig. 417-2). (Reproduced with permission from J Herz et al: Myeloid cells in the central nervous system. *Immunity* 46:943, 2017.)

classical complement pathway molecules, including C1q, complement receptor 3 (CR3), and CR5.

Microglia are located throughout the brain parenchyma, whereas brain macrophages occur primarily in perivascular regions, including the meninges and choroid plexus. Brain macrophages are believed to be derived from yolk sac precursors that appear to enter the brain at an early developmental stage and propagate locally, although some choroid plexus macrophages may also be replenished at low levels from the bloodstream on a continuing basis. Under inflammatory conditions, large numbers of hematogenously derived monocytes enter the brain parenchyma. In the EAE model (Fig. 424-1), macrophages derived from bone marrow monocytes, but not microglia, are the critical population that initiates inflammatory demyelination at paraxonal regions near nodes of Ranvier. Brain macrophages have multiple proinflammatory functions, including promoting adhesion, attraction, and activation of B and T lymphocytes; providing antigen-specific activation of T cells via antigen presentation of specific immunogenic peptides, including autoantigens, complexed to surface class II major histocompatibility complex (MHC II) molecules; and contributing to cell injury through generation of oxidative stress and cytotoxicity. By contrast, microglia have been traditionally thought to downregulate inflammatory responses and promote tissue repair in EAE. This model of the relative roles of macrophage and microglial cells is certainly an oversimplification, and more nuanced functions of these cell types can be revealed by single-cell sequencing methods, depending on the specific context and environmental cues.

Evidence also supports a primary role for microglia and brain macrophages in neurodegenerative diseases, in contrast to earlier views in which their role was seen as largely secondary and involving phagocytosis of cell debris. Approximately half of all genes implicated in genome-wide association studies in AD implicate innate immune processes and microglia. Under different experimental conditions, these cells can be either protective or pathogenic. As examples of the former, macrophages could promote spatial memory in mice when activated by interleukin (IL)-4 produced by invading lymphocytes. Also, secretion of BDNF by microglia promoted synaptic plasticity and improved learning and memory. Microglia and brain macrophages also promoted clearance of pathogenic β -amyloid aggregates in AD-prone mice; also, disruption of brain macrophages by knockout of CCR2, a chemokine required for entry of bloodstream monocytes into the CNS, exacerbated AD pathology.

On the other hand, disease-worsening effects of microglia and macrophages are likely to predominate in other situations. A direct role for microglia in human AD was suggested by genetic evidence implicating the phagocytosis-associated gene TREM2 in AD susceptibility. TREM2 is a microglial receptor that can bind amyloid, induce proliferation and migration of microglia, and possibly limit the spread of disease-associated AD aggregates. Loss-of-function mutations in TREM2 increase AD risk threefold. In a mouse model of AD, overexpression of TREM2 blocked AD pathology and rescued performance on tests of learning and memory. A clinical trial testing the value of an agonist monoclonal antibody against TREM2 is underway.

Other immune system genes implicated in susceptibility to AD and other late-life dementias also represent promising targets for future therapy. Activation of the classical complement cascade, noted above, is assuming an increased role in concepts of pathogenesis, as follows: synapses targeted for elimination express the complement proteins C1q and C3, the levels of which increase in the presence of excess β -amyloid; C3-bearing synapses are then targeted for elimination by microglia that express the complement 3 receptor (CR3); and knockout of C3 can rescue the clinical and pathologic abnormalities associated with neurodegeneration in AD-prone mice.

In familial frontotemporal degeneration (FTD) due to mutations of progranulin (Chap. 432), a prominent immune pathology has also been identified, with activated microglia expressing high levels of proinflammatory cytokines. When progranulin is deleted in mice, an age-dependent microglial activation phenotype results, associated with upregulation of complement and other genes associated with innate immunity, enhanced pruning of inhibitory synapses, and behavioral

manifestations reminiscent of human FTD. Moreover, inhibition of complement activation can rescue all of these deficits. These data indicate a primary role for microglial activation in FTD caused by mutations in progranulin, likely mediated through enhanced lysosomal trafficking, increased production of C3 complement, and excessive synaptic pruning in brain regions affected in FTD. Although it is likely that the specific mechanisms of complement-dependent neurodegeneration will differ in distinct neurodegenerative conditions, these data provide hope that complement-pathway interventions could represent an approach to control of neurodegenerative pathologies mediated at least in part through the innate immune system.

ASTROCYTES

Astrocytes represent half or more of all cells in the CNS. Traditionally thought to function as simple interstitial supporting cells that provide scaffolds for neuronal migration and contribute to homeostasis, emerging data indicate far more pleiotropic functions for this cell type. Astrocytes, like microglia, play profound roles in the life of synapses by secreting factors (such as apolipoprotein E, thrombospondins, and glypcans) that regulate development, maintenance, and pruning of presynaptic and postsynaptic structures. Influenced by local neuronal activity, astrocytes actively phagocytose synapses. Pruning of synapses and clearance of apoptotic cells by astrocytes are mediated through the scavenger receptor multiple EGF-like domains 10 (Megf10), a high-affinity receptor for C1Q. Astrocytes also participate in dynamic regulation of vascular tone, in part through astrocyte-astrocyte communication mediated through gap junctions and calcium waves modulated by neuronal activity; support blood-brain barrier and glymphatic (see below) integrity through extension of foot processes to vascular structures and expression of aquaporin-4 water channels; and carry out additional metabolic functions essential for maintenance of neuron health.

One characteristic of the response to many types of brain injury is reactive astrogliosis, or the formation of a glial scar. Recent work has highlighted the transcriptional and functional heterogeneity of reactive astrocytes that, depending on the context, could promote neurotoxicity or aid in protection and repair. In a model of brain ischemia, reactive astrocytes promoted tissue repair after injury. By contrast, in other inflammatory and degenerative states, reactive astrocytes appear to actively contribute to the injury process. Secreted products of activated microglia, specifically IL-1 α , TNF, and C1q, can induce astrocytes to transform to a disease-promoting phenotype. Such cells lose the capacity to phagocytose synapses and myelin debris, and become toxic in vitro to neurons and mature oligodendrocytes, possibly via complement-mediated damage. Interestingly, OPCs, abundant in active lesions of MS (Chap. 444) despite the inflammatory milieu, are resistant to astrocyte-mediated killing. Reactive astrocytes could promote damage in disorders as varied as AD (Chap. 431), Parkinson's disease (PD) (Chap. 435), and ALS (Chap. 437), despite the distinct etiologies and pathologies of these conditions.

LYMPHATICS OF THE CENTRAL NERVOUS SYSTEM

Two recently identified lymphatic structures of the CNS are the glymphatic and deep dural lymphoid systems, responsible for clearance of debris in the CNS, and likely also serving roles in immune surveillance. The brain has traditionally been considered to lack a classical lymphatic system, and immune responses against antigens are less effectively generated in the CNS than in other organ systems, a concept termed *immune privilege*. However, the immune privilege status of the brain is only relative and not absolute. Also, given the high metabolic demands of the brain, some mechanism for efficient removal of solute and debris must be present. One well-established pathway involves the passive flow of solutes from the brain parenchyma into the cerebrospinal fluid (CSF), and their exit via the arachnoid granulations, as well as along cranial and spinal nerve roots to a series of lymphoid structures located in the cribriform plate, nasal mucosa, and elsewhere.

The *glymphatic system* derives its name from a distinctive architecture involving lymphoid-like structures and astroglial cells.

3296 CSF synthesized in the arachnoid villi circulates through the ventricles and subarachnoid space surrounding the convexities of the brain and spinal cord, and exits through conduits surrounding arterioles penetrating into the brain parenchyma. These spaces are lined by endothelial cells internally, and by astrocyte foot processes that form the external walls. Aided by arterial propulsion, CSF moves out of these specialized conduits and into astrocytes via foot processes rich in aquaporin-4 water channels, and then in the interstitium of brain parenchyma picks up solutes and particulate debris that are then carried to perivenous spaces where they passage to exit the brain and drain into the lymphatic system. In mice, knockout of aquaporin-4 markedly reduced the flow of interstitial fluids in the brain, underscoring the critical role of astrocyte uptake of CSF in this process. Interstitial flow in the CNS is also impaired with aging, possibly related to changes in astrocytic aquaporin-4 expression. A fascinating aspect of the glymphatic system is that the transport of fluids and solutes accelerates with sleep, arguing for a critical role for sleep in promoting clearance of debris needed to meet the high metabolic demands of the nervous system. Furthermore, in disease models, aggregated proteins associated with neurodegenerative disease, such as β -amyloid associated with AD (Chap. 431), were also more efficiently cleared during sleep. Indeed, in mice genetically engineered to produce excess β -amyloid and develop AD-like cognitive decline, sleep deprivation increased accumulation of amyloid plaques. Glymphatic pathways are also likely to represent an important egress pathway for lymphocytes in the CNS and a route for lymphocyte encounters with CNS antigens in cervical lymph nodes. In this regard, deep cervical lymph nodes may be a site for antigen-specific stimulation of B cells in MS (Chap. 444).

A second recently identified pathway consists of a plexus of small lymphatic-like vessels located on the external surface of meningeal arteries and deep dural sinuses (including the sagittal and transverse sinuses), structures that exit the brain along the surface of veins and arteries and drain to the deep cervical lymph nodes. These conduits are comprised of cells that appear to represent a lymphoid drainage system distinct from vascular endothelium. These sinus-associated lymphoid structures may be most important in clearing solutes from the CSF, in contrast to the glymphatic system that likely functions to remove waste products from the brain interstitium; however, the exact functions of these two systems and their interrelationships are only beginning to be understood.

MICROBIOTA AND NEUROLOGIC DISEASE

The human microbiome (Chap. 471) represents the collective set of genes from the 10^{14} organisms living in our gut, skin, mucosa, and other sites. For each gene encoded in the human genome, 1000 microbial genes exist within our bodies, and these can encode a wide variety of molecules that directly or indirectly affect nervous system development, maintenance, and function. Different microbial communities are associated with different genetic backgrounds, ethnicities, diets, and environments. In any individual, the predominant gut microbiota can be remarkably stable over decades, but also can be altered by exposure to certain microbial species, for example by ingestion of probiotics.

Gut microbes can shape immune responses through the interaction of their metabolism with that of humans. These gut-brain interactions are likely to be important in understanding the pathogenesis of many autoimmune neurologic diseases. For example, mice treated with broad-spectrum antibiotics are resistant to EAE, an effect associated with decreases in production of proinflammatory cytokines and conversely more production of the immunosuppressive cytokines IL-10 and IL-13 as well as an increase in regulatory T and B lymphocytes. Oral administration of polysaccharide A (PSA) from *Bacillus fragilis* also protects mice from EAE, via increases in IL-10. Intestinal microbiota from patients with MS were found to promote EAE when transferred to germ-free mice, possibly due to imbalances between bacterial species that promote inflammation (such as *Akkermansia muciniphila* and *Acinetobacter calcoaceticus*) and those that induce regulatory immune responses (such as *Parabacteroides distasonis*).

In addition to nonspecific effects on immune homeostasis mediated by cytokines and regulatory lymphocytes, some microbial proteins

might trigger a cross-reactive immune response against a homologous protein in the nervous system, a mechanism termed *molecular mimicry*. Examples include cross-reactivity between the astrocyte water channel aquaporin-4 and an ABC transporter permease from *Clostridia perfringens* in neuromyelitis optica (Chap. 445); HLA molecules with *A. muciniphila* peptides in MS (Chap. 444); the neural ganglioside Gm1 and similar sialic acid-containing structures from *Campylobacter jejuni* in Guillain-Barré syndrome (Chap. 447); and the sleep-promoting protein hypocretin and hemagglutinin from an H1N1 influenza virus in narcolepsy (Chap. 31).

Microbial genes also encode molecules that can affect development of neurons and glia, and influence myelination and plasticity. Bacterial-derived short-chain fatty acids, for example, regulate production of brain-derived neurotrophic factor (BDNF). Bacteria also produce a variety of neurotransmitters including γ -aminobutyric acid (GABA) and serotonin, and other neuroactive peptides that can modulate the hypothalamic-pituitary axis. Gut microbiota also influence development and activity of the enteric nervous system, which communicates bidirectionally with the CNS via the vagus nerve that innervates the upper gut and proximal colon. As these gut-brain relationships become better defined, a role for the microbial environment in the pathogenesis of a much wider spectrum of neurologic conditions and behaviors seems likely, extending well beyond the traditional boundaries of immune-mediated pathologies. In this regard, it has long been known that gut bacteria can influence brain function, based mostly on classic studies demonstrating that products of gut microbes can worsen hepatic encephalopathy, forming the basis of treatment with antibiotics for this condition.

Mice that develop in a germ-free environment display less anxiety, lower responses to stressful situations, more exploratory locomotive behaviors, and impaired memory formation compared with non-germ-free counterparts. These behaviors were related to changes in gene expression in pathways related to neural signaling, synaptic function, and modulation of neurotransmitters. Moreover, this behavior could be reversed when the germ-free mice were co-housed with non-germ-free mice. Intestinal microbiota were also found to be required for the normal development and function of brain microglia, potentially linking these behavioral effects to specific cellular targets in the CNS. Remarkably, the actions of gut microbial species on microglia appear to be sex- and age-specific.

The vagus nerve has been implicated in anxiety- and depression-like behaviors in mice. Ingestion of *Lactobacillus rhamnosus* induced changes in expression of the inhibitory neurotransmitter GABA_Ab in neurons of the limbic cortex, hippocampus, and amygdala, associated with reduced levels of corticosteroids and reduced anxiety- and depression-like behaviors. Remarkably, these changes could be blocked by vagotomy.

A related area of emerging interest is in a possible contribution of the gut microbiome to autism and related disorders. Children with autistic spectrum disorders (ASD) have long been known to have gastrointestinal disturbances, and the severity of dysbiosis appears to correlate with the severity of autism. In several murine models of autism, manipulation of the gut microbiome ameliorated the behavioral abnormalities. A role for the proinflammatory cytokine IL-17 was implicated as a possible mediator in producing the ASD-like changes. In mice, an ASD-like disorder could be induced in offspring after injecting the pregnant mother with the viral RNA mimic, polyinosinic:polycytidyllic acid (poly I:C); remarkably, oral treatment of offspring with *B. fragilis* corrected a range of autistic behaviors in these mice and also improved GI dysfunction. These preclinical data led to a small uncontrolled study of fecal gut transplantation in children with ASD that reported encouraging results, but will need to be confirmed in rigorous controlled trials.

There has been considerable interest in the possible role of the microbiome in a variety of vascular, traumatic, and neurodegenerative diseases, possibly mediated in part through actions on innate immunity and microglia. In SOD1 transgenic ALS-prone mice, a germ-free environment exacerbated disease progression, and symptoms could be ameliorated by increasing levels of *A. muciniphila* or its nicotinamide

(vitamin B3) metabolite; a small preliminary clinical trial of nicotinamide supplementation subsequently reported encouraging results in ALS patients.

In a PD model, injection of misfolded α -synuclein into the gut triggered deposition of α -synuclein in the brain, an effect that was blocked when the vagus nerve was severed. This supported a prion mechanism (see below) for PD pathogenesis, in which vagal transport of aggregated α -synuclein might seed the CNS via the vagus nerve. The concept of a gut origin of PD is also consistent with clinical and pathologic studies, and is further strengthened by epidemiologic data indicating that vagotomy may be protective against PD. In related work, a protein of *Escherichia coli*, named Curli, has been shown to misfold and potentially serve as a template for subsequent propagation of misfolded α -synuclein. The possibility that a bacterial protein could initiate the cascade of events leading to PD is an extraordinary, but still unproven, hypothesis.

PATHOLOGIC PROTEINS, PRIONS, AND NEURODEGENERATION FIG. 424 3

■ PROTEIN AGGREGATION AND CELL DEATH

The term *protein aggregation* has become widely used to describe easily recognizable hallmarks of neurodegeneration. While such neuropathologic hallmarks including plaques, neurofibrillary tangles (NFTs), and inclusion bodies are often thought to cause neurologic dysfunction, numerous new discoveries over the past several decades have rendered this view increasingly unlikely. Instead, protein aggregates represent accumulations of toxic proteins that may become less harmful when they are sequestered into plaques, NFTs, and inclusion bodies.

Most mutations in the amyloid precursor protein (APP) gene causing familial AD are concentrated within the A β peptide. Many of

these mutations increase production of the A β 42 peptide composed of β -amyloid with 42 amino acids, which has an increased propensity to adopt a prion conformation, as compared to β -amyloid with 40 amino acids. In contrast, mutations in the APP that reduce the production of β -amyloid protect against the development of AD and are associated with preserved cognition in the elderly. The most common cause of NFTs is AD, but the precise molecular events that produce tangles is unknown. Mutations in the MAPT gene encoding tau stimulate NFT formation in familial frontotemporal dementia, inherited progressive supranuclear palsy, and other familial tauopathies. Like AD, the majority of most tauopathies as well as PD are sporadic.

The second most common neurodegenerative disease is PD. The saga of α -synuclein and PD begins in 1996 with the identification of a mutation in a family of Greek descent. With this family and others, there were sufficient patients to establish genetic linkage. Soon thereafter, immunostaining showed that α -synuclein was present in Lewy bodies, and the following year staining of glial cytoplasmic inclusions (GCIs) was identified in the brains of deceased multiple-system atrophy (MSA) patients. Subsequently, brains from deceased MSA patients transmitted the disease to transgenic mice, establishing that the α -synucleinopathies are prion diseases. Before the α -synuclein (SCNA) gene was found to cause familial PD, other genes such as the leucine-rich repeat kinase 2 (*LRRK2*) were found to modify the onset of PD; other similar PD modifier genes include *parkin*, *PINK1*, and *DJ-1*. *PINK1* is a mitochondrial kinase (see below), and *DJ-1* is a protein involved in protection from oxidative stress. Parkin, which causes autosomal recessive early-onset PD-like illness, is a ubiquitin ligase. The characteristic histopathologic feature of PD is the Lewy body, an eosinophilic cytoplasmic inclusion that contains both neurofilaments and α -synuclein. Huntington's disease (HD) and cerebellar degenerations are associated with expansions of polyglutamine repeats in

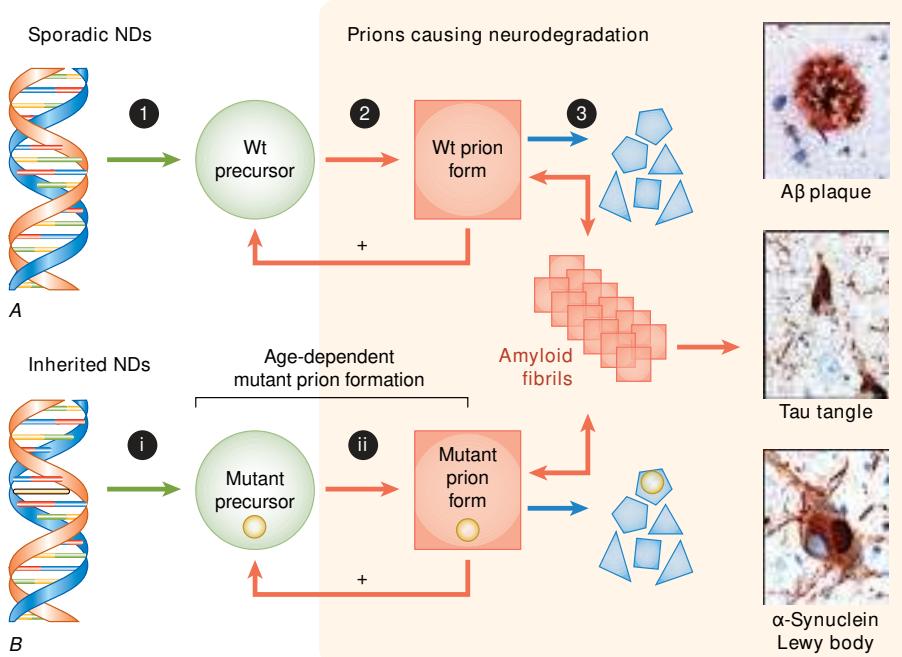


FIGURE 424-3 Neurodegeneration caused by prions. **A.** In sporadic neurodegenerative diseases (NDs), wild-type (Wt) prions multiply through self-propagating cycles of posttranslational modification, during which the precursor protein (green circle) is converted into the prion form (red square), which generally is high in β -sheet content. Pathogenic prions are most toxic as oligomers and less toxic after polymerization into amyloid fibrils. The small polygons (blue) represent proteolytic cleavage products of the prion. Depending on the protein, the fibrils coalesce into A β amyloid plaques in AD, neurofibrillary tangles in AD and other tauopathies, or Lewy bodies in PD and Dementia with Lewy bodies. Drug targets for the development of therapeutics include: (1) lowering the precursor protein, (2) inhibiting prion formation, and (3) enhancing prion clearance. **B.** Late-onset heritable neurodegeneration argues for two discrete events: The (i) first event is the synthesis of mutant precursor protein (green circle), and the (ii) second event is the age-dependent formation of mutant prions (red square). The highlighted yellow bar in the DNA structure represents mutation of a base pair within an exon, and the small yellow circles signify the corresponding mutant amino acid substitution. Green arrows represent a normal process; red arrows, a pathogenic process; and blue arrows, a process that is known to occur but unknown whether it is normal or pathogenic. (Reproduced with permission from SB Prusiner: Biology and genetics of prions causing neurodegeneration. *Annu Rev Genet* 47:601, 2013.)

proteins, which aggregate to produce neuronal intranuclear inclusions. Familial ALS is associated with superoxide dismutase (SOD1) mutations and cytoplasmic inclusions containing superoxide dismutase. An important finding was the discovery that ubiquitinated inclusions observed in most cases of ALS and the most common form of frontotemporal dementia are composed of TAR DNA-binding protein 43 (*TDP-43*). Subsequently, mutations in the *TDP-43* gene, and in the fused in sarcoma gene (*FUS*), were found in familial ALS. Both of these proteins are involved in transcription regulation as well as RNA metabolism.

Another key mechanism linked to cell death is mitochondrial dynamics, which refers to the processes involved in movement of mitochondria, as well as in mitochondrial fission and fusion, which play a critical role in mitochondrial turnover and in replenishment of damaged mitochondria. Mitochondrial dysfunction is strongly linked to the pathogenesis of a number of neurodegenerative diseases such as Friedreich's ataxia, which is caused by mutations in an iron-binding protein that plays an important role in transferring iron to iron-sulfur clusters in aconitase and complex I and II of the electron transport chain. Mitochondrial fission is dependent on the dynamin-related proteins (Drp1), which bind to its receptor Fis, whereas mitofusins 1 and 2 (MFN 1/2) and optic atrophy protein 1 (OPA1) are responsible for fusion of the outer and inner mitochondrial membrane, respectively. Mutations in MFN2 cause Charcot-Marie-Tooth neuropathy type 2A, and mutations in OPA1 cause autosomal dominant optic atrophy. Both β -amyloid and mutant huntingtin protein induce mitochondrial fragmentation and neuronal cell death associated with increased activity of Drp1. In addition, mutations in genes causing autosomal recessive PD, *parkin* and *PINK1*, cause abnormal mitochondrial morphology and result in impairment of the ability of the cell to remove damaged mitochondria by autophagy.

As noted above, one major scientific question is whether protein aggregates directly contribute to neuronal death or whether they are merely secondary bystanders. A focus in all the neurodegenerative diseases is on small-protein aggregates termed *oligomers*. How many monomers polymerize into a particular disease-specific oligomer has been elusive. Whether oligomers are the toxic species of β -amyloid, α -synuclein, or proteins with expanded polyglutamines such as the one causing HD remains to be established. Protein aggregates are usually ubiquitinated, which targets them for degradation by the 26S component of the proteasome. An inability to degrade protein aggregates could lead to cellular dysfunction, impaired axonal transport, and cell death by apoptotic mechanisms.

Autophagy is the degradation of cytosolic components in lysosomes. There is increasing evidence that autophagy plays an important role in degradation of protein aggregates in the neurodegenerative diseases, and it is impaired in AD, PD, FTD, and HD. Autophagy is particularly important to the health of neurons, and failure of autophagy contributes to cell death. In HD, a failure of cargo recognition occurs, contributing to protein aggregates and cell death.

There is other evidence for lysosomal dysfunction and impaired autophagy in PD. Mutations in glucocerebrosidase (*GBA*) are associated with 5% of all PD cases as well as 8–9% of patients with dementia with Lewy bodies. Notably, glucocerebrosidase and enzymatic activity are reduced in the substantia nigra of sporadic PD patients. α -Synuclein is degraded by chaperone-mediated and macro autophagy. The degradation of α -synuclein has been shown to be impaired in transgenic mice deficient in glucocerebrosidase and α -synuclein inhibits the activity of glucocerebrosidase; thus, there appears to be bidirectional feedback between α -synuclein and glucocerebrosidase.

The retromer complex is a conserved membrane-associated protein complex that functions in the endosome-to-Golgi complex. The retromer complex contains a cargo selective complex consisting of VPS35, VPS26, and VPS29, along with a sorting nexin dimer. Mutations in VPS35 were shown to be a cause of late-onset autosomal dominant PD. The retromer also traffics APP away from endosomes, where it is cleaved to generate β -amyloid. Deficiencies of VPS35 and VPS26 were also identified in hippocampal brain tissue from AD. A potential therapeutic approach to these diseases might therefore be to use chaperones

to stabilize the retromer and reduce the generation of β -amyloid and α -synuclein.

PRIONS AND NEURODEGENERATIVE DISEASES

As we have learned more about the etiology and pathogenesis of the neurodegenerative diseases, it has become clear that the histologic abnormalities that were once curiosities, in fact, are likely to reflect the etiologies. For example, the amyloid plaques in kuru and Creutzfeldt-Jakob disease (CJD) are filled with the PrP^{Sc} prions that have assembled into fibrils. The past three decades have witnessed an explosion of new knowledge about prions. For many years, kuru, CJD, and scrapie of sheep were thought to be caused by slow-acting viruses, but a large body of experimental evidence argues that the infectious pathogens causing these diseases are devoid of nucleic acid. Such pathogens are called prions, which are composed of host-encoded proteins that adopt alternative conformations that undergo self-propagation (Chap. 430). Prions impose their conformations on the normal, precursor proteins, which in turn become self-templating resulting in faithful copies; most prions are enriched for β -sheet and can assemble into amyloid fibrils.

Similar to the plaques in kuru and CJD that are composed of PrP prions, the amyloid plaques in AD are filled with A β prions that have polymerized into fibrils. This relationship between the neuropathologic findings and the etiologic prion was strengthened by the genetic linkage between familial CJD and mutations in the PrP gene, as well as (as noted above) between familial AD and mutations in the *APP* gene. Moreover, a mutation in the *APP* gene that prevents A β peptide formation was correlated with a decreased incidence of AD in Iceland.

The heritable neurodegenerative diseases offer an important insight into the pathogenesis of the more common, sporadic ones. Although the mutant proteins that cause these disorders are expressed in the brains of people early in life, the diseases do not occur for many decades. Many explanations for the late onset of familial neurodegenerative diseases have been offered, but none is supported by substantial experimental evidence. The late onset might be due to a second event in which a mutant protein, after its conversion into a prion, begins to accumulate at some rather advanced age. Such a formulation is also consistent with data showing that the protein quality-control mechanisms diminish in efficiency with age. Thus, the prion forms of both wild-type and mutant proteins are likely to be efficiently degraded in younger people but are less well handled in older individuals. This explanation is consistent with the view that neurodegenerative diseases are disorders of the aging nervous system.

A new classification for neurodegenerative diseases can be proposed based on not only the traditional phenotypic presentation and neuropathology, but also the prion etiology (Table 424-1). Over the past decade, an expanding body of experimental data has accumulated connecting prions in each of these illnesses. In addition to kuru and CJD, Gerstmann-Sträussler-Scheinker disease (GSS) and fatal insomnia in humans are caused by PrP^{Sc} prions. In animals, PrP^{Sc} prions cause scrapie of sheep and goats, bovine spongiform encephalopathy (BSE), chronic wasting disease (CWD) of deer and elk, feline spongiform encephalopathy, and transmissible mink encephalopathy (TME). Similar to PrP, A β , tau, α -synuclein, superoxide dismutase 1 (SOD1), and possibly huntingtin all adopt alternative conformations that become self-propagating, and thus, each protein can become a prion and be transferred to synaptically connected neurons. Moreover, each of these prions causes a distinct constellation of neurodegenerative diseases.

Evidence for a prion etiology of AD comes from a series of transmission experiments initially performed in marmosets and subsequently in transgenic mice expressing the mutant APP from which the A β peptide is derived (Table 424-1). Synthetic mutant A β peptides folded into a β -sheet-rich conformation exhibited prion infectivity in cultured cells. Studies of the tau protein have shown that it not only features in the pathogenesis of AD, but also causes the frontotemporal dementias including chronic traumatic encephalopathy, which has been reported in both contact sport athletes and military personnel who have suffered traumatic brain injuries. A series of incisive studies using cultured cells and Tg mice have demonstrated that both tau and A β prions are

TABLE 424-1 Prion-Based Classification of Neurodegenerative Diseases

NEURODEGENERATIVE DISEASE	CAUSATIVE PRION PROTEINS
Creutzfeldt-Jakob disease (CJD)	PrP ^{Sc}
Kuru	PrP ^{Sc}
Gerstmann-Sträussler-Scheinker disease (GSS)	PrP ^{Sc}
Fatal insomnia	PrP ^{Sc}
Bovine spongiform encephalopathy (BSE)	PrP ^{Sc}
Scrapie	PrP ^{Sc}
Chronic wasting disease (CWD)	PrP ^{Sc}
Feline spongiform encephalopathy	PrP ^{Sc}
Transmissible mink encephalopathy	PrP ^{Sc}
Alzheimer's disease (AD)	A β → tau
Down syndrome	A β → tau
ALS-PDC of Guam	A β → tau
Parkinson's disease (PD)	α -Synuclein
Dementia with Lewy bodies	α -Synuclein
Multiple-system atrophy	α -Synuclein
Frontotemporal dementias (FTDs)	Tau, TDP43, FUS (C9orf72, progranulin)
Posttraumatic FTD	Tau
Chronic traumatic encephalopathy (CTE)	Tau
Amyotrophic lateral sclerosis (ALS)	SOD1, TDP43, FUS (C9orf72)
Huntington's disease (HD)	Huntingtin

found together in the brains of AD patients. These findings indicated that AD is a double-prion disease (Table 424-1); unexpectedly, two more double-prion diseases have been identified recently. Patients with Down syndrome, from 6–72 years of age, all had both A β and tau prions in their brains with the frequent diagnosis of AD. The third double-prion disease has been found in the Chamorro people on Guam as well as Japanese living on the Kii peninsula: both groups of people develop ALS with dementia and both have A β and tau prions in their brains.

In contrast to A β and tau prions, α -synuclein prions cause very different illnesses, i.e., PD, dementia with Lewy bodies (DLB), and MSA. Brains from MSA patients inoculated into Tg(SCNA A53T) mice died ~90 days after intracerebral inoculation, whereas mutant α -synuclein (A53T) prions formed spontaneously in Tg mouse brains that killed recipient Tg mice in ~200 days (Table 424-1).

For many years, the most frequently cited argument against prions was the existence of strains that produced distinct clinical presentations and different patterns of neuropathologic lesions. Some investigators argued that the biologic information carried in different prion strains could be encoded only within a nucleic acid. Subsequently, many studies demonstrated that strain-specified variation is enciphered in the conformation of PrP^{Sc}, but the molecular mechanisms responsible for the storage of this biologic information remains enigmatic. The neuroanatomical patterns of prion deposition have been shown to be dependent on the particular strain of prion. Convincing evidence in support of this proposition has been accumulated for PrP, A β , tau, and α -synuclein prions. The most persuasive information on prion strains comes from studies in yeast where the tools of yeast genetics allowed incisive investigations to be performed in ways that could not be accomplished in mammals.

Although the number of prions identified in mammals and in fungi continues to expand, the existence of prions in other phylogeny remains undetermined. Some mammalian prions perform vital functions and do not cause disease; such nonpathogenic prions include the cytoplasmic polyadenylation element-binding (CPEB) protein, the mitochondrial antiviral-signaling (MAVS) protein, and T cell-restricted intracellular antigen 1 (TIA-1).

Many but not all prion proteins adopt a β -sheet-rich conformation and appear to readily oligomerize as this process becomes self-propagating. Control of the self-propagating state of benign mammalian

prions is less well understood than that of pathogenic mammalian prions, which appear to multiply exponentially. We do not know if prions multiply as monomers or as oligomers; notably, the ionizing radiation target size of PrP^{Sc} prions suggests it is a trimer. The oligomeric states of pathogenic mammalian prions are thought to be toxic; larger polymers, such as amyloid fibrils, seem to be a mechanism for minimizing toxicity.

To date, there is no medication that halts or even slows one human neurodegenerative disease. The development of drugs designed to inhibit the conversion of the normal precursor proteins into prions or to enhance the degradation of prions focuses on the initial step in prion accumulation. Although a dozen drugs that cross the blood-brain barrier have been identified that prolong the lives of mice infected with scrapie prions, none has been identified that extends the lives of Tg mice that replicate human CJD prions. Despite doubling or tripling the length of incubation times in mice inoculated with scrapie prions, all of the mice eventually succumb to illness. Because all of the treated mice develop neurologic dysfunction at the same time, the mutation rate as judged by drug resistance is likely to approach 100%, which is much higher than mutation rates recorded for bacteria and viruses. Mutations in prions seem likely to represent conformational variants that are selected for in mammals where survival becomes limited by the fastest-replicating prions. The results of these studies make it likely that cocktails of drugs that attack a variety of prion conformers will be required for the development of effective therapeutics.

NEURAL STEM CELL BIOLOGY

Normal and genetically modified ("transgenic") mice are the most widely used model systems to study features of human nervous system diseases. However, modeling genetic diseases in rodents is limited to the relatively small number of monogenic human diseases where the specific gene mutations are known, and is further limited by species differences. The latter can be particularly important in brain regions such as the cerebral cortex that have undergone significant evolutionary expansion in humans. These shortcomings, which likely contribute to the low probability that therapeutic efficacy translates from animal models to humans, can potentially be overcome through stem cell models that enable the use of human cells and tissues to model human diseases. The advent of new stem cell technologies is transforming our understanding of the pathobiology of human neurologic diseases. Stem cell platforms are being used to screen for therapeutic agents, to uncover adverse drug effects, and to discover novel therapeutic targets.

Among the most exciting recent advances in stem cell technology is the ability to convert somatic cells, either skin fibroblasts or blood cells, into pluripotent stem cells known as induced pluripotent stem cells (iPSCs). This technology has introduced an entirely new and powerful approach to study the pathobiology of heritable diseases. Pluripotent stem cells can be easily obtained through minimally invasive procedures such as a skin biopsy or blood sample, and converted to pluripotency through application of a cocktail of reprogramming factors to create iPSCs. Initially, a set of four programming factors, Oct3/4, Klf-4, Sox2, and c-Myc, was delivered to cells using lentiviruses that stably integrated the reprogramming factor genes into the iPSC genome, potentially altering disease phenotypes and also abrogating expression of native genes at the DNA sites where the factors integrated. Newer techniques have been developed that use nonintegrating approaches such as through the use of Sendai virus, messenger RNA (mRNA), or episomal vectors that circumvent these problems. Once created, iPSC lines can be expanded indefinitely to produce a limitless supply of stem cells. These cells are the starting material for the derivation of specific cell types based on protocols that use small molecules, proteins, or direct gene induction to recapitulate developmental programs. Most current protocols derive neuronal progenitor through dual-SMAD inhibition, a step that involves the use of small-molecule inhibitors to block endoderm and mesodermal cell fates, thereby creating neural cells by default. Multiple protocols have been developed over the last decade for creating large numbers of human neuron progenitor cell types and directing them toward specific nervous system cell fates, including neuron subtypes from multiple regions of brain and

spinal cord as well as retinal cells, glial cells including astrocytes and oligodendrocytes, immune cells, and peripheral nervous system cells.

The primary medical benefit of iPSC technology is that it enables the creation of patient-specific cells or tissues that are genetically matched to individual patients. This approach enables the study of not only monogenetic disorders but also sporadic forms of disease and complex polygenic disorders including those with unidentified risk loci. Furthermore, by deriving iPSC cell lines from multiple patients, it would be possible to explore how disease phenotypes may vary according to genetic background. Another approach that has been used to generate specific neuron and glial cell types from somatic cells such as fibroblasts is through direct reprogramming. This approach relies on a cocktail of specific transcription factors to directly convert somatic cells into the alternate desired cell type. This approach bypasses the epigenetic reset that accompanies cells as they are reprogrammed to a pluripotent state. The advantage of this approach is that age-related epigenetic signatures are not erased, so that derived neurons may more readily reflect diseases that manifest in older cells.

Despite the advantages of using *in vitro* models of nervous system diseases derived from patient-specific iPSCs, several potential roadblocks remain. There are no standard reprogramming or derivation protocols, and the different methods can result in considerable variability in the disease phenotypes reported by different laboratories. Confidence in the specificity of a particular phenotype is therefore increased if it has been validated across multiple laboratories. There is also the problem of inherent variability between patient lines that may result from their different genetic backgrounds. One solution, available only in the case of monogenic disorders, is to use isogenic controls generated using gene editing, such as with CRISPR-Cas9 technology, to create disease and control lines on an identical genetic background. However, because differences in genetic background can influence the penetrance of a particular trait, it will still be necessary to compare disease lines from multiple patients to discern a true disease phenotype. For polygenic disorders where the causative mutations are unknown, it will not be possible to create isogenic controls, and in these situations the best strategy for improving reliability and sensitivity is to compare lines from multiple patients.

■ ORGANOID

Most nervous system disorders, including autism spectrum disorder, schizophrenia, PD, AD, and ALS are complex disorders, resulting from an unknown combination of gene mutations, and manifest not only in specific cell types, but also in alterations of the local tissue environment. These disorders are difficult to model in animals, but they are approachable using three-dimensional human iPSC stem cell models, often referred to as “organoids.” Organoids are derived from pluripotent stem cells that are directed along a tissue-specific lineage through the timed application of growth factors, genes, or small-molecule activators or inhibitors, and allowed to aggregate into three-dimensional structures. With time, cell intrinsic programs are spontaneously engaged and the cellular aggregates begin to self-organize and develop into structures that recapitulate the complex topographical and cellular diversity of normal organ development. In this way it has been possible to create, at least in part, *in vitro* brainlike organoids that resemble the human forebrain at early stages of development. When allowed to develop from an anterior neural tube stage, these structures can become heterogeneous, containing regions with forebrain, midbrain, and/or hindbrain identity, and can often include retina-like structures. The high degree of variability in such “whole-brain organoids” can be a liability for controlled studies, and can be reduced by the use of more directed protocols that restrict outcomes to more defined brain regions, such as forebrain, cortex, or ganglionic eminence. A variety of protocols have now been developed to generate organoids with specific regional identity, and fusing organoids of different regional identity with each other has been used to reproduce cellular interactions such as neuronal migration across regions. Many protocols are focused on modeling cortical development, and they can reproduce developmental features including a diversity of progenitor and neuronal cell types topographically distributed within ventricular

and subventricular progenitor regions and rudimentary cortical layers. However, the organoids follow a human developmental timetable and still remain at stages roughly comparable to late fetal development even after 6–9 months of culture. Moreover they lack key cell types such as endothelial cells, pericytes, and microglia, and have few if any astrocytes or oligodendrocytes. Nonetheless, while still only reflecting rudimentary organizational and compositional features, organoids have become attractive models to study human brain development and the pathophysiology of human nervous system diseases in the context of a partially organized brainlike structure.

■ BRAIN DEVELOPMENT AND DEVELOPMENTAL DISORDERS: MICROCEPHALY AND LISSENCEPHALY

Transcriptional analysis has suggested that the neurons produced by most stem cell protocols resemble early- to mid-gestational stages of human brain development. The immaturity of stem cell-derived human neurons may limit their utility for modeling adult diseases but it does make them ideally suited for the study of brain development and the pathophysiology of neurodevelopmental disorders.

Primary autosomal recessive microcephaly (MCPH) is a rare neurodevelopmental disorder producing severe microcephaly with simplified cortical gyration and intellectual disability. MCPH was one of the first disorders to be studied using cerebral organoids. Mutations in genes encoding microtubule spindle components and spindle-associated proteins are the most frequent causes of congenital microcephaly. Among them is cyclin-dependent kinase 5 related activator protein 2 (CDK5RAP2). Skin fibroblasts derived from a single microcephalic patient carrying a mutation in CDK5RAP2 were used to generate four iPSC lines. Cerebral organoids grown from these cell lines contained fewer proliferating progenitor cells and showed premature neural differentiation compared to wild-type controls. Introducing functional CDK5RAP2 by electroporation partially rescued the disease phenotype, supporting the notion that failure of the founder population of neural progenitors to properly expand underlies the smaller brain. This study demonstrated that brain organoids derived from patients with microcephaly can be used to reproduce features of the disease, but did not reveal new insights or disease features of CDK5RAP2 microcephaly that had not already been described in mouse models.

In a study using cortical organoids to model Miller-Dieker syndrome (MDS), a severe congenital form of lissencephaly or “smooth-brain,” features of the human disease were observed that had not been noted in murine models. Classical lissencephaly is a genetic neurologic disorder associated with mental retardation and intractable epilepsy, and MDS is a severe form of the disorder. Cortical folding in humans begins toward the end of the second trimester, a stage of development that has not yet been modeled in organoids, but gyrencephaly depends upon earlier events such as neural progenitor cell proliferation and neuronal migration, which can be modeled in organoids. The human organoid model of MDS exhibited several neural progenitor cell phenotypes that had already been reported in mouse models, including altered mitotic spindle orientation and neuronal migration defects. But the organoids also displayed a mitotic defect in a specific neural stem cell subtype, the outer radial glia cell (oRG), that had not been observed in mice. oRG cells are enriched in the outer subventricular zone, a proliferative region that is large in primates and not present in rodents. These cells are particularly numerous in the developing human cortex and are thought to underlie the developmental and evolutionary expansion of the human cortex. oRG cells from MDS patients behaved abnormally and had arrested or delayed mitoses. MDS organoids also identified noncell autonomous defects in *Wnt* signaling as an underlying mechanism. These insights into mechanistic and cell type specific features of human disease highlight how organoid technology can provide new and valuable perspectives on the pathophysiology of disorders of *in utero* development.

■ ACQUIRED NEURODEVELOPMENTAL DISORDERS: ZIKA

The recent outbreak of Zika virus (ZIKV) and associated microcephaly cases in the Americas provided a test case for the utility of brain

organoids to model acquired human microcephaly. Despite a correlation between Zika infection rates and the incidence of congenital microcephaly, compelling evidence that ZIKV caused microcephaly was lacking in the early phases of the epidemic. The causal link between ZIKV and congenital microcephaly was buttressed by two studies in 2016 that used human iPSC-derived neural progenitor cells and organoids to demonstrate ZIKV tropism for human neural progenitor cells. Neural progenitor cells (radial glia) were readily infected *in vitro* with subsequent progenitor cell death and involution of organoid size. Forebrain organoids were further used to highlight the role of the flavivirus entry factor, AXL, in determining viral tropism, and were also used to explore the disease mechanism by demonstrating upregulation of the innate immune receptor toll-like receptor 3 (TLR) in response to ZIKV infection. Stem cell-derived models of human brain development have also demonstrated centrosomal abnormalities in radial glia and alteration in the cleavage plane of mitotic radial glia associated with premature neural differentiation. Mouse models are also being used to study the pathophysiology of congenital ZIKV syndrome, but the availability of unlimited numbers of human neural cells produced using stem cell technology has enabled high-throughput screening assays to test libraries of clinically approved compounds for potential therapeutic agents. This strategy has already highlighted several compounds that could potentially help protect against ZIKV microcephaly.

■ NEURODEVELOPMENTAL DISORDERS: AUTISM AND SCHIZOPHRENIA

Autism spectrum disorders (ASDs) are complex and heterogeneous neurodevelopmental disorders usually manifesting in childhood with difficulties in social interaction, verbal and nonverbal communication, and repetitive behaviors. The cellular and molecular mechanisms underlying ASD are thought to arise at stages of fetal brain development, making them well-suited for exploration using human iPSC-derived disease models. iPSC-derived neurons have been used to study the pathophysiology of disorders associated with ASD that are caused by monogenic mutations, including Fragile X, Rett, and Timothy syndromes.

Fragile X is the most common heritable cause of intellectual disability, affecting 1 in 4000 males and 1 in 8000 females, and is a leading genetic cause of ASD. Patients also have speech delay, growth and motor abnormalities, hyperactivity, and anxiety. The causative mutation lies in the *FMRI* gene and produces a CGG triplet repeat expansion from a normal number of 5–20 to >200, leading to epigenetic silencing of the *FMRI* gene and loss of the fragile X mental retardation protein. The epigenetic mechanism means that unlike a simple gene deletion that would lead to ubiquitous loss of expression, the *FMRI* locus becomes hypermethylated and epigenetically silenced during differentiation; thus *FMRI* protein is expressed by the early embryo and becomes absent only around the beginning of the second trimester. Interestingly, this expression pattern is recapitulated during cellular differentiation in stem cell models. Pluripotent Fragile X stem cell lines have been derived from embryos identified through pre-implantation genetic diagnosis and by reprogramming skin fibroblasts from Fragile X patients to create iPSC lines. In both cases *FMRI* was expressed by the pluripotent stem cells but underwent transcriptional silencing following differentiation. Fragile X stem cell lines can therefore be used to study the mechanism of *FMRI* silencing, an effort that is ongoing. Neurons generated from Fragile X iPSC cells reproduce features observed in neurons from transgenic *FMRI* mouse models and patients, including stunted neurites with decreased branching, increasing confidence in the iPSC model. In addition to providing a model that can be used to study disease pathogenesis, Fragile X iPSC-derived neurons could be used to screen for potential therapeutic agents or gene-editing strategies that could be able to remove the repressive epigenetic marks induced by the mutation and rescue the phenotype.

Rett syndrome is an X-linked neurodevelopmental disorder with dominant inheritance caused by a mutation in the *MECP2* gene. Because males carrying one copy of the defect gene usually die in infancy, most patients are girls. Random inactivation of the X

chromosome in girls results in mosaic cellular expression of the mutation that circumvents fatality and produces a variable phenotype. The symptoms are present in early childhood and include microcephaly associated with developmental delay, autistic-like behaviors and cognitive dysfunction, seizures and repetitive motor actions; these then progress to include difficulties with gait, swallowing, and breathing before usually stabilizing with patients surviving to adulthood. The pathophysiology of Rett syndrome is presumed to involve abnormal epigenetic regulation leading to decreased transcriptional repression of genes whose overexpression produces the disease phenotype, although this concept has been contested. In one of the first studies to use iPSC modeling to study Rett syndrome, it was discovered that when fibroblasts from patients were reprogrammed to pluripotent stem cells, X inactivation was erased. In apparent recapitulation of endogenous events, X chromosome inactivation re-occurred during neuronal differentiation, producing a mosaic of cells carrying the mutant gene intermingled with normal cells. Rett neurons had fewer dendritic spines and synapses, smaller cell bodies, and reduced network activity. Another iPSC model of Rett syndrome highlighted the potential role of altered inhibitory function. Rett neurons were found to have a deficit of potassium/chloride cotransporter (KCC2) that is developmentally regulated and normally leads to a switch in GABA signaling from excitatory at embryonic ages to inhibitory by birth. In Rett neurons, KCC2 expression level was low, and the functional switch in GABA effects was delayed, contributing to some of the disease features and possibly accounting for the developmental onset of the disease. One curious feature of some iPSC Rett lines was that despite the mosaic expression of the mutation, disease phenotypes were observed in all cells. Possibly, this could reflect a noncell autonomous effect, but as in all iPSC disease models, confidence in disease-specific features will be increased when similar phenotypes are seen across multiple independent studies.

Timothy syndrome, another severe neurodevelopmental disease associated with ASD, has been modeled using iPSC-derived organoids. Timothy syndrome is caused by a mutation in the *CACNA1C* gene coding for a voltage-gated calcium channel, and neuron defects in Timothy syndrome organoids were rescued by selectively altering calcium channel activity. In one study two separate organoids were produced with different regional identity, one represented neocortex and one a more ventral structure known as the medial ganglionic eminence, which is the source of most cortical interneurons. The two organoids were then fused together to allow the interneurons to migrate into the cortex, mimicking their endogenous behavior. The ability to model interneuron migration led to the discovery of a cell-autonomous migration defect in the disease-carrying neurons.

The majority of nervous system diseases, including ASD, are polygenic and cannot be modeled in animals but can be modeled using patient-derived iPSCs. For example, a subset of patients with ASD have large head size, and a cohort of patients with this phenotype was used to generate iPSCs that were converted to neural progenitor cells and forebrain neurons. The progenitors had an accelerated cell cycle and produced an excess of inhibitory interneurons and had exuberant cellular overgrowth of neurites and synapses. This last feature is in contrast to the decrease in spines and synapses observed in other iPSC models of ASD such as Fragile X and Rett syndrome and underscores the need for replication and validation of purported disease phenotypes given the high variability based on differences between stem cell lines, protocols, patient genetic background, and other factors. Moreover, the clinical features of most neuropsychiatric diseases reflect disorders in processes such as circuit formation and refinement that occur after birth and may be difficult to capture at the fetal stage of development reflected in stem cell models.

Patient stem cells have also been used by multiple groups to study the pathophysiology of schizophrenia, producing a variety of diverse and sometimes contradictory results. Reports claim obvious phenotypes such as disruptions in the adherens junctions of forebrain radial glia or aberrant neuronal migration, although such gross abnormalities observed at the equivalent of *in utero* stages of development seem very unlikely to underlie a disease that usually manifests at adolescence or young adulthood. Other studies report abnormalities related to

abnormal microRNA expression, disordered cyclic AMP and *Wnt* signaling, abnormal stress responses, diminished neuronal connectivity, fewer neuronal processes, problems with neuronal differentiation, and mitochondrial abnormalities, among others. While the pathophysiology of as complex a neurodevelopmental disorder as schizophrenia may be multidimensional, it is unclear which, if any, of the reported findings in iPSC models reflect the true pathology of schizophrenia. Progress will likely depend on the adoption of more standard and reproducible protocols, more rigorous identification of cell types, markers of regional identity, and indicators of maturity.

■ ALZHEIMER'S DISEASE

As noted above, the leading concept of AD pathogenesis, the amyloid hypothesis, suggests that an imbalance between production and clearance of β -amyloid leads to excessive accumulation of β -amyloid peptide and the formation of NFTs within neurons, composed of aggregated hyperphosphorylated tau proteins. Additionally, aggregates of amyloid fibrils are deposited outside neurons in the form of neuritic plaques. Recent failures of anti- β -amyloid therapies, which were highly effective in mouse models, have led to a search for alternative models that might be more predictive of therapeutic effectiveness in humans. Among the causes of familial AD are mutations in genes involved in β -amyloid production, including amyloid precursor protein (APP) and presenilin 1 and 2. Shortly after the introduction of iPSC technology, human stem cell-derived neurons were generated from patients carrying mutations in AD-causative genes as well as from sporadic AD cases. The disease neurons developed hallmarks of AD including intracellular accumulation of β -amyloid and phosphorylated tau, as well as secretion of APP cleavage products, features that could be reduced by adding β - or γ -secretase inhibitors or β -amyloid-specific antibodies. The neurons also demonstrated other disease features observed in postmortem AD tissues. However, extracellular β -amyloid aggregation and NFTs were not robustly modeled in these two-dimensional systems, presumably because secreted factors were able to readily diffuse away. The use of three-dimensional organoids to model AD overcame this limitation, presumably by recreating a more faithful extracellular matrix. Organoid models promoted the aggregation of β -amyloid, and more readily recapitulated the pathologic features of AD, including the formation of NFTs and neuritic plaques.

It is hoped that the new stem cell models, particularly organoid models, will accelerate our understanding of AD by enabling the study of human disease-carrying cells in a quasi *in situ* setting. These new models may lead to discovery of novel druggable targets and new diagnostic and prognostic biomarkers. One concern is that the pathogenic features of AD usually appear in the sixth or seventh decade of life and progress slowly over years, while most protocols for the derivation of human cortical neurons generate cells over weeks or months and most remain comparable to immature neurons at fetal stages of development. Nonetheless, these young cells have been used to model neurodegenerative diseases such as AD and HD that strike patients in middle to late adulthood. Possibly the onset of disease phenotype is accelerated in stem cell models due to increased cellular stress, which appears to be a feature of stem cell culture, or disease features may actually have a subtle onset at earlier stages than generally suspected. Indeed, 3-year-old children at genetic risk of developing early-onset AD appear to have smaller hippocampal size and lower scores on memory tests than children in a nonrisk group. The phenotypes of adult neurodegenerative diseases that are visible at fetal stages may or may not correspond to those manifest at later, adult stages, but they may offer the possibility of devising preventative strategies effective at very early stages of the disease.

■ CELL TYPE DISORDERS: ALS AND HUNTINGTON'S DISEASE

In diseases such as ALS, PD, and HD, that mostly target specific neuron subtypes, stem cells provide an ideal means to study the vulnerable human cell populations. By enabling the production of unlimited numbers of normal and diseased human midbrain dopaminergic neurons for the study of PD, medium spiny striatal neurons for HD, and spinal

and cortical motor neurons for ALS, iPSC approaches have the potential to transform our understanding and management of these diseases. Stem cell-derived neurons serve as platforms to explore mechanisms of cell vulnerability, to screen drugs for neural protection, and potentially to derive neurons for replacement therapy.

■ AMYOTROPHIC LATERAL SCLEROSIS

One of the first protocols for producing neurons of a specific subtype from embryonic stem cells recapitulated normal developmental programs to generate mouse spinal motor neurons. Pluripotent mouse stem cells underwent neural induction and adopted a caudal identity through the application of retinoic acid, and subsequently adopted motor neuron fate through the action of Sonic hedgehog (Shh), a ventralizing factor. Generating human motor neurons proved more complex, requiring additional steps, such as early exposure to the growth factor, FGF2. The first application of stem cell-derived motor neurons to study ALS involved the use of mouse motor neurons generated from transgenic mice expressing a mutation in the superoxide dismutase 1 (SOD1) gene, the most common mutation responsible for familial ALS. Only 5–10% of ALS cases are familial, but the known mutations provide a useful entry point to tease apart the causative pathophysiology. Mutations in SOD1 produce ALS through a toxic gain-of-function for which the mechanism remains unclear, despite the use of multiple transgenic animal and iPSC models. The use of mouse ESC-derived motor neurons, however, demonstrated that toxic factors secreted by SOD1 astrocytes contribute to the death of motor neurons. Interestingly, stem cell-derived interneurons were spared, indicating a specific vulnerability of motor neurons. These findings helped establish the notion that a noncell autonomous toxic mechanism contributes to ALS pathogenesis and may ultimately lead to novel treatment strategies. These findings also highlight that modeling the full pathophysiology of ALS may require the reproduction of a complex environment including motor neurons, astrocytes, and possibly additional cell types such as microglia. A variety of approaches including co-culture of specific cell types, three-dimensional spinal cord organoids, and microfluidic organ-on-chip models are being explored to achieve a more complete facsimile of spinal cord organization. Similar to other neurologic disorders where a clearly defined phenotype has been observed in human stem cell-derived models, there is hope that drug screening using human disease-expressing cells will identify a potential therapeutic compound.

■ HUNTINGTON'S DISEASE

HD is caused by an expansion in CAG triplet repeats in the huntingtin gene, which leads to an expanded polyglutamine tract in the huntingtin protein. HD is dominantly inherited, with symptoms of cognitive decline and uncontrollable gait and limb motions beginning in the third to fifth decade of life with progression to dementia and death approximately 20 years later. Mutant huntingtin causes a toxic gain-of-function, with the degree of effect related to the CAG repeat length. For example, a CAG length of 40–60 repeats produces adult-onset HD, whereas repeats of 60 or more produce juvenile-onset disease. Although it has been 25 years since the discovery of this causative mutation, the disease mechanism remains poorly understood. Excess huntingtin protein and protein fragments accumulate in specific subtypes of neurons where they misfold and form aggregates that are visible as cellular inclusions. Affected cells eventually die, possibly as a result of metabolic toxicity. The medium spiny neurons of the striatum are the most vulnerable neurons, spurring ongoing attempts to produce replacement cells derived from stem cells, but neuron loss is widespread including in the cortex, complicating a cell replacement approach for this disease. HD iPSCs have been generated from patients with various CAG repeat lengths, but those from juvenile-onset disease with the longest repeat lengths have been favored as being most likely to express robust disease phenotypes at an early stage. This is particularly important given the immature stage of maturation of stem cell-derived human neurons. This approach has been able to produce disease phenotypes observed in patients including huntingtin protein aggregation, decreased metabolic capacity, increased oxidative stress

with mitochondrial fragmentation, and apoptosis enhanced by withdrawal of growth factor support. However, many of these phenotypes were observed in pluripotent cells prior to neural differentiation and in neural progenitors and a broad array of CNS neurons in contrast to the cell type-specific features of the disease. Nonetheless, neurons that assumed striatal fate appear to be more vulnerable to stress and apoptosis than other cell types. As with other iPSC models of nervous system diseases, there have so far been few efforts to validate results in multiple iPSC lines having different genetic backgrounds but with similar CAG repeat lengths. An HD consortium has been formed to address this problem by generating a series of iPSC lines from multiple patients. An alternative strategy to validate disease phenotypes has been to use gene editing to create isogenic iPSC lines that are corrected to produce wild-type control and HD iPSC lines against the same genetic background.

FUTURE PERSPECTIVES

Despite early successes, it may prove difficult to reconstitute neurodegenerative disease conditions in human cells *in vitro* over a short course of time because the pathogenic changes of degenerative diseases progress slowly and commence in the later stages of life. The differentiation and maturation of human neurons from stem cell lines occur over a span of months, which may not be long enough to establish the aged-brain conditions under which patients develop robust neurodegenerative pathology. Possible manipulation through gene editing or by application of aging-associated stresses, such as DNA-damaging agents or proteasome inhibitors, may accelerate the expression of degenerative phenotypes in human iPSC-derived cellular models. Stem cell-derived organoid models are also ideal platforms to apply methods for cellular-level visualization such as clarity and multi-electrode recording techniques to better evaluate three-dimensional organoid structures and explore early-forming circuits. These applications are only just beginning.

Two-dimensional cell cultures are ideal for production and evaluation of large numbers of specific cells of a particular identity, but may not provide the complex extracellular environment necessary to model certain disease processes, such as extracellular protein aggregation. These features can be best modeled using three-dimensional organoids, but current methods do not reproduce all the relevant features of brain tissue. Optimization will be needed to better reproduce the cellular composition of brain, including endothelial cells, astrocytes, microglia, and oligodendrocytes. It may also be necessary to combine different brain regions generated separately, possibly by fusion of tissues such as dorsal cortex, subpallium, thalamus, retina, and others. However, currently there is a limited ability to recreate tissues or neurons with regional brain identity, such as hippocampus, thalamus, or cerebellum. More faithful organoid models could also emerge through the application of bioengineered scaffolds, matrices, or perfusion systems that might allow the growth of larger structures. Of course, not all aspects of mature brain architecture and function will be modeled by these tissue structures, particularly as they represent fetal stages of development, but perhaps the most precocious events in disease etiology can be captured and investigated and these may share mechanistic pathways with disease features that manifest at later stages.

The current excitement surrounding human stem cells has more to do with their promise to improve on animal models of disease than their potential as a source for cell-based therapies. Even without new insights into disease pathogenesis, there is promise that iPSC models such as brain organoids will act as drug-screening platforms for discovery of novel therapeutics and for detection of off-target and toxic effects. The failure of many neurotherapeutic approaches to translate from animal models to clinical practice underscores the need for better predictive models, and stem cell models and brain organoids based on human cells may be ideally suited to bridge this divide.

A CURRENT PERSPECTIVE ON NEURAL STEM CELLS IN THE CLINIC

The prospect of stem cell therapies to treat diseases or injuries of the nervous system has captured the attention of researchers, clinicians, and the public. The pace of research is usually slow and deliberate, but

in the stem cell arena there has been enormous pressure to accelerate the pace of progress in order to bring cell-based therapies to the clinic. Expectations have been raised, and clinics have already begun offering unproven or dangerous treatments to a public that is ill-informed and vulnerable to exploitation. Nonetheless, there is cautious optimism that stem cells will eventually realize the promise of regenerative therapy for at least some currently untreatable or incurable nervous system diseases.

Pursuit of a cell-based therapy for PD has been ongoing for many decades. Following anecdotal success in a handful of patients who appeared to improve following striatal grafts of fetal midbrain dopaminergic cells, two National Institutes of Health funded, double-blind control studies were launched in the 1990s. However, only a small number of younger patients showed some benefit, and several patients developed spontaneous dyskinetic movements related to the therapy. These efforts constituted a failed trial as the treated patients who did not experience side effects failed to improve significantly. However, techniques to extract dopaminergic cells from fetal tissue have been improved, and on the basis of encouraging results in individual transplanted patients, some of whom have managed to go off their Parkinson's medication, a new trial of fetal cell transplantation for PD has started in Europe. This is a very consequential trial, as a poor clinical outcome could dampen enthusiasm for the planned follow-up stem cell trials in PD and possibly in other disorders as well.

Meanwhile, the dyskinesias that curtailed the NIH trials in the 1990s were eventually ascribed to an abundance of serotonergic neurons that were inadvertently included in some of the cell grafts. Protocols for deriving dopaminergic neurons from stem cells could potentially avoid this complication by providing a more purified cell population, and several groups around the world have been aggressively pursuing a stem cell-based approach to PD. In 2018, researchers from Kyoto University in Japan started a phase 1/2 clinical trial to treat PD using stem cells. The investigators chose to use iPSCs derived from a healthy person who had the most common HLA haplotype in Japan. The iPSCs were used to make dopamine-secreting neurons. Seven patients will have the reprogrammed stem cells surgically delivered into the brain and be followed for 2 years postinjection to assess safety and possible efficacy. The U.S. Food and Drug Administration (FDA) recently approved the first clinical trial of a stem cell-derived dopamine neuron for the treatment of PD in the United States. These cells, derived from an embryonic stem cell line, will be delivered to 10 patients in a phase 1 clinical trial to assess safety, tolerability, and preliminary efficacy. A European trial led by scientists in Sweden and the UK is expected to begin soon and will also use dopamine-secreting midbrain-like neurons derived from embryonic stem cells.

One of the first cell-based clinical trials for a neurologic disease targeted patients suffering from an untreatable childhood disorder, Batten disease. Batten disease is an autosomal recessive metabolic disorder resulting from an inability to synthesize a lysosomal enzyme critical to brain function. The phase 1 trial involved six patients with infantile and late-infantile forms of the disease who received neural stem cells rather than any specific postmitotic cell type. Neural stem cells derived from donated fetal tissue were expanded *in vitro* prior to surgical grafting into the brain. This approach was not without risk, as the neural stem cells were proliferating and could potentially form an abnormal growth. The rationale was that the cells would be capable of synthesizing and secreting the missing lysosomal enzyme and would therefore serve as a delivery device. Animal studies using a transgenic mouse model of Batten disease demonstrated rescue, and this promising result led to a small phase 1 trial. The phase 1 study was considered a success as no adverse events were reported and the cells appeared to be safe, though there was no clinical improvement and no clear evidence of whether the cells had dispersed, transformed into neurons or glia, or indeed survived at all. Despite clearing the phase 1 trial, the company did not pursue further trials for Batten disease, but instead initiated clinical trials using the same cell product for several other indications, including an inherited fatal dysmyelination syndrome known as Pelizaeus-Merzbacher disease (PMD). The human neural stem cells have both neurogenic and gliogenic potential, and when delivered to

white matter regions in experimental animals, most persisting cells had become oligodendrocytes. This supported use of the cells to promote myelin formation in conditions such as PMD. The company also initiated trials in spinal cord injury. However, the spinal cord trial failed to achieve sufficient benefit in phase 2 and the company ceased its work on stem cell therapies.

Spinal cord injury is an attractive target for novel therapies because there are more than 1 million patients suffering from spinal cord injuries worldwide, with no effective treatment options. Not surprisingly, there has been intense interest in achieving a stem cell treatment for this condition and dozens of early-stage clinical trials, and anecdotal treatment results have been reported by investigators around the globe. The vast majority have not been blinded controlled trials, but rather individual reports treating a handful of patients and somewhat surprisingly, most are using mesenchymal (MSC) or hematopoietic stem cells that normally generate either bone, cartilage, fat, or blood cells. As described below, the rationale for the use of MSCs for neurologic conditions is based on vague and poorly understood mechanisms of action.

A series of stem cell trials designed to treat subacute spinal cord injury is underway in the United States and Europe that are using neural stem cells or their derivatives as potential therapeutic agents. The first to enter clinical trials in the United States was based on a protocol designed to generate oligodendrocytes from pluripotent embryonic stem cells. Evidence of efficacy was obtained in animal models following surgical grafting of cells to sites of spinal cord injury. However, evidence of myelination of host axons was minimal, and other mechanisms were invoked for improvement in gait, including trophic support and immune modulation. Regulatory permission for a phase 1 trial for subacute midthoracic injury was initially stalled by concern over abnormal growths at sites of cell deposit in some animals, but this was satisfactorily addressed and patient trials commenced. However, following a change in leadership, the stem cell program was terminated. The program was acquired by another company that has resumed the spinal cord injury trial and received regulatory approval to advance to include cervical-level injuries. The current phase 1/2a multicenter clinical trial is an open-label, single-arm trial testing three sequential escalating doses administered 21–42 days postinjury in 25 patients with subacute severe cervical spinal cord injuries. No adverse events have been reported for 21 patients at 2 years posttreatment. A later stage comparative clinical trial is now planned to probe for possible efficacy.

A team from Yale University working with Japanese scientists treated 13 patients with intravenous infusions of stem cells extracted from the patients' own bone marrow. The patients were treated around 40 days after their injury. They reported no adverse events and some improvement in sensation and movement. The paper reporting these results was published in 2021, but in 2018, on the basis of the results, unpublished at the time, Japan's health ministry gave conditional approval for the treatment, called Stemirac. This became the first stem cell therapy for spinal cord injury to receive government approval for sale to patients. But the approval of a therapy that may carry risk following a small, unblinded, and uncontrolled study without actual proof of efficacy raised considerable concern among scientists in the stem cell community. Charging patients for such an unproven therapy raises even more ethical concerns. Patients can now be charged for their treatment while trials to test efficacy are proceeding.

The possibility of treating ALS by replacing dying motor neurons with stem cell-derived substitutes has excited interest, but this prospect seems very remote. Even if new neurons are able to integrate into spinal cord circuits and become properly innervated, they would have to grow long axons that would take many months to years to project to appropriate targets and attract myelinating Schwann cells. Furthermore, cells would need to be grafted at multiple spinal cord and brainstem levels, and the upper motor neuron deficit would need to be treated by replacing projecting neurons in the motor cortex. An additional complication is the recent finding that spinal motor neurons have unique segmental identity, and replacement cells might need to be generated with a range of molecular identities in order to integrate

at multiple spinal levels. This would still leave unaddressed the toxic effects recently shown to be produced in ALS by diseased astrocytes and microglia that could attack the replacement cells. A more tractable near-term solution would be to graft support cells that could rescue or protect endogenous motor neurons from damage. This approach was tried in a mouse model of ALS. Human stem cell-derived neural progenitor cells engineered to express GDNF, a growth factor known to provide trophic support for neurons, were grafted to the spinal cord of young ALS mice. The cells dispersed and were able to rescue motor neurons, a very promising result, but disappointingly, the animals became weak and died at the same rate as untreated control animals. However, ALS is a deadly disease with no known treatment. In the hope that patients will respond differently from mice, a phase 1/2a clinical trial based on this approach was approved by the FDA in 2016 and completed in 2019.

Among the many MSC-based clinical trials for ALS, two are particularly notable. Corestem, a stem cell company in South Korea, launched a phase 1 open-label study demonstrating the safety and feasibility of intrathecal injections of autologous bone marrow-derived MSCs in seven patients with ALS. This was followed by a phase 2 trial that demonstrated safety and efficacy for slowing disease progression. On the basis of these results, Corestem received conditional approval in South Korea in 2014 to market the first stem cell therapy for ALS. By 2021, more than 300 patients had received this cell treatment. However, full approval is contingent on the results of a randomized, double-blind, placebo-controlled, multicenter phase 3 study, which has yet to occur. The importance of conducting proper phase 3 clinical trials to determine therapeutic efficacy in ALS is underscored by the recent experience of BrainStorm Cell Therapeutics. In 2016, the company reported preliminary positive results for its bone marrow MSC cell therapy in an uncontrolled study of nearly 50 ALS patients. Based on those results, the company launched a multicenter, placebo-controlled, randomized, double-blind trial of 189 ALS patients. In a press release on November 27, 2020, the company reported that there was no significant clinical improvement in the treatment group. Interestingly, despite the failed clinical trial, a public campaign led by ALS patients and advocates called on the FDA to approve the stem cell treatment. The social media response prompted the FDA to take the unusual step of releasing a public statement underscoring the lack of efficacy.

Following Shinya Yamanaka's discovery of iPSCs, the Japanese government has invested in bringing iPSC-derived cell therapy to the clinic. Banks of iPSC lines selected to capture the diversity of HLA haplotypes found in the Japanese population are being produced in the hope that these will allow cell therapies to be matched to individual patient haplotypes in order to avoid immune rejection. While these stem cell banks were still being produced, the first Japanese study to use stem cells was approved in August, 2013, and involved patients who were to receive customized therapy using cells derived from their own skin fibroblasts. The targeted disease was age-related macular degeneration, a common cause of blindness in the elderly that results from loss of retinal pigment epithelial (RPE) cells. RPE cells are relatively easy to generate from pluripotent stem cells, making replacement therapy an attractive target in this condition. A challenge is to coax the replacement cells to recreate an epithelium in the subretinal space. The Japanese approach involves surgical insertion of a biofilm seeded with RPE cells into the retina. One patient was treated with his/her own stem cell-derived RPE cells, but prior to treating a second patient, the genome of the RPE cell line was sequenced, and a mutation was discovered in a known oncogene. The trial was halted and a decision made to discontinue the effort for customized cell therapy in favor of using RPE cells derived from the national repository of banked iPSC lines, which undergo extensive gene sequencing and quality controls. This outcome serves as a caution for the challenges involved in bringing a customized cell therapy to the clinic.

By far the largest number of human trials have been performed using MSCs sourced from a variety of sites including bone marrow, peripheral blood, adipose tissue, umbilical cord, etc. Interest in the potential utility of MSCs for regenerative therapy began with the optimistic report that bone marrow stem cells were pluripotent and

capable of generating nerve and heart muscle as well as blood cells. The possibility that easily obtainable MSCs could be used to regenerate injured or diseased cells or organs to treat diseases ranging from stroke, neurodegenerative disease, myocardial infarct, and even diabetes, generated enormous enthusiasm. The enthusiasm proved irresistible to many, and even after the initial reports were discredited—MSCs turned out not to be pluripotent stem cells as initially thought—a veritable flood of papers began to appear claiming disease-modifying activity of MSCs in mouse models of almost every degenerative disease and injury model. But when it became clear that the MSCs were not transforming into or generating new neurons or cardiac myocytes, alternative mechanisms of action were invoked, including the release of trophic factors, cytokines, or inflammatory modulators that were credited with producing their remarkable restorative effects. The relative ease with which blood or adipose tissue can be harvested from patients or donors and MSCs extracted has led to a rapidly expanding number of clinical trials for conditions ranging from stroke and MS to AD, ALS, and PD. Furthermore, a loophole in the regulatory framework of the FDA allows autologous cell therapy to escape regulation provided that the cells have not been significantly processed. This lax regulation has spawned a veritable industry of stem cell clinics making unsubstantiated claims of success in treating nervous system diseases. Patients have died from treatments in unregulated clinics operating in countries around the world and three patients became blind in a well-publicized incident following stem cell treatments delivered by a Florida clinic. The “stem cells” were derived from the patients’ own fat tissue and blood. These activities represent the dark side of the stem cell revolution perpetrated by practitioners who exploit the desperation of patients and their families. Legitimate and effective stem cell therapies will emerge over time, but given the prevalence and abundance of misleading information available on the Internet and elsewhere, a trusted and well-informed physician can play a key role in helping patients navigate the current cell therapy minefield.

FURTHER READING

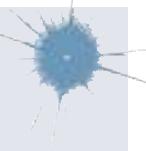
- A JI et al: Expanding spectrum of prion diseases. *Emerg Top Life Sci* 4:155, 2020.
- B A et al: Are organoids ready for prime time? *Cell Stem Cell* 27:361, 2020.
- D GI et al: Neuron-oligodendrocyte interactions in the structure and integrity of axons. *Front Cell Dev Biol* 9:653101, 2021.
- H S et al: Microglia in neurodegeneration. *Nat Neurosci* 21:1359, 2018.
- H S et al: Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* 352:712, 2016.
- K ER et al (eds): *Principles of Neural Science*, 6th ed. McGraw Hill, New York, 2021.
- L Q, B BA: Microglia and macrophages in brain homeostasis and disease. *Nat Rev Immunol* 18:225, 2018.
- L C et al: Remyelination in multiple sclerosis: From basic science to clinical translation. *Lancet Neurol* 19:678, 2020.
- M LH et al: The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol* 19:241, 2021.
- N P et al: Recent progress in translational engineered in vitro models of the central nervous system. *Brain* 143:3181, 2020.
- P -R SE, C JR: Building a (w)rapport between neurons and oligodendroglia: Reciprocal interactions underlying adaptive myelination. *Neuron* 109:1258, 2021.
- P SB et al: Evidence for α -synuclein prions causing multiple system atrophy in humans with parkinsonism. *Proc Natl Acad Sci USA* 112:E5308, 2015.
- S D et al: Clear up this stem-cell mess. *Nature* 561:455, 2018.
- T L: The US Direct-to-Consumer Marketplace for Autologous Stem Cell Interventions. *Perspect Biol Med* 61:7, 2018.
- Y S: Pluripotent stem cell-based cell therapy—promise and challenges. *Cell Stem Cell* 27:523, 2020.

Section 2 Diseases of the Central Nervous System

425

Seizures and Epilepsy

Vikram R. Rao, Daniel H. Lowenstein



A *seizure* (from the Latin *sacire*, “to take possession of”) is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Depending on the distribution of discharges, this abnormal brain activity can have various manifestations, ranging from dramatic convulsive activity to experiential phenomena not readily discernible by an observer. Although a variety of factors influence the incidence and prevalence of seizures, ~5–10% of the population will have at least one seizure, with the highest incidence occurring in early childhood and late adulthood.

The meaning of the term *seizure* needs to be carefully distinguished from that of epilepsy. *Epilepsy* describes a condition in which a person has a risk of *recurrent seizures* due to a chronic, underlying process. This definition implies that a person with a single seizure, or recurrent seizures due to correctable or avoidable circumstances, does not necessarily have epilepsy (although a single seizure associated with clinical or electroencephalographic features portending high risk of recurrence may establish the diagnosis of epilepsy). Epilepsy refers to a clinical phenomenon rather than a single disease entity, because many forms and causes exist. However, among the many causes of epilepsy, there are various *epilepsy syndromes* in which the clinical and pathologic characteristics are distinctive and suggest a specific underlying etiology.

Using the definition of epilepsy as two or more unprovoked seizures, the incidence of epilepsy is ~0.3–0.5% in different populations throughout the world, and the prevalence of epilepsy has been estimated at 5–30 persons per 1000.

CLASSIFICATION OF SEIZURES

Determining the type of seizure that has occurred is essential for focusing the diagnostic approach on particular etiologies, selecting appropriate therapy, and providing information regarding prognosis. The International League Against Epilepsy (ILAE) Commission on Classification and Terminology updated their approach to classification of seizures in 2017 (Table 425-1). This system is based on the clinical features of seizures and associated electroencephalographic findings. Other potentially distinctive features such as etiology or cellular substrate are not considered in this classification system, although this will undoubtedly change in the future as more is learned about the pathophysiological mechanisms that underlie specific seizure types.

A fundamental principle is that seizures may be either focal or generalized. *Focal seizures* originate within networks limited to one brain region (note that the term *partial seizures* is no longer used). *Generalized seizures* arise within and rapidly engage networks distributed

TABLE 425-1 Classification of Seizures^a

1. Focal Onset
(Can be further described as having intact or impaired awareness, motor or nonmotor onset, or evolve from focal to bilateral tonic clonic)
2. Generalized Onset
 - a. Motor
 - Tonic-clonic
 - Other motor (e.g., atonic, myoclonic)
 - b. Nonmotor (absence)
3. Unknown Onset
 - a. Motor, nonmotor, or unclassified

^aBased on the 2017 International League Against Epilepsy classification of seizure types (Data from RS Fisher et al: Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58:522, 2017.)

across both cerebral hemispheres. Focal seizures are often associated with structural abnormalities of the brain. In contrast, generalized seizures may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution. There are clear exceptions in both cases, however.

■ FOCAL ONSET SEIZURES

Focal seizures arise from a neuronal network either discretely localized within one brain region or more broadly distributed but still within a cerebral hemisphere. With the new classification system, the subcategories of “simple focal seizures” and “complex focal seizures” have been eliminated. Instead, the classification emphasizes the effect on awareness (intact or impaired) and nature of the onset (motor or nonmotor). Focal seizures can also evolve into generalized seizures. In the past, this was referred to as *focal seizures with secondary generalization*, but the new system relies on descriptions of the type of generalized seizures that evolve from the focal seizure.

The routine interictal (i.e., between seizures) electroencephalogram (EEG) in patients with focal seizures is often normal or may show brief discharges termed *epileptiform spikes*, or *sharp waves*. Because focal seizures can arise from the medial temporal lobe or inferior frontal lobe (i.e., regions distant from the scalp), the EEG recorded during the seizure may be nonlocalizing. However, the region of seizure onset may be detected using surgically placed intracranial electrodes.

Focal Seizures with Intact Awareness Focal seizures can have motor manifestations (such as tonic, clonic, or myoclonic movements) or nonmotor manifestations (such as sensory, autonomic, or emotional symptoms) without impairment of awareness. For example, a patient having a focal motor seizure arising from the right primary motor cortex near the area controlling hand movement will note the onset of involuntary movements of the contralateral left hand. Since the cortical region controlling hand movement is immediately adjacent to the region for facial expression, the seizure may also cause abnormal movements of the face synchronous with the movements of the hand. The EEG recorded with scalp electrodes during the seizure (i.e., an ictal EEG) may show abnormal discharges in a very limited region over the appropriate area of cerebral cortex if the seizure focus involves the cerebral convexity.

Three additional features of focal motor seizures are worth noting. First, in some patients, the abnormal motor movements may begin in a very restricted region, such as the fingers, and gradually progress (over seconds to minutes) to include a larger portion of the extremity. This phenomenon, described by Hughlings Jackson and known as a “Jacksonian march,” represents the spread of seizure activity over a progressively larger region of motor cortex. Second, patients may experience a localized paresis (Todd’s paralysis) for minutes to many hours in the involved region following the seizure. Third, in rare instances, the seizure may continue for hours or days. This condition, termed *epilepsia partialis continua*, is often refractory to medical therapy.

Focal seizures may also manifest as changes in somatic sensation (e.g., paresthesias), vision (flashing lights or formed hallucinations), equilibrium (sensation of falling or vertigo), or autonomic function (flushing, sweating, piloerection). Focal seizures arising from the temporal or frontal cortex may also cause alterations in hearing, olfaction, or emotional state. This includes the sensation of unusual, intense odors (e.g., burning rubber or kerosene) or sounds (crude or highly complex sounds), or an epigastric sensation that rises from the stomach or chest to the head. Some patients describe odd, internal feelings such as fear, a sense of impending change, detachment, depersonalization, *déjà vu*, or illusions that objects are growing smaller (*micropsia*) or larger (*macropsia*). These subjective, “internal” events that are not directly observable by someone else are referred to as *auras*.

Focal Seizures with Impaired Awareness Focal seizures may also be accompanied by a transient impairment of the patient’s ability to maintain normal contact with the environment. The patient is unable to respond appropriately to visual or verbal commands during the seizure and has impaired recollection or awareness of the ictal phase. The seizures frequently begin with an aura (i.e., a focal seizure

without cognitive disturbance) that is stereotypic for the patient. The start of the ictal phase is often a motionless stare, which marks the onset of the period of impaired awareness. The impaired awareness is usually accompanied by *automatisms*, which are involuntary, automatic behaviors that have a wide range of manifestations. Automatisms may consist of very basic behaviors, such as chewing, lip smacking, swallowing, or “picking” movements of the hands, or more elaborate behaviors, such as a display of emotion or running. The patient is typically confused following the seizure, and the transition to full recovery of consciousness may range from seconds up to an hour or longer. Examination immediately following the seizure may show an anterograde amnesia or transient neurologic deficits (such as aphasia, hemi-neglect, or visual loss) caused by postictal inhibition of the cortical regions most involved in the seizure.

The range of potential clinical behaviors linked to focal seizures is so broad that extreme caution is advised before concluding that stereotypic episodes of bizarre or atypical behavior are not due to seizure activity. In such cases, additional detailed EEG studies may be helpful.

■ EVOLUTION OF FOCAL SEIZURES TO GENERALIZED SEIZURES

Focal seizures can spread to involve both cerebral hemispheres and produce a generalized seizure, usually of the tonic-clonic variety (discussed below). This evolution is observed frequently following focal seizures arising from a region in the frontal lobe, but may also be associated with focal seizures occurring elsewhere in the brain. A focal seizure that evolves into a generalized seizure is often difficult to distinguish from a primary generalized onset tonic-clonic seizure, because bystanders tend to emphasize the more dramatic, generalized convulsive phase of the seizure and overlook the more subtle, focal symptoms present at onset. In some cases, the focal onset of the seizure becomes apparent only when a careful history identifies a preceding aura. Often, however, the focal onset is not clinically evident and may be established only through careful EEG analysis. Nonetheless, distinguishing between these two entities is extremely important, because there may be substantial differences in the evaluation and treatment of epilepsies characterized by focal versus generalized onset seizures.

■ GENERALIZED ONSET SEIZURES

Generalized seizures arise at some point in the brain but immediately and rapidly engage neuronal networks in both cerebral hemispheres. Several types of generalized seizures have features that place them in distinctive categories and facilitate clinical diagnosis.

Typical Absence Seizures Typical absence seizures are characterized by sudden, brief lapses of consciousness without loss of postural control. The seizure usually lasts for only seconds, consciousness returns as suddenly as it was lost, and there is no postictal confusion. Although the brief loss of consciousness may be clinically inapparent or the sole manifestation of the seizure discharge, absence seizures are usually accompanied by subtle, bilateral motor signs such as rapid blinking of the eyelids, chewing movements, or small-amplitude, clonic movements of the hands.

Typical absence seizures are associated with a group of genetically determined epilepsies with onset usually in childhood (ages 4–10 years) or early adolescence and are the main seizure type in 15–20% of children with epilepsy. The seizures can occur hundreds of times per day, but the child may be unaware of or unable to convey their existence. Because the clinical signs of the seizures are subtle, especially to parents who may not have had previous experience with seizures, it is not surprising that the first clue to absence epilepsy is often unexplained “daydreaming” and a decline in school performance recognized by a teacher. Indeed, absence epilepsy is often misdiagnosed as an attention deficit disorder.

The electrophysiologic hallmark of typical absence seizures is a burst of generalized, symmetric, 3-Hz, spike-and-slow-wave discharges that begins and ends suddenly, superimposed on a normal EEG background. Periods of spike-and-slow-wave discharges lasting more than a few seconds usually correlate with clinical signs, but the EEG often shows many more brief bursts of abnormal cortical activity than were

suspected clinically. Hyperventilation tends to provoke these electrographic discharges and even the seizures themselves and is routinely used when recording the EEG.

Atypical Absence Seizures Atypical absence seizures have features that deviate both clinically and electrophysiologically from typical absence seizures. For example, the lapse of consciousness is usually of longer duration and less abrupt in onset and cessation, and the seizure is accompanied by more obvious motor signs that may include focal or lateralizing features. The EEG shows a generalized, slow spike-and-slow-wave pattern with a frequency of ≤ 2.5 per second, as well as other abnormal activity. Atypical absence seizures are usually associated with diffuse or multifocal structural abnormalities of the brain and therefore may accompany other signs of neurologic dysfunction such as mental retardation. Furthermore, the seizures are less responsive to anticonvulsants compared to typical absence seizures.

Generalized, Tonic-Clonic Seizures Generalized onset tonic-clonic seizures are the main seizure type in ~10% of all persons with epilepsy. They are also the most common seizure type resulting from metabolic derangements and are therefore frequently encountered in many different clinical settings. The seizure usually begins abruptly without warning, although some patients describe vague premonitory symptoms in the hours leading up to the seizure. This prodrome is distinct from the stereotypic auras associated with focal seizures that generalize. The initial phase of the seizure is usually tonic contraction of muscles throughout the body, accounting for a number of the classic features of the event. Tonic contraction of the muscles of expiration and the larynx at the onset will produce a loud moan or “ictal cry.” Respirations are impaired, secretions pool in the oropharynx, and cyanosis develops. Contraction of the jaw muscles may cause biting of the tongue. A marked enhancement of sympathetic tone leads to increases in heart rate, blood pressure, and pupillary size. After 10–20 s, the tonic phase of the seizure typically evolves into the clonic phase, produced by the superimposition of periods of muscle relaxation on the tonic muscle contraction. The periods of relaxation progressively increase until the end of the ictal phase, which usually lasts no more than 1 min. The postictal phase is characterized by unresponsiveness, muscular flaccidity, and excessive salivation that can cause stridorous breathing and partial airway obstruction. Bladder or bowel incontinence may occur at this point. Patients gradually regain consciousness over minutes to hours, and during this transition, there is typically a period of postictal confusion. Patients subsequently complain of headache, fatigue, and muscle ache that can last for many hours. The duration of impaired consciousness in the postictal phase can be extremely long (i.e., many hours) in patients with prolonged seizures or underlying central nervous system (CNS) diseases such as alcoholic cerebral atrophy.

The EEG during the tonic phase of the seizure shows a progressive increase in generalized low-voltage fast activity, followed by generalized high-amplitude, polyspike discharges. In the clonic phase, the high-amplitude activity is typically interrupted by slow waves to create a spike-and-slow-wave pattern. Generalized seizures tend to terminate synchronously over widespread brain regions. The postictal EEG shows diffuse suppression of all cerebral activity, then slowing that gradually recovers as the patient awakens.

There are a number of variants of generalized motor seizures, including pure tonic and pure clonic seizures. Brief tonic seizures lasting only a few seconds are especially noteworthy since they are usually associated with specific epilepsy syndromes having mixed seizure phenotypes, such as the Lennox-Gastaut syndrome (discussed below).

Atonic Seizures Atonic seizures are characterized by sudden loss of postural muscle tone lasting 1–2 s. Consciousness is briefly impaired, but there is usually no postictal confusion. A very brief seizure may cause only a quick head drop or nodding movement, whereas a longer seizure will cause the patient to collapse (hence, the less formal term, *drop attacks*). This can be extremely dangerous, because there is a substantial risk of direct head injury with the fall. The EEG shows brief, generalized spike-and-wave discharges followed immediately by diffuse slow waves that correlate with the loss of muscle tone. Similar to

pure tonic seizures, atonic seizures are usually seen in association with known epilepsy syndromes.

Myoclonic Seizures Myoclonus is a sudden and brief muscle contraction that may involve one part of the body or the entire body. A normal, common physiologic form of myoclonus is the sudden jerking movement observed while falling asleep. Pathologic myoclonus is most commonly seen in association with metabolic disorders, degenerative CNS diseases, or anoxic brain injury (Chap. 307). Although the distinction from other forms of myoclonus is imprecise, myoclonic seizures are considered to be true epileptic events because they are caused by cortical (vs subcortical or spinal) dysfunction. The EEG shows bilaterally synchronous spike-and-slow-wave discharges immediately prior to the movement and muscle artifact associated with the myoclonus. Myoclonic seizures usually coexist with other forms of generalized seizures but are the predominant feature of juvenile myoclonic epilepsy (JME) (discussed below).

Epileptic Spasms Epileptic spasms are characterized by a briefly sustained flexion or extension of predominantly proximal muscles, including truncal muscles. The EEG usually shows hypsarrhythmia, which consist of diffuse, giant slow waves with a chaotic background of irregular, multifocal spikes and sharp waves. During the clinical spasm, there is a marked suppression of the EEG background (the “electrodecremental response”). The electromyogram (EMG) also reveals a characteristic rhomboid pattern that may help distinguish spasms from brief tonic and myoclonic seizures. Epileptic spasms occur predominantly in infants and likely result from differences in neuronal function and connectivity in the immature versus mature CNS.

EPILEPSY SYNDROMES

Epilepsy syndromes are disorders in which epilepsy is a predominant feature, and there is sufficient evidence (e.g., through clinical, EEG, radiologic, or genetic observations) to suggest a common underlying mechanism. Three important epilepsy syndromes are listed below; additional examples with a known genetic basis are shown in Table 425-2.

JUVENILE MYOCLONIC EPILEPSY

JME is a generalized seizure disorder of unknown cause that appears in early adolescence and is usually characterized by bilateral myoclonic jerks that may be single or repetitive. The myoclonic seizures are most frequent in the morning after awakening and can be provoked by sleep deprivation. Consciousness is preserved unless the myoclonus is especially severe. Many patients also experience generalized tonic-clonic seizures, and up to one-third have absence seizures. Although complete remission is uncommon, the seizures usually respond well to appropriate anticonvulsant medication. There is often a family history of epilepsy, and genetic studies suggest a polygenic cause.

LENNOX GASTAUT SYNDROME

Lennox-Gastaut syndrome occurs in children and is defined by the following triad: (1) multiple seizure types (usually including generalized tonic-clonic, atonic, and atypical absence seizures); (2) an EEG showing slow (<3 Hz) spike-and-wave discharges and a variety of other abnormalities; and (3) impaired cognitive function in most but not all cases. Lennox-Gastaut syndrome is associated with CNS disease or dysfunction from a variety of causes, including de novo mutations, developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions. The multifactorial nature of this syndrome suggests that it is a nonspecific response of the brain to diffuse neuronal dysfunction. Unfortunately, many patients have a poor prognosis due to the underlying CNS disease and the physical and psychosocial consequences of severe, poorly controlled epilepsy.

MESIAL TEMPORAL LOBE EPILEPSY SYNDROME

Mesial temporal lobe epilepsy (MTLE) is the most common syndrome associated with focal seizures with impairment of consciousness and is an example of an epilepsy syndrome with distinctive clinical, EEG, and pathologic features (Table 425-3). High-resolution magnetic resonance imaging (MRI) can detect the characteristic hippocampal

TABLE 425-2 Examples of Genes Associated with Epilepsy Syndromes^a

GENE (LOCUS)	FUNCTION OF GENE	CLINICAL SYNDROME	COMMENTS
<i>CHRNA4</i> (20q13.2)	Nicotinic acetylcholine receptor subunit; mutations cause alterations in Ca^{2+} flux through the receptor; this may reduce the amount of GABA release in presynaptic terminals	Sleep-related hypermotor epilepsy (SHE); childhood onset; brief, nighttime seizures with prominent motor movements; often misdiagnosed as primary sleep disorder	Rare; first identified in a large Australian family; other families found to have mutations in <i>CHRNA2</i> or <i>CHRN2B</i> ; and some families appear to have mutations at other loci
<i>KCNQ2</i> (20q13.3)	Voltage-gated potassium channel subunits; mutation in pore regions may cause a 20–40% reduction of potassium currents, which will lead to impaired repolarization	Self-limited familial neonatal epilepsy; autosomal dominant inheritance; onset in first week of life in infants who are otherwise normal; remission usually within weeks to months; long-term epilepsy in 10–15%	Rare; other families found to have mutations in <i>KCNQ3</i> sequence and functional homology to <i>KCNQ1</i> , mutations of which cause long QT syndrome and a cardiac-auditory syndrome
<i>SCN1A</i> (2q24.3)	α -Subunit of a voltage-gated sodium channel; numerous mutations affecting sodium currents that cause either gain or loss of function; network effects appear related to expression in excitatory or inhibitory cells	Very common cause of Dravet syndrome (severe myoclonic epilepsy of infancy) and some cases of Lennox-Gastaut syndrome. Also found in other syndromes, including genetic epilepsy with febrile seizures plus (GEFS+); autosomal dominant inheritance; presents with febrile seizures at median 1 year, which may persist >6 years, then variable seizure types not associated with fever	Incidence of Dravet syndrome is 1 in 20,000 births, and de novo <i>SCN1A</i> mutation is found in ~80% of cases. Incidence in GEFS+ uncertain; identified in other families with mutations in other sodium channel subunits (<i>SCN2B</i> and <i>SCN2A</i>) and GABA _A receptor subunit (<i>GABRG2</i> and <i>GABRA1</i>); significant phenotypic heterogeneity within same family, including members with febrile seizures only. Avoid sodium channel-blocking antiseizure medications
<i>LGI1</i> (10q24)	Leucine-rich glioma-inactivated 1 gene; previous evidence for role in glial tumor progression; recent studies suggest an influence in the postnatal development of glutamatergic circuits in the hippocampus	Autosomal dominant epilepsy with auditory features (ADEAF); a form of lateral temporal lobe epilepsy with auditory symptoms or aphasia as a major focal seizure manifestation; age of onset usually between 10 and 25 years	Mutations found in up to 50% of families containing two or more subjects with focal epilepsy with ictal auditory symptoms, suggesting that at least one other gene may underlie this syndrome
<i>DEPDC5</i> (22q12.2)	Disheveled, Egl-10, and pleckstrin domain containing protein 5; exerts an inhibitory effect on mammalian target of rapamycin (mTOR)-mediated processes, such as cell growth and proliferation	Autosomal dominant familial focal epilepsy with variable foci (FFEVF); family members have seizures originating from different cortical regions; neuroimaging usually normal but may harbor subtle malformations; recent studies also suggest association with benign epilepsy with centrotemporal spikes	Study of families with the limited number of affected members revealed mutations in ~12% of families; thus, may be a relatively common cause of lesion-negative focal epilepsies with suspected genetic basis. Also associated with mutations in the GATOR1 genes <i>NPRL2</i> and <i>NPRL3</i>
<i>SLC2A1</i> (1p34.2)	Glucose transporter protein type 1 (GLUT1); transports glucose across the blood-brain barrier	Loss of function of one allele leads to GLUT1 deficiency, a severe metabolic encephalopathy including intractable epilepsy, complex motor dysfunction, and intellectual disability. Milder GLUT1 deficiency causes a combination of movement disorder (paroxysmal exertional dyskinesia) and epilepsy with prominent absence seizures, though intellect is often normal	Milder forms of epilepsy due to GLUT1 deficiency may respond to standard antiseizure medications, but the gold standard treatment for refractory forms is the ketogenic diet, which bypasses defective glucose transport to provide an alternative energy supply to the brain
<i>CSTB</i> (21q22.3)	Cystatin B, a noncaspase cysteine protease inhibitor; normal protein may block neuronal apoptosis by inhibiting caspases directly or indirectly (via cathepsins), or controlling proteolysis	Progressive myoclonus epilepsy (PME) (Unverricht-Lundborg disease); autosomal recessive inheritance; age of onset between 6 and 15 years, myoclonic seizures, ataxia, and progressive cognitive decline; brain shows neuronal degeneration	Overall rare, but relatively common in Finland and western Mediterranean (>1 in 20,000); precise role of cystatin B in human disease unknown, although mice with null mutations of cystatin B have similar syndrome
<i>EPMA2</i> (6q24)	Laforin, a protein tyrosine phosphatase (PTP); involved in glycogen metabolism and may have antiapoptotic activity	Progressive myoclonus epilepsy (Lafora's disease); autosomal recessive inheritance; age of onset 6–19 years, death within 10 years; brain degeneration associated with polyglucosan intracellular inclusion bodies in numerous organs	Most common PME in southern Europe, Middle East, northern Africa, and Indian subcontinent; genetic heterogeneity; unknown whether seizure phenotype due to degeneration or direct effects of abnormal laforin expression
<i>Doublecortin</i> (Xq21-24)	Doublecortin, expressed primarily in frontal lobes; directly regulates microtubule polymerization and bundling	Classic lissencephaly associated with severe mental retardation and seizures in males; subcortical band heterotopia with more subtle findings in females (presumably due to random X inactivation); X-linked dominant	Relatively rare but of uncertain incidence; recent increased ascertainment due to improved imaging techniques; relationship between migration defect and seizure phenotype unknown

^aThe first five syndromes listed in the table (SHE, benign familial neonatal convulsions, GEFS+, ADEAF, and FFEVF) are examples of genetic epilepsies associated with identified gene mutations. The last three syndromes are examples of the numerous Mendelian disorders in which seizures are one part of the phenotype.

Abbreviations: GABA, γ -aminobutyric acid; PME, progressive myoclonus epilepsy.

sclerosis that appears to be essential in the pathophysiology of MTLE for many patients (Fig. 425-1). Recognition of this syndrome is especially important because it tends to be refractory to treatment with anticonvulsants but responds well to surgical intervention. Advances in the understanding of basic mechanisms of epilepsy have come through studies of experimental models of MTLE, discussed below.

THE CAUSES OF SEIZURES AND EPILEPSY

Seizures are a result of a shift in the normal balance of excitation and inhibition within the CNS. Given the numerous properties that control neuronal excitability, it is not surprising that there are many

different ways to perturb this normal balance and, therefore, many different causes of both seizures and epilepsy. Three clinical observations emphasize how a variety of factors determine why certain conditions may cause seizures or epilepsy in a given patient.

1. *The normal brain is capable of having a seizure under the appropriate circumstances, and there are differences between individuals in the susceptibility or threshold for seizures.* For example, seizures may be induced by high fevers in children who are otherwise normal and who never develop other neurologic problems, including epilepsy. However, febrile seizures occur only in a relatively small proportion

TABLE 425-3 Characteristics of the Mesial Temporal Lobe Epilepsy Syndrome

History	
History of febrile seizures	Rare generalized seizures
Family history of epilepsy	Seizures may remit and reappear
Early onset	Seizures often intractable
Clinical Observations	
Aura common	Postictal disorientation
Behavioral arrest/stare	Memory loss
Complex automatisms	Dysphasia (with focus in dominant hemisphere)
Unilateral posturing	
Laboratory Studies	
Unilateral or bilateral anterior temporal spikes on EEG	
Hypometabolism on interictal PET	
Hyperperfusion on ictal SPECT	
Material-specific memory deficits on intracranial amobarbital (Wada) test	
MRI Findings	
Small hippocampus with increased signal on T2-weighted sequences and loss of trilaminar hippocampal internal architecture	
Small temporal lobe	
Enlarged temporal horn	
Pathologic Findings	
Highly selective loss of specific cell populations within hippocampus in most cases, granule cell layer dispersion, gliosis	

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

of children. This implies there are various underlying *endogenous factors* that influence the threshold for having a seizure. Some of these factors are genetic, as a family history of epilepsy has a clear influence on the likelihood of seizures occurring in otherwise normal individuals. Normal development also plays an important role, because the brain appears to have different seizure thresholds at different maturational stages.

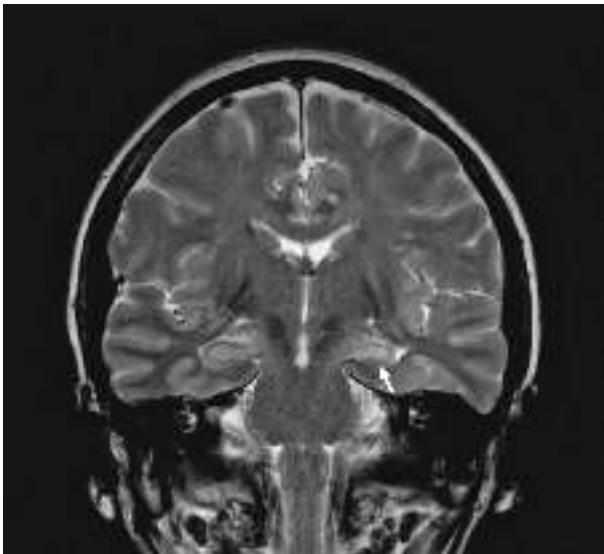


FIGURE 425-1 Mesial temporal lobe epilepsy. The electroencephalogram and seizure semiology were consistent with a left temporal lobe focus. This coronal high-resolution T2-weighted fast spin echo magnetic resonance image obtained at 3 Tesla is at the level of the hippocampal bodies and shows abnormal high signal intensity, blurring of internal laminar architecture, and reduced size of the left hippocampus (arrow) relative to the right. This triad of imaging findings is consistent with hippocampal sclerosis.

2. There are a variety of conditions that have an extremely high likelihood of resulting in a chronic seizure disorder. One of the best examples of this is severe, penetrating head trauma, which is associated with up to a 45% risk of subsequent epilepsy. The high propensity for severe traumatic brain injury to lead to epilepsy suggests that the injury results in a long-lasting pathologic change in the CNS that transforms a presumably normal neuronal network into one that is abnormally hyperexcitable. This process is known as *epileptogenesis*, and the specific changes that result in a lowered seizure threshold can be considered *epileptogenic factors*. Other processes associated with epileptogenesis include stroke, infections, and abnormalities of CNS development. Likewise, the genetic abnormalities associated with epilepsy likely involve processes that trigger the appearance of specific sets of epileptogenic factors.

3. *Seizures are episodic.* Seizures occur intermittently, and, depending on the underlying cause, people with epilepsy may feel completely normal for months or even years between seizures. This implies there are important provocative or *precipitating factors* that induce seizures in people with epilepsy. Similarly, precipitating factors are responsible for causing the single seizure in someone without epilepsy. Precipitants include those due to intrinsic physiologic processes, such as psychological or physical stress, sleep deprivation, or hormonal changes. They also include exogenous factors such as exposure to toxic substances, certain medications, and intermittent photic stimulation from strobe lights or some video games.

These observations emphasize the concept that the many causes of seizures and epilepsy result from a dynamic interplay between endogenous factors, epileptogenic factors, and precipitating factors. The potential role of each needs to be considered when determining the appropriate management of a patient with seizures. For example, the identification of predisposing factors (e.g., family history of epilepsy) in a patient with febrile seizures may increase the necessity for closer follow-up and a more aggressive diagnostic evaluation. Finding an epileptogenic lesion may help in the estimation of seizure recurrence and duration of therapy. Removal or modification of a precipitating factor may be an effective and safer method for preventing further seizures than the prophylactic use of anticonvulsant drugs. An emerging concept holds that underlying seizure risk itself fluctuates cyclically, potentially explaining why the same precipitating factor (e.g., a missed dose of antiseizure medication) can be well tolerated on some occasions but result in a seizure on others.

■ CAUSES ACCORDING TO AGE

In practice, it is useful to consider the etiologies of seizures based on the age of the patient, because age is one of the most important factors determining both the incidence and the likely causes of seizures or epilepsy (Table 425-4). During the *neonatal period and early infancy*, potential causes include hypoxic-ischemic encephalopathy, trauma, CNS infection, congenital CNS abnormalities, and metabolic disorders. Babies born to mothers using neurotoxic drugs such as cocaine, heroin, or ethanol are susceptible to drug-withdrawal seizures in the first few days after delivery. Hypoglycemia and hypocalcemia, which can occur as secondary complications of perinatal injury, are also causes of seizures early after delivery. Seizures due to inborn errors of metabolism usually present once regular feeding begins, typically 2–3 days after birth. Pyridoxine (vitamin B₆) deficiency, an important cause of neonatal seizures, can be effectively treated with pyridoxine replacement. The idiopathic or inherited forms of benign neonatal seizures are also seen during this time period.

The most common seizures arising in *late infancy and early childhood* are febrile seizures, which are seizures associated with fevers but without evidence of CNS infection or other defined causes. The overall prevalence is 3–5% and even higher in some parts of the world such as Asia. Patients often have a family history of febrile seizures or epilepsy. Febrile seizures usually occur between 3 months and 5 years of age and have a peak incidence between 18 and 24 months. The typical scenario is a child who has a generalized, tonic-clonic seizure during a febrile illness in the setting of a common childhood infection such as otitis

TABLE 425-4 Causes of Seizures

Neonates (<1 month)	Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma CNS infection Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) Drug withdrawal Developmental disorders Genetic disorders
Infants and children (>1 month and <12 years)	Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders Trauma
Adolescents (12–18 years)	Trauma Genetic disorders Infection Illicit drug use Brain tumor
Young adults (18–35 years)	Trauma Alcohol withdrawal Illicit drug use Brain tumor Autoantibodies
Older adults (>35 years)	Cerebrovascular disease Brain tumor Alcohol withdrawal Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia, hyperglycemia) Alzheimer's disease and other degenerative CNS diseases Autoantibodies

Abbreviation: CNS, central nervous system.

media, respiratory infection, or gastroenteritis. The seizure is likely to occur during the rising phase of the temperature curve (i.e., during the first day) rather than well into the course of the illness. A *simple* febrile seizure is a single, isolated event, brief, and symmetric in appearance. *Complex* febrile seizures are characterized by repeated seizure activity, a duration >15 minutes, or by focal features. Approximately one-third of patients with febrile seizures will have a recurrence, but <10% have three or more episodes. Recurrences are much more likely when the febrile seizure occurs in the first year of life. Simple febrile seizures are not associated with an increase in the risk of developing epilepsy, while complex febrile seizures have a risk of 2–5%; other risk factors include the presence of preexisting neurologic deficits and a family history of nonfebrile seizures.

Childhood marks the age at which many of the well-defined epilepsy syndromes present. Some children who are otherwise normal develop idiopathic, generalized tonic-clonic seizures without other features that fit into specific syndromes. Temporal lobe epilepsy usually presents in childhood and may be related to mesial temporal lobe sclerosis (as part of the MTLE syndrome) or other focal abnormalities such as cortical dysgenesis. Other types of focal seizures, including those that evolve into generalized seizures, may be the relatively late manifestation of a developmental disorder, an acquired lesion such as head trauma, CNS infection (especially viral encephalitis), or very rarely, a CNS tumor.

The period of *adolescence and early adulthood* is one of transition during which the idiopathic or genetically based epilepsy syndromes, including JME and juvenile absence epilepsy, become less common, while epilepsies secondary to acquired CNS lesions begin to predominate. Seizures that arise in patients in this age range may be associated

with head trauma, CNS infections (including parasitic infections such as cysticercosis), brain tumors, congenital CNS abnormalities, illicit drug use, or alcohol withdrawal. Autoantibodies directed against CNS antigens such as potassium channels or glutamate receptors are a cause of epilepsy that also begins to appear in this age group (although cases of autoimmunity are being increasingly described in the pediatric population), including patients without an identifiable cancer. This etiology should be suspected when a previously normal individual presents with a particularly aggressive seizure pattern developing over weeks to months and characterized by increasingly frequent and prolonged seizures, especially when combined with psychiatric symptoms and changes in cognitive function (Chap. 94).

Head trauma is a common cause of epilepsy in adolescents and adults. The head injury can be caused by a variety of mechanisms, and the likelihood of developing epilepsy is strongly correlated with the severity of the injury. A patient with a penetrating head wound, depressed skull fracture, intracranial hemorrhage, or prolonged post-traumatic coma or amnesia has a 30–50% risk of developing epilepsy, whereas a patient with a closed head injury and cerebral contusion has a 5–25% risk. Recurrent seizures usually develop within 1 year after head trauma, although intervals of >10 years are well known. In controlled studies, mild head injury, defined as a concussion with amnesia or loss of consciousness of <30 min, was found to be associated with only a slightly increased likelihood of epilepsy. Nonetheless, most epileptologists know of patients who have focal seizures within hours or days of a mild head injury and subsequently develop chronic seizures of the same type; such cases may represent rare examples of chronic epilepsy resulting from mild head injury.

The causes of seizures in *older adults* include cerebrovascular disease, trauma (including subdural hematoma), CNS tumors, and degenerative diseases. Cerebrovascular disease may account for ~50% of new cases of epilepsy in patients >65 years. Acute seizures (i.e., occurring at the time of the stroke) are seen more often with embolic rather than hemorrhagic or thrombotic stroke. Chronic seizures typically appear months to years after the initial event and are associated with all forms of stroke.

Metabolic disturbances such as electrolyte imbalance, hypo- or hyperglycemia, renal failure, and hepatic failure may cause seizures at any age. Similarly, endocrine disorders, hematologic disorders, vasculitides, and many other systemic diseases may cause seizures over a broad age range. A wide variety of medications and abused substances are known to precipitate seizures as well (Table 425-5).

BASIC MECHANISMS

MECHANISMS OF SEIZURE INITIATION AND PROPAGATION

Focal seizure activity can begin in a very discrete region of cortex and then slowly invade the surrounding regions. The hallmark of an established seizure is typically an electrographic “spike” due to intense near-simultaneous firing of a large number of local excitatory neurons, resulting in an apparent hypersynchronization of the excitatory bursts across a relatively large cortical region. The bursting activity in individual neurons (the “paroxysmal depolarization shift”) is caused by a relatively long-lasting depolarization of the neuronal membrane due to influx of extracellular calcium (Ca^{2+}), which leads to the opening of voltage-dependent sodium (Na^+) channels, influx of Na^+ , and generation of repetitive action potentials. This is followed by a hyperpolarizing afterpotential mediated by γ -aminobutyric acid (GABA) receptors or potassium (K^+) channels, depending on the cell type. The synchronized bursts from a sufficient number of neurons result in summation of field potentials producing a so-called spike discharge on the EEG.

The spreading seizure waveform is thought to slow and ultimately halt by intact hyperpolarization and a “surround” inhibition created by feedforward activation of inhibitory neurons. With sufficient activation, there is a recruitment of surrounding neurons via a number of synaptic and nonsynaptic mechanisms, including (1) an increase in extracellular K^+ , which blunts hyperpolarization and depolarizes

TABLE 425-5 Drugs and Other Substances That Can Cause Seizures

Alkylating agents (e.g., busulfan, chlorambucil)
Antimalarials (chloroquine, mefloquine)
Antimicrobials/antivirals
β -Lactam and related compounds
Quinolones
Acyclovir
Isoniazid
Ganciclovir
Anesthetics and analgesics
Meperidine
Fentanyl
Tramadol
Local anesthetics
Dietary supplements
Ephedra (ma huang)
Ginkgo
Immunomodulatory drugs
Cyclosporine
OKT3 (monoclonal antibodies to T cells)
Tacrolimus
Interferons
Psychotropics
Antidepressants (e.g., bupropion)
Antipsychotics (e.g., clozapine)
Lithium
Radiographic contrast agents
Drug withdrawal
Alcohol
Baclofen
Barbiturates (short-acting)
Benzodiazepines (short-acting)
Zolpidem
Drugs of abuse
Amphetamine
Cocaine
Phencyclidine
Methylphenidate
Flumazenil ^a

^aIn benzodiazepine-dependent patients.

neighboring neurons; (2) accumulation of Ca^{2+} in presynaptic terminals, leading to enhanced neurotransmitter release; (3) depolarization-induced activation of the *N*-methyl- α -aspartate (NMDA) subtype of the excitatory amino acid receptor, which causes additional Ca^{2+} influx and neuronal activation; and (4) ephaptic interactions related to changes in tissue osmolarity and cell swelling. The recruitment of a sufficient number of neurons leads to the propagation of excitatory currents into contiguous areas via local cortical connections and to more distant areas via long commissural pathways such as the corpus callosum.

Many factors control neuronal excitability, and thus, there are many potential mechanisms for altering a neuron's propensity to have bursting activity. Mechanisms *intrinsic* to the neuron include changes in the conductance of ion channels, response characteristics of membrane receptors, cytoplasmic buffering, second-messenger systems, and protein expression as determined by gene transcription, translation, and posttranslational modification. Mechanisms *extrinsic* to the neuron include changes in the amount or type of neurotransmitters present at the synapse, modulation of receptors by extracellular ions and other molecules, and temporal and spatial properties of synaptic and

nonsynaptic input. Nonneuronal cells, such as astrocytes and oligodendrocytes, have an important role in many of these mechanisms as well.

Certain recognized causes of seizures are explained by these mechanisms. For example, accidental ingestion of domoic acid, an analogue of glutamate (the principal excitatory neurotransmitter in the brain) produced by naturally occurring microscopic algae, causes profound seizures via direct activation of excitatory amino acid receptors throughout the CNS. Penicillin, which can lower the seizure threshold in humans and is a potent convulsant in experimental models, reduces inhibition by antagonizing the effects of GABA at its receptor. The basic mechanisms of other precipitating factors of seizures, such as sleep deprivation, fever, alcohol withdrawal, hypoxia, and infection, are not as well understood but presumably involve analogous perturbations in neuronal excitability. Similarly, the endogenous factors that determine an individual's seizure threshold may relate to these properties as well.

Knowledge of the mechanisms responsible for initiation and propagation of most generalized seizures (including tonic-clonic, myoclonic, and atonic types) remains rudimentary and reflects the limited understanding of the connectivity of the brain at a systems level. Much more is understood about the origin of generalized spike-and-wave discharges in absence seizures. These appear to be related to oscillatory rhythms normally generated during sleep by circuits connecting the thalamus and cortex. This oscillatory behavior involves an interaction between GABA_B receptors, T-type Ca^{2+} channels, and K^+ channels located within the thalamus. Pharmacologic studies indicate that modulation of these receptors and channels can induce absence seizures, and there is good evidence that the genetic forms of absence epilepsy may be associated with mutations of components of this system.

MECHANISMS OF EPILEPTOGENESIS

Epileptogenesis refers to the transformation of a normal neuronal network into one that is chronically hyperexcitable. There is often a delay of months to years between an initial CNS injury such as trauma, stroke, or infection and the first clinically evident seizure. The injury appears to initiate a process that gradually lowers the seizure threshold in the affected region until a spontaneous seizure occurs. In many genetic and idiopathic forms of epilepsy, epileptogenesis is presumably determined by developmentally regulated events.

Pathologic studies of the hippocampus from patients with temporal lobe epilepsy suggest that some forms of epileptogenesis are related to *structural changes in neuronal networks*. For example, many patients with MTLE have a highly selective loss of neurons that normally contribute to inhibition of the main excitatory neurons within the dentate gyrus. There is also evidence that, in response to the loss of neurons, there is reorganization of surviving neurons in a way that affects the excitability of the network. Some of these changes can be seen in experimental models of prolonged electrical seizures or traumatic brain injury. Thus, an initial injury such as head injury may lead to a very focal, confined region of structural change that causes local hyperexcitability. The local hyperexcitability leads to further structural changes that evolve over time until the focal lesion produces clinically evident seizures. Similar models have provided strong evidence for long-term alterations in *intrinsic, biochemical properties of cells* within the network such as chronic changes in glutamate or GABA receptor function. Induction of inflammatory cascades may be a critical factor in these processes as well.

GENETIC CAUSES OF EPILEPSY

The most important recent progress in epilepsy research has been the identification of genetic mutations associated with a variety of epilepsy syndromes (Table 425-2). Although most of the mutations identified to date cause rare forms of epilepsy, their discovery has led to extremely important conceptual advances. For example, it appears that many of the inherited epilepsies are due to mutations affecting ion channel function. These syndromes are therefore part of the larger group of channelopathies causing paroxysmal disorders such as cardiac arrhythmias, episodic ataxia, periodic weakness, and familial hemiplegic migraine. Other gene mutations are proving to be associated

3312 with pathways influencing CNS development, synaptic physiology, or neuronal homeostasis. *De novo* mutations may explain a significant proportion of these syndromes, especially those with onset in early childhood. A current challenge is to identify the multiple susceptibility genes that underlie the more common forms of idiopathic epilepsies. Ion channel mutations and copy number variants may contribute to causation in a subset of these patients.

MECHANISMS OF ACTION OF ANTISEIZURE DRUGS

Antiseizure drugs appear to act primarily by blocking the initiation or spread of seizures. This occurs through a variety of mechanisms that modify the activity of ion channels or neurotransmitters, and in most cases, the drugs have pleiotropic effects. The mechanisms include inhibition of Na^+ -dependent action potentials in a frequency-dependent manner (e.g., phenytoin, carbamazepine, lamotrigine, topiramate, zonisamide, lacosamide, rufinamide, cenobamate), inhibition of voltage-gated Ca^{2+} channels (phenytoin, gabapentin, pregabalin), facilitating the opening of potassium channels (ezogabine), attenuation of glutamate activity (lamotrigine, topiramate, felbamate, perampanel), potentiation of GABA receptor function (benzodiazepines and barbiturates), increase in the availability of GABA (valproic acid, gabapentin, tiagabine), and modulation of release of synaptic vesicles (levetiracetam, brivaracetam). Two of the effective drugs for absence seizures, ethosuximide and valproic acid, probably act by inhibiting T-type Ca^{2+} channels in thalamic neurons. Cannabidiol (CBD), a derivative of cannabis plants, is effective for reducing seizures in children with Dravet syndrome and Lennox-Gastaut syndrome but does not act through endogenous cannabinoid receptors. Rather, CBD has a multimodal mechanism of action involving modulation of intracellular calcium via G protein-coupled receptor 55, extracellular calcium influx via transient receptor potential vanilloid type 1 (TRPV1) channels, and adenosine-mediated signaling.

In contrast to the relatively large number of antiseizure drugs that can attenuate seizure activity, there are currently no drugs known to prevent the formation of a seizure focus following CNS injury. The eventual development of such “antiepileptogenic” drugs will provide an important means of preventing the emergence of epilepsy following injuries such as head trauma, stroke, and CNS infection.

APPROACH TO THE PATIENT

SEIZURE

When a patient presents shortly after a seizure, the first priorities are attention to vital signs, respiratory and cardiovascular support, and treatment of seizures if they resume (see “Treatment: Seizures and Epilepsy”). Life-threatening conditions such as CNS infection, metabolic derangement, or drug toxicity must be recognized and managed appropriately.

When the patient is not acutely ill, the evaluation will initially focus on whether there is a history of earlier seizures (Fig. 425-2). If this is the first seizure, then the emphasis will be to (1) establish whether the reported episode was a seizure rather than another paroxysmal event, (2) determine the cause of the seizure by identifying risk factors and precipitating events, and (3) decide whether antiseizure drug therapy is required in addition to treatment for any underlying illness.

In the patient with prior seizures or a known history of epilepsy, the evaluation is directed toward (1) identification of the underlying cause and precipitating factors, and (2) determination of the adequacy of the patient’s current therapy.

HISTORY AND EXAMINATION

The first goal is to determine whether the event was truly a seizure. An in-depth history is essential, because *in many cases the diagnosis of a seizure is based solely on clinical grounds—the examination and laboratory studies are often normal*. Questions should focus on the symptoms before, during, and after the episode in order to differentiate a seizure

from other paroxysmal events (see “Differential Diagnosis of Seizures” below). Seizures frequently occur out-of-hospital, and the patient may be unaware of the ictal and immediate postictal phases; thus, witnesses to the event should be interviewed carefully.

The history should also focus on risk factors and predisposing events. Clues for a predisposition to seizures include a history of febrile seizures, a family history of seizures, and, of particular importance, earlier auras or brief seizures not recognized as such. Epileptogenic factors such as prior head trauma, stroke, tumor, or CNS infection should be identified. In children, a careful assessment of developmental milestones may provide evidence for underlying CNS disease. Precipitating factors such as sleep deprivation, systemic diseases, electrolyte or metabolic derangements, acute infection, drugs that lower the seizure threshold (Table 425-5), or alcohol or illicit drug use should also be identified.

The general physical examination includes a search for signs of infection or systemic illness. Careful examination of the skin may reveal signs of neurocutaneous disorders, such as tuberous sclerosis or neurofibromatosis, or chronic liver or renal disease. A finding of organomegaly may indicate a metabolic storage disease, and limb asymmetry may provide a clue to brain injury early in development. Signs of head trauma and use of alcohol or illicit drugs should be sought. Auscultation of the heart and carotid arteries may identify an abnormality that predisposes to cerebrovascular disease.

All patients require a complete neurologic examination, with particular emphasis on eliciting signs of cerebral hemispheric disease (Chap. 422). Careful assessment of mental status (including memory, language function, and abstract thinking) may suggest lesions in the anterior frontal, parietal, or temporal lobes. Testing of visual fields will help screen for lesions in the optic pathways and occipital lobes. Screening tests of motor function such as pronator drift, deep tendon reflexes, gait, and coordination may suggest lesions in motor (frontal) cortex, and cortical sensory testing (e.g., double simultaneous stimulation) may detect lesions in the parietal cortex.

LABORATORY STUDIES

Routine blood studies are indicated to identify the more common metabolic causes of seizures such as abnormalities in electrolytes, glucose, calcium, or magnesium, and hepatic or renal disease. A screen for toxins in blood and urine should also be obtained from all patients in appropriate risk groups, especially when no clear precipitating factor has been identified. A lumbar puncture is indicated if there is any suspicion of meningitis or encephalitis, and it is mandatory in all patients infected with HIV, even in the absence of symptoms or signs suggesting infection. Testing for autoantibodies in the serum and cerebrospinal fluid (CSF) should be considered in patients presenting with fulminant onset of epilepsy associated with other abnormalities such as psychiatric symptoms or cognitive disturbances.

ELECTROPHYSIOLOGIC STUDIES

The electrical activity of the brain (the EEG) is easily recorded from electrodes placed on the scalp. The potential difference between pairs of electrodes on the scalp (bipolar derivation) or between individual scalp electrodes and a relatively inactive common reference point (referential derivation) is amplified and displayed on a computer monitor, oscilloscope, or paper. Digital systems allow the EEG to be reconstructed and displayed with any desired format and to be manipulated for more detailed analysis and also permit computerized techniques to be used to detect certain abnormalities. The characteristics of the normal EEG depend on the patient’s age and level of arousal. The rhythmic activity normally recorded represents the postsynaptic potentials of vertically oriented pyramidal cells of the cerebral cortex and is characterized by its frequency. In normal awake adults lying quietly with the eyes closed, an 8- to 13-Hz alpha rhythm is seen posteriorly in the EEG, intermixed with a variable amount of generalized faster (beta) activity (>13 Hz); the alpha rhythm is attenuated when the eyes are opened (Fig. 425-3). During drowsiness, the alpha rhythm is also attenuated; with light sleep, slower activity in the theta (4–7 Hz) and delta (<4 Hz) ranges becomes more conspicuous.

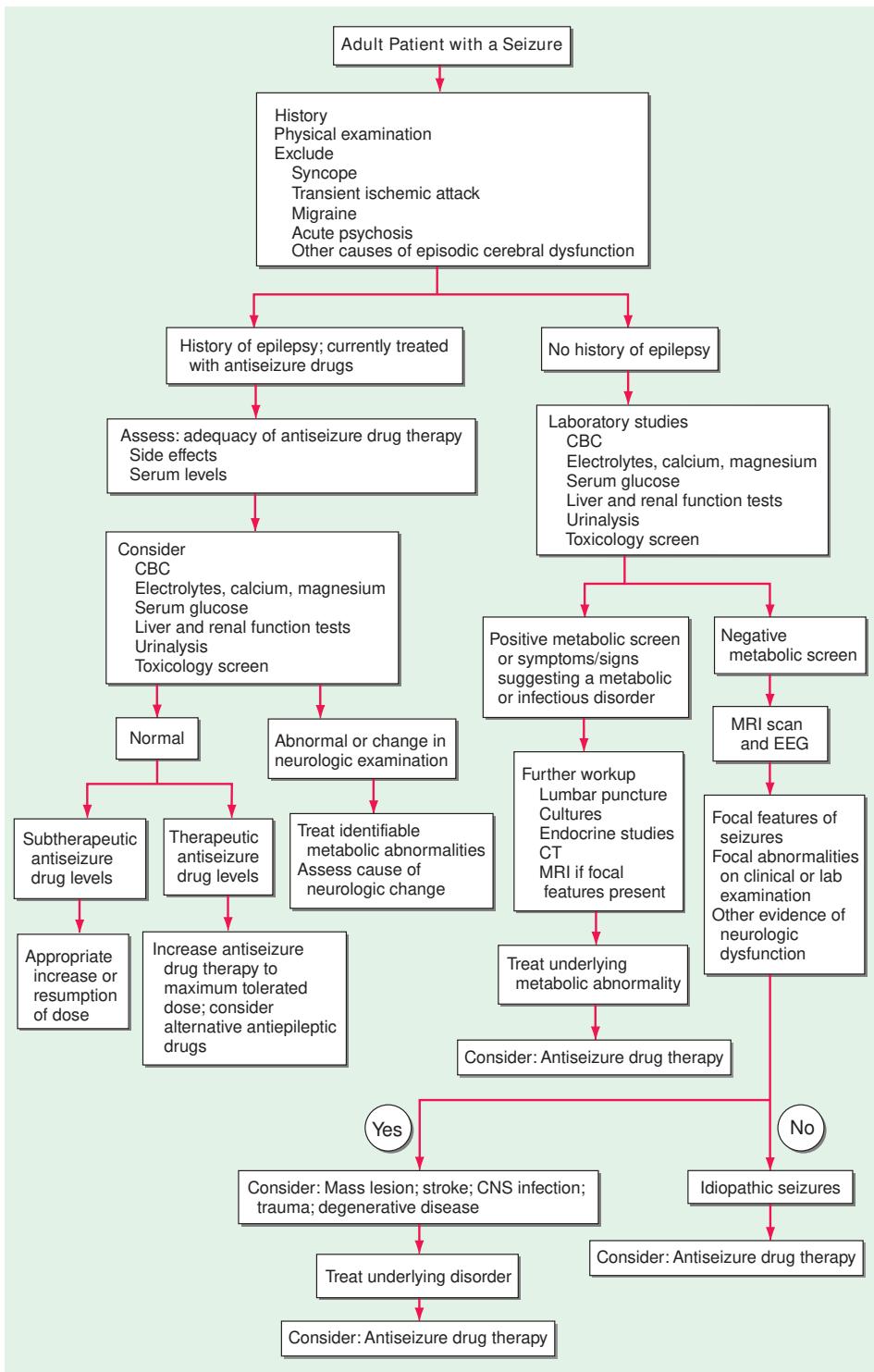


FIGURE 425-2 Evaluation of the adult patient with a seizure. CBC, complete blood count; CNS, central nervous system; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.

All patients who have a possible seizure disorder should be evaluated with an EEG as soon as possible. In the evaluation of a patient with suspected epilepsy, the presence of *electrographic seizure activity* during the clinically evident event (i.e., abnormal, repetitive, rhythmic activity

having a discrete onset and termination) clearly establishes the diagnosis. The EEG is always abnormal during generalized tonic-clonic seizures. The absence of electrographic seizure activity does not exclude a seizure disorder, however, because focal seizures may originate from

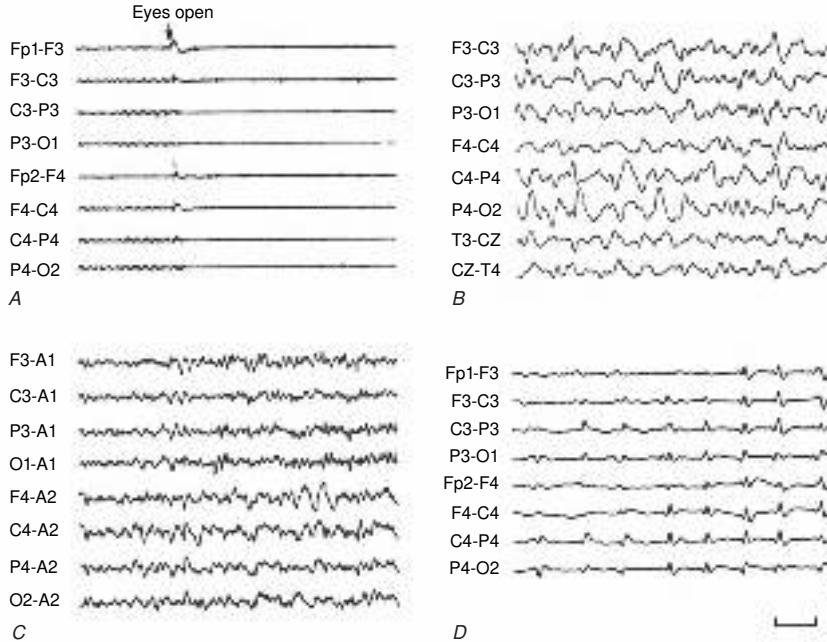


FIGURE 425-3 Electroencephalograms. *A*, Normal electroencephalogram (EEG) showing a posteriorly situated 9-Hz alpha rhythm that attenuates with eye opening. *B*, Abnormal EEG showing irregular diffuse slow activity in an obtunded patient with encephalitis. *C*, Irregular slow activity in the right central region, on a diffusely slowed background, in a patient with a right parietal glioma. *D*, Periodic complexes occurring once every second in a patient with Creutzfeldt-Jakob disease. Horizontal calibration: 1 s; vertical calibration: 200 µV in *A*, 300 µV in other panels. In this and the following figure, electrode placements are indicated at the left of each panel and accord with the international 10–20 system. *A*, earlobe; *C*, central; *F*, frontal; *Fp*, frontal polar; *O*, occipital; *P*, parietal; *T*, temporal. Right-sided placements are indicated by even numbers, left-sided placements by odd numbers, and midline placements by *Z*. (Reproduced with permission from MJ Aminoff: Aminoff's Electrodiagnosis in Clinical Neurology, 6th ed. Oxford: Elsevier Saunders, 2012.)

a region of the cortex that cannot be detected by standard scalp electrodes. Because seizures are typically infrequent and unpredictable, it is often not possible to obtain the EEG during a clinical event. In such situations, activating procedures are generally undertaken while the EEG is recorded in an attempt to provoke abnormalities. These procedures commonly include hyperventilation (for 3 or 4 min), photic stimulation, sleep, and sleep deprivation on the night prior to the recording. Continuous monitoring for prolonged periods in video-EEG telemetry units for hospitalized patients or the use of portable equipment to record the EEG continuously for ≥24 h in ambulatory patients has made it easier to capture the electrophysiologic correlates of clinical events. In particular, video-EEG telemetry is now a routine approach for the accurate diagnosis of epilepsy in patients with poorly characterized events or seizures that are difficult to control.

The EEG may also be helpful in the interictal period by showing certain abnormalities that are highly supportive of the diagnosis of epilepsy. Such *epileptiform activity* consists of bursts of abnormal discharges containing spikes or sharp waves. The presence of epileptiform activity is not entirely specific for epilepsy, but it has a much greater prevalence in patients with epilepsy than in other individuals. However, even in an individual who is known to have epilepsy, the initial routine interictal EEG may be normal 50–80% of the time. Thus, the EEG has limited sensitivity and cannot establish the diagnosis of epilepsy in many cases.

The EEG is also used for classifying seizure disorders and aiding in the selection of anticonvulsant medications (Fig. 425-4). For example, episodic generalized spike-wave activity is usually seen in patients with typical absence epilepsy and may be seen with other generalized epilepsy syndromes. Focal interictal epileptiform discharges would support the diagnosis of a focal seizure disorder such as temporal lobe epilepsy or frontal lobe seizures, depending on the location of the discharges.

The routine scalp-recorded EEG may also be used to assess the prognosis of seizure disorders; in general, a normal EEG implies a better prognosis, whereas an abnormal background or frequent epileptiform activity suggests a worse outcome. Unfortunately, the EEG has not proved to be useful in predicting which patients with predisposing conditions such as head injury or brain tumor will go on to develop epilepsy, because in such circumstances epileptiform activity is commonly encountered regardless of whether seizures occur.

Magnetoencephalography (MEG) provides another way of looking non-invasively at cortical activity. Instead of measuring electrical activity of the brain, it measures the small magnetic fields that are generated by this activity. The epileptiform activity seen on MEG can be analyzed, and its source in the brain can be estimated using a variety of mathematical techniques. These source estimates can then be plotted on an anatomic image of the brain such as an MRI (discussed below) to generate a magnetic source image (MSI). MSI can be useful to localize potential seizure foci.

BRAIN IMAGING

Almost all patients with new-onset seizures should have a brain imaging study to determine whether there is an underlying structural abnormality that

is responsible. The only potential exception to this rule is children who have an unambiguous history and examination suggestive of a benign, generalized seizure disorder such as absence epilepsy. MRI has been shown to be superior to computed tomography (CT) for the detection of cerebral lesions associated with epilepsy. In some cases, MRI will identify lesions such as tumors, vascular malformations, or other pathologies that need urgent therapy. The availability of newer MRI methods, such as three-dimensional structural imaging at sub-millimeter resolution, has increased the sensitivity for detection of abnormalities of cortical architecture, including hippocampal atrophy associated with mesial temporal sclerosis, as well as abnormalities of neuronal migration. In such cases, the findings provide an explanation for the patient's seizures and point to the need for chronic antiseizure drug therapy or possible surgical resection.

In the patient with a suspected CNS infection or mass lesion, CT scanning should be performed emergently when MRI is not immediately available. Otherwise, it is usually appropriate to obtain an MRI study within a few days of the initial evaluation. Functional imaging procedures such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are also used to evaluate certain patients with medically refractory seizures (discussed below).

GENETIC TESTING

With the increasing recognition of specific gene mutations causing epilepsy, genetic testing is beginning to emerge as part of the diagnostic evaluation of patients with epilepsy. In addition to providing a definitive diagnosis (which may be of great benefit to the patient and family members and curtail the pursuit of additional, unrevealing laboratory testing), genetic testing may offer a guide for therapeutic options (see section "Selection of Antiseizure Drugs" below). Genetic testing is currently being done mainly in infants and children with epilepsy syndromes thought to have a genetic cause but should also be considered

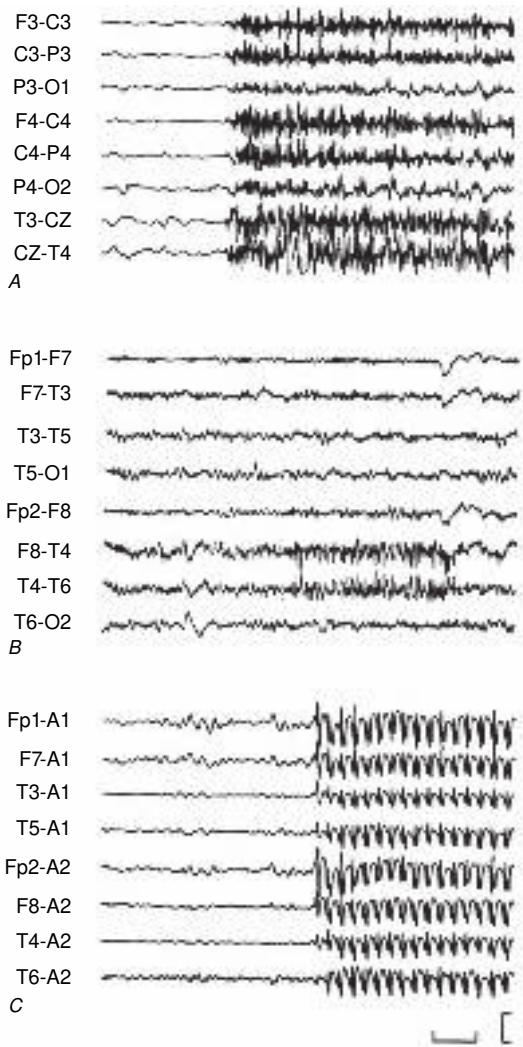


FIGURE 425-4 Electrographic seizures. *A*, Onset of a tonic seizure showing generalized repetitive sharp activity with synchronous onset over both hemispheres. *B*, Burst of repetitive spikes occurring with sudden onset in the right temporal region during a clinical spell characterized by transient impairment of awareness. *C*, Generalized 3-Hz spike-wave activity occurring synchronously over both hemispheres during an absence seizure. Horizontal calibration: 1 s; vertical calibration: 400 μ V in *A*, 200 μ V in *B*, and 750 μ V in *C*. (Reproduced with permission from MJ Aminoff: *Aminoff's Electrodiagnosis in Clinical Neurology*, 6th ed. Oxford: Elsevier Saunders, 2012.)

in older patients with a history suggesting an undiagnosed genetic epilepsy syndrome that began early in life.

DIFFERENTIAL DIAGNOSIS OF SEIZURES

Disorders that may mimic seizures are listed in Table 425-6. In most cases, seizures can be distinguished from other conditions by meticulous attention to the history and relevant laboratory studies. On occasion, additional studies such as video-EEG monitoring, sleep studies, tilt-table analysis, or cardiac electrophysiology may be required to reach a correct diagnosis. Two of the more common nonepileptic syndromes in the differential diagnosis are discussed below.

■ SYNCOPES

(See also Chap. 21) The diagnostic dilemma encountered most frequently is the distinction between a generalized seizure and syncope. Observations by the patient and bystanders that can help differentiate

TABLE 425-6 Differential Diagnosis of Seizures

Syncope	Transient ischemic attack (TIA)
Vasovagal syncope	Basilar artery TIA
Cardiac arrhythmia	Sleep disorders
Valvular heart disease	Narcolepsy/cataplexy
Cardiac failure	Benign sleep myoclonus
Orthostatic hypotension	Movement disorders
Psychological disorders	Tics
Psychogenic seizure	Nonepileptic myoclonus
Hyperventilation	Paroxysmal choreoathetosis
Panic attack	Special considerations in children
Metabolic disturbances	Breath-holding spells
Alcoholic blackouts	Migraine with recurrent abdominal pain and cyclic vomiting
Delirium tremens	Benign paroxysmal vertigo
Hypoglycemia	Apnea
Hypoxia	Night terrors
Psychoactive drugs (e.g., hallucinogens)	Sleepwalking
Migraine	
Confusional migraine	
Basilar migraine	

between the two are listed in Table 425-7. Characteristics of a seizure include the presence of an aura, cyanosis, unconsciousness, motor manifestations lasting >15 s, postictal disorientation, muscle soreness, and sleepiness. In contrast, a syncopal episode is more likely if the event was provoked by acute pain or emotional stress or occurred immediately after arising from the lying or sitting position. Patients with syncope often describe a stereotyped transition from consciousness to unconsciousness that includes tiredness, sweating, nausea, and tunneling of vision, and they experience a relatively brief loss of consciousness. Headache or incontinence usually suggests a seizure but may on occasion also occur with syncope. A brief period (i.e., 1–10 s) of convulsive motor activity is frequently seen immediately at the onset of a syncopal episode, especially if the patient remains in an upright posture after fainting (e.g., in a dentist's chair) and therefore has a sustained decrease in cerebral perfusion. Rarely, a syncopal episode can

TABLE 425-7 Features That Distinguish Generalized Tonic-Clonic Seizure from Syncope

FEATURES	SEIZURE	SYNCOPE
Immediate precipitating factors	Usually none	Emotional stress, Valsalva, orthostatic hypotension, cardiac etiologies
Premonitory symptoms	None or aura (e.g., odd odor)	Tiredness, nausea, diaphoresis, tunneling of vision
Posture at onset	Variable	Usually erect
Transition to unconsciousness	Often immediate	Gradual over seconds ^a
Duration of unconsciousness	Minutes	Seconds
Duration of tonic or clonic movements	30–60 s	Never >15 s
Facial appearance during event	Cyanosis, frothing at mouth	Pallor
Disorientation and sleepiness after event	Many minutes to hours	<5 min
Aching of muscles after event	Often	Sometimes
Biting of tongue	Sometimes	Rarely
Incontinence	Sometimes	Sometimes
Headache	Sometimes	Rarely

^aMay be sudden with certain cardiac arrhythmias.

3316 induce a full tonic-clonic seizure. In such cases, the evaluation must focus on both the cause of the syncopal event as well as the possibility that the patient has a propensity for recurrent seizures. Postictal symptoms can be very helpful when differentiating convulsive syncope from seizure, as confusion and disorientation are typically much less prominent following syncope.

■ PSYCHOGENIC SEIZURES

Psychogenic seizures are nonepileptic behaviors that resemble seizures. They are often part of a conversion reaction precipitated by underlying psychological distress. Certain behaviors such as side-to-side turning of the head, ictal eye closure, asymmetric and large-amplitude shaking movements of the limbs, twitching of all four extremities without loss of consciousness, and pelvic thrusting are more commonly associated with psychogenic rather than epileptic seizures. Psychogenic seizures often last longer than epileptic seizures and may wax and wane over minutes to hours. However, the distinction is sometimes difficult on clinical grounds alone, and there are many examples of diagnostic errors made by experienced epileptologists. This is especially true for psychogenic seizures that resemble focal seizures, because the behavioral manifestations of focal seizures (especially of frontal lobe origin) can be extremely unusual, and in both cases, the routine surface EEG may be normal. Video-EEG monitoring is very useful when historic features are nondiagnostic. Generalized tonic-clonic seizures always produce marked EEG abnormalities during and after the seizure. For suspected focal seizures, the use of additional electrodes may help to localize a seizure focus. Measurement of serum prolactin levels may also help to distinguish between epileptic and psychogenic seizures. Most generalized seizures and some focal seizures are accompanied by a rise in serum prolactin during the immediate 30-min postictal period, whereas psychogenic seizures are not, though this is not always reliable because baseline prolactin levels are rarely available and certain medications can elevate prolactin levels. The diagnosis of psychogenic seizures also does not exclude a concurrent diagnosis of epilepsy, because the two may coexist.

TREATMENT

Seizures and Epilepsy

Therapy for a patient with a seizure disorder is almost always multimodal and includes treatment of underlying conditions that cause or contribute to the seizures, avoidance of precipitating factors, suppression of recurrent seizures by prophylactic therapy with antiseizure medications or surgery, and addressing a variety of psychological and social issues. Treatment plans must be individualized, given the many different types and causes of seizures as well as the differences in efficacy and toxicity of antiseizure medications for each patient. In almost all cases, a neurologist with experience in the treatment of epilepsy should design and oversee implementation of the treatment strategy. Furthermore, patients with refractory epilepsy or those who require polypharmacy with antiseizure drugs should remain under the regular care of a neurologist.

TREATMENT OF UNDERLYING CONDITIONS

If the sole cause of a seizure is a metabolic disturbance such as an abnormality of serum electrolytes or glucose, then treatment is aimed at reversing the metabolic problem and preventing its recurrence. Therapy with antiseizure drugs is usually unnecessary unless the metabolic disorder cannot be corrected promptly and the patient is at risk of having further seizures. If the apparent cause of a seizure was a medication (e.g., theophylline) or illicit drug use (e.g., cocaine), then appropriate therapy is avoidance of the drug; there is usually no need for antiseizure medications unless subsequent seizures occur in the absence of these precipitants.

Seizures caused by a structural CNS lesion such as a brain tumor, vascular malformation, or brain abscess may not recur after appropriate treatment of the underlying lesion. However, despite removal of the structural lesion, there is a risk that the seizure focus will remain in the surrounding tissue or develop de novo as a result of

gliosis and other processes induced by surgery, radiation, or other therapies. Most patients are therefore maintained on an antiseizure medication for at least 1 year, and an attempt is made to withdraw medications only if the patient has been completely seizure free. If seizures are refractory to medication, the patient may benefit from surgical removal of the seizure-producing brain tissue (see below).

AVOIDANCE OF PRECIPITATING FACTORS

Unfortunately, little is known about the specific factors that determine precisely when a seizure will occur in a patient with epilepsy. An almost universal precipitating factor for seizures is sleep deprivation, so patients should do everything possible to optimize their sleep quality. Many patients can identify other particular situations that appear to lower their seizure threshold; these situations should be avoided. For example, patients may note an association between alcohol intake and seizures, and they should be encouraged to modify their drinking habits accordingly. There are also relatively rare cases of patients with seizures that are induced by highly specific stimuli such as a video game monitor, music, or an individual's voice ("reflex epilepsy"). Because there is often an association between stress and seizures, stress reduction techniques such as physical exercise, meditation, or counseling may be helpful.

ANTISEIZURE DRUG THERAPY

Antiseizure drug therapy is the mainstay of treatment for most people with epilepsy. The overall goal is to completely prevent seizures without causing any untoward side effects, preferably with a single medication and a dosing schedule that is easy for the patient to follow. Seizure classification is an important element in designing the treatment plan, because some antiseizure drugs have different activities against various seizure types. However, there is considerable overlap between many antiseizure drugs such that the choice of therapy is often determined more by anticipated side effects, drug-drug interactions, medical comorbidities, dosing frequency, and cost.

When to Initiate Antiseizure Drug Therapy Antiseizure drug therapy should be started in any patient with recurrent seizures of unknown etiology or a known cause that cannot be reversed. Whether to initiate therapy in a patient with a single seizure is controversial. Patients with a single seizure due to an identified lesion such as a CNS tumor, infection, or trauma, in which there is strong evidence that the lesion is epileptogenic, should be treated. The risk of seizure recurrence in a patient with an apparently unprovoked or idiopathic seizure is uncertain, with estimates ranging from 31 to 71% in the first 12 months after the initial seizure. This uncertainty arises from differences in the underlying seizure types and etiologies in various published epidemiologic studies. Generally accepted risk factors associated with recurrent seizures include the following: (1) prior brain insult such as a stroke or trauma, (2) an EEG with epileptiform abnormalities, (3) a significant brain imaging abnormality, or (4) a nocturnal seizure. Most patients with one or more of these risk factors should be treated. Issues such as employment or driving may influence the decision regarding whether to start medications as well. For example, a patient with a single, idiopathic seizure whose job depends on driving may prefer taking an anti-seizure drug rather than risk a seizure recurrence and the potential loss of driving privileges.

Selection of Antiseizure Drugs Antiseizure drugs available in the United States are shown in Table 425-8, and the main pharmacologic characteristics of commonly used drugs are listed in Table 425-9. Worldwide, older medications such as phenytoin, valproic acid, carbamazepine, phenobarbital, and ethosuximide are generally used as first-line therapy for most seizure disorders because, overall, they are as effective as recently marketed drugs and significantly less expensive overall. Most of the new drugs that have become available in the past decade are used as add-on or alternative therapy, although many are now also being used as first-line monotherapy.

TABLE 425-8 Selection of Antiepileptic Drugs

GENERALIZED-ONSET TONIC-CLONIC	FOCAL	TYPICAL ABSENCE	ATYPICAL ABSENCE, MYOCLONIC, ATONIC
First-Line			
Lamotrigine	Lamotrigine	Valproic acid	Valproic acid
Valproic acid	Carbamazepine	Ethosuximide	Lamotrigine
	Oxcarbazepine	Lamotrigine	Topiramate
	Eslicarbazepine		
	Phenytoin		
	Levetiracetam		
Alternatives			
Zonisamide ^a	Zonisamide ^a	Clonazepam	Clonazepam
Phenytoin	Brivaracetam	Zonisamide	Felbamate
Levetiracetam	Topiramate	Levetiracetam	Globazam
Carbamazepine	Valproic acid		Rufinamide
Oxcarbazepine	Tiagabine ^a		
Topiramate	Gabapentin ^a		
Phenobarbital	Lacosamide ^a		
Primidone	Phenobarbital		
Felbamate	Primidone		
Perampanel	Felbamate		
	Perampanel		

^aAs adjunctive therapy.

In addition to efficacy, factors influencing the choice of an initial medication include the convenience of dosing (e.g., once daily vs three or four times daily) and potential side effects. In this regard, a number of the newer drugs have the advantage of reduced drug-drug interactions and easier dosing. Almost all of the commonly used antiseizure drugs can cause similar, dose-related side effects such as sedation, ataxia, and diplopia. Long-term use of some agents in adults, especially the elderly, can lead to osteoporosis. Close follow-up is required to ensure these side effects are promptly recognized and reversed. Most of the older drugs and some of the newer ones can also cause idiosyncratic toxicity such as rash, bone marrow suppression, or hepatotoxicity. Although rare, these side effects should be considered during drug selection, and patients must be instructed about symptoms or signs that should signal the need to alert their health care provider. For some drugs, laboratory tests (e.g., complete blood count and liver function tests) are recommended prior to the institution of therapy (to establish baseline values) and during initial dosing and titration of the agent. Monitoring serum concentrations of antiseizure medications can help determine when a therapeutic dose has been reached, though clinical response is paramount (see below).

An important advance in the care of people with epilepsy has been the application of genetic testing to help guide the choice of therapy (as well as establishing the underlying cause of a patient's syndrome). For example, the identification of a mutation in the *SLC2A1* gene, which encodes the glucose type 1 transporter (GLUT-1) and is a cause of GLUT-1 deficiency, should prompt immediate treatment with the ketogenic diet. Mutations of the *ALDH7A1* gene, which encodes antiquitin, can cause alterations in pyridoxine metabolism that are reversed by treatment with pyridoxine. There is also mounting evidence that certain gene mutations may indicate better or worse response to specific antiseizure drugs. For example, patients with mutations in the sodium channel subunit *SCN1A* should generally avoid taking phenytoin or lamotrigine, whereas patients with mutations in the *SCN2A* or *SCN8A* sodium channel subunits appear to respond favorably to high-dose phenytoin. Genetic testing may also help predict antiseizure drug toxicity. Studies have shown that Asian individuals carrying the human leukocyte antigen (HLA) allele HLA-B*1502 are at particularly

high risk of developing serious skin reactions from carbamazepine, phenytoin, oxcarbazepine, and lamotrigine. HLA-A*31:01 has also been found to be associated with carbamazepine-induced hypersensitivity reactions in patients of European or Japanese ancestry. As a result, racial background and genotype are additional factors to consider in drug selection.

Antiseizure Drug Selection for Focal Seizures Carbamazepine (or related drugs, oxcarbazepine and eslicarbazepine), lamotrigine, phenytoin, and levetiracetam are currently the drugs of choice approved for the initial treatment of focal seizures, including those that evolve into generalized seizures. Overall, they have very similar efficacy, but differences in pharmacokinetics and toxicity are the main determinants for use in a given patient. For example, an advantage of carbamazepine (which is also available in an extended-release form) is that its metabolism follows first-order pharmacokinetics, which allows for a linear relationship between drug dose, serum levels, and toxicity. Carbamazepine can cause leukopenia, aplastic anemia, or hepatotoxicity and would therefore be contraindicated in patients with predispositions to these problems. Oxcarbazepine has the advantage of being metabolized in a way that avoids an intermediate metabolite associated with some of the side effects of carbamazepine. Oxcarbazepine also has fewer drug interactions than carbamazepine. Eslicarbazepine has a long serum half-life and is dosed once daily.

Lamotrigine tends to be well tolerated in terms of side effects and has mood-stabilizing properties that can be beneficial. However, patients need to be particularly vigilant about the possibility of a skin rash during the initiation of therapy. This can be extremely severe and lead to Stevens-Johnson syndrome if unrecognized and if the medication is not discontinued immediately. This risk can be reduced by the use of low initial doses and slow titration. Lamotrigine must be started at even lower initial doses when used as add-on therapy with valproic acid, because valproic acid inhibits lamotrigine metabolism and results in a substantially prolonged half-life.

Phenytoin has a relatively long half-life and offers the advantage of once- or twice-daily dosing compared to twice- or thrice-daily dosing for many of the other drugs. However, phenytoin shows properties of nonlinear kinetics, such that small increases in phenytoin doses above a standard maintenance dose can precipitate marked side effects. This is one of the main causes of acute phenytoin toxicity (dizziness, diplopia, ataxia). Long-term use of phenytoin is associated with untoward cosmetic effects (e.g., hirsutism, coarsening of facial features, gingival hypertrophy) and effects on bone metabolism. Due to these side effects, phenytoin is often avoided in young patients who are likely to require the drug for many years.

Levetiracetam has the advantage of having no known clinically relevant drug-drug interactions, making it especially useful in the elderly and patients on other medications. However, a significant number of patients taking levetiracetam complain of irritability, anxiety, and other psychiatric symptoms.

Topiramate can be used for both focal and generalized seizures. Similar to some of the other antiseizure drugs, topiramate can cause significant psychomotor slowing and other cognitive problems. Additionally, it should not be used in patients at risk for the development of glaucoma or renal stones.

Valproic acid is an effective alternative for some patients with focal seizures, especially when the seizures generalize. Gastrointestinal side effects are fewer when using the delayed-release formulation (Depakote). Laboratory testing is required to monitor toxicity because valproic acid can rarely cause reversible bone marrow suppression and hepatotoxicity. This drug should generally be avoided in patients with preexisting bone marrow or liver disease. Valproic acid also has relatively high risks of unacceptable adverse effects for women of childbearing age, including hyperandrogenism, that may affect fertility and teratogenesis (e.g., neural tube defects) in offspring. Irreversible, fatal hepatic failure appearing as an idiosyncratic rather than dose-related side effect is a relatively rare

TABLE 425-9 Dosage and Adverse Effects of Commonly Used Antiepileptic Drugs

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS ^a
						NEUROLOGIC	SYSTEMIC	
Brivaracetam	Brivailact	Focal onset	100–200 mg/d; bid	7–10 h	Not established	Fatigue Dizziness Weakness Ataxia Mood changes	Gastrointestinal irritation	May increase carbamazepine-epoxide causing decreased tolerability May increase phenytoin
Cannabidiol	Epidiolex	Dravet and Lennox-Gastaut syndromes	10–20 mg/kg per d; bid	18–32 h	Not established	Sedation	Elevated transaminases Anorexia Weight loss Diarrhea	Increases clobazam causing somnolence
		Tuberous sclerosis complex-associated seizures						
Carbamazepine	Tegretol ^c	Tonic-clonic Focal onset	600–1800 mg/d (15–35 mg/kg, child); bid (capsules or tablets), tid-qid (oral suspension)	10–17 h (variable due to autoinduction: complete 3–5 wk after initiation)	4–12 µg/mL	Ataxia Dizziness Diplopia Vertigo	Aplastic anemia Leukopenia Gastrointestinal irritation Hepatotoxicity Hyponatremia Rash	Level decreased by enzyme-inducing drugs ^b Level increased by erythromycin, propoxyphene, isoniazid, cimetidine, fluoxetine
Clobazam	Onfi	Lennox-Gastaut syndrome	10–40 mg/d (5–20 mg/d for patients <30 kg body weight); bid	36–42 h (71–82 h for less active metabolite)	Not established	Fatigue Sedation Ataxia Aggression Insomnia	Constipation Anorexia Skin rash	Level increased by CYP2C19 inhibitors
Clonazepam	Klonopin	Absence Atypical absence Myoclonic	1–12 mg/d; qd-tid	24–48 h	10–70 ng/mL	Ataxia Sedation Lethargy	Anorexia	Level decreased by enzyme-inducing drugs ^b
Esllicarbazepine	Aptiom	Focal onset	400–1600 mg/d; qd	20–24 h	10–35 µg/mL (as oxcarbazepine mono-hydroxy derivative)	Sedation Ataxia Dizziness Diplopia Vertigo	See carbamazepine	Level decreased by enzyme-inducing drugs ^b
Ethosuximide	Zarontin	Absence	750–1250 mg/d (20–40 mg/kg); qd-bid	60 h, adult 30 h, child	40–100 µg/mL	Ataxia Lethargy Headache	Gastrointestinal irritation Skin rash Bone marrow suppression	Level decreased by enzyme-inducing drugs ^b Level increased by valproic acid
Felbamate	Felbatol	Focal onset Lennox-Gastaut syndrome Tonic-clonic	2400–3600 mg/d, tid-qid	16–22 h	30–60 µg/mL	Insomnia Dizziness Sedation Headache	Aplastic anemia Hepatic failure Weight loss Gastrointestinal irritation	Increases phenytoin, valproic acid, active carbamazepine metabolite
Gabapentin	Neurontin	Focal onset	900–2400 mg/d; tid-qid	5–9 h	2–20 µg/mL	Sedation Dizziness Ataxia Fatigue	Gastrointestinal irritation Weight gain Edema	No known significant interactions
Lacosamide	Vimpat	Focal onset	200–400 mg/d; bid	13 h	Not established	Dizziness Ataxia Diplopia Vertigo	Gastrointestinal irritation Cardiac conduction (PR interval prolongation)	Level decreased by enzyme-inducing drugs ^b
Lamotrigine	Lamictal ^d	Focal onset Tonic-clonic Atypical absence Myoclonic Lennox-Gastaut syndrome	150–500 mg/d; bid (immediate release), daily (extended release) (lower daily dose for regimens with valproic acid; higher daily dose for regimens with an enzyme inducer)	25 h 14 h (with enzyme inducers), 59 h (with valproic acid)	2.5–20 µg/mL	Dizziness Diplopia Sedation Ataxia Headache	Skin rash Stevens-Johnson syndrome	Level decreased by enzyme-inducing drugs ^b and oral contraceptives Level increased by valproic acid

(Continued)

TABLE 425-9 Dosage and Adverse Effects of Commonly Used Antiepileptic Drugs (Continued)

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS ^a
						NEUROLOGIC	SYSTEMIC	
Levetiracetam	Keppra	Focal onset	1000–3000 mg/d; bid (immediate release), daily (extended release)	6–8 h	5–45 µg/mL	Sedation Fatigue Incoordination Mood changes	Anemia Leukopenia	No known significant interactions
Oxcarbazepine ^c	Trileptal	Focal onset Tonic-clonic	900–2400 mg/d (30–45 mg/kg, child); bid	10–17 h (for active metabolite)	10–35 µg/mL	Fatigue Ataxia Dizziness Diplopia Vertigo Headache	See carbamazepine	Level decreased by enzyme-inducing drugs ^b May increase phenytoin
Perampanel	Fycompa	Focal onset Tonic-clonic	4–12 mg; qd	105 h	Not established	Dizziness Somnolence Aggression Ataxia Anxiety Paranoia	Headache Nausea	Level decreased by enzyme-inducing drugs ^b
Phenobarbital	Luminal	Tonic-clonic Focal onset	60–180 mg/d; qd-tid	90 h	10–40 µg/mL	Sedation Ataxia Confusion Dizziness Decreased libido Depression	Skin rash	Level increased by valproic acid, phenytoin
Phenytoin ^c (diphenylhydantoin)	Dilantin	Tonic-clonic Focal onset	300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); qd-tid	24 h (wide variation, dose-dependent)	10–20 µg/mL	Dizziness Diplopia Ataxia Incoordination Confusion	Gingival hyperplasia Lymphadenopathy Hirsutism Osteomalacia Facial coarsening Skin rash	Level increased by isoniazid, sulfonamides, fluoxetine Level decreased by enzyme-inducing drugs ^b Altered folate metabolism
Primidone	Mysoline	Tonic-clonic Focal onset	750–1000 mg/d; bid-tid	Primidone, 8–15 h Phenobarbital, 90 h	Primidone, 4–12 µg/mL Phenobarbital, 10–40 µg/mL	Same as phenobarbital		Level increased by valproic acid Level decreased by phenytoin (increased conversion to phenobarbital)
Rufinamide	Banzel	Lennox-Gastaut syndrome	3200 mg/d (45 mg/kg, child); bid	6–10 h	Not established	Sedation Fatigue Dizziness Ataxia Headache Diplopia	Gastrointestinal irritation Leukopenia Cardiac conduction (QT interval shortening)	Level decreased by enzyme-inducing drugs ^b Level increased by valproic acid May increase phenytoin
Tiagabine	Gabitril	Focal onset	32–56 mg/d; bid-qid (as adjunct to enzyme-inducing antiepileptic drug regimen)	2–5 h (with enzyme inducer), 7–9 h (without enzyme inducer)	Not established	Confusion Sedation Depression Dizziness Speech or language problems Paresthesias Psychosis	Gastrointestinal irritation	Level decreased by enzyme-inducing drugs ^b
Topiramate ^c	Topamax	Focal onset Tonic-clonic Lennox-Gastaut syndrome	200–400 mg/d; bid (immediate release), daily (extended release)	20 h (immediate release), 30 h (extended release)	2–20 µg/mL	Psychomotor slowing Sedation Speech or language problems Fatigue Paresthesias	Renal stones (avoid use with other carbonic anhydrase inhibitors) Glaucoma Weight loss Hypohidrosis	Level decreased by enzyme-inducing drugs ^b

(Continued)

TABLE 425-9 Dosage and Adverse Effects of Commonly Used Antiepileptic Drugs (Continued)

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS ^a
						NEUROLOGIC	SYSTEMIC	
Valproic acid (valproate sodium, divalproex sodium)	Depakene	Tonic-clonic	750–2000 mg/d (20–60 mg/kg); bid–qid (immediate and delayed release), daily (extended release)	15 h	50–125 µg/mL	Ataxia Sedation Tremor	Hepatotoxicity Thrombocytopenia Gastrointestinal irritation Weight gain Transient alopecia Hyperammonemia	Level decreased by enzyme-inducing drugs ^b
	Depakote	Absence Atypical absence Myoclonic Focal onset Atonic						
Zonisamide	Zonegran	Focal onset Tonic-clonic	200–400 mg/d; qd–bid	50–68 h	10–40 µg/mL	Sedation Dizziness Confusion Headache Psychosis	Anorexia Renal stones Hypohidrosis	Level decreased by enzyme-inducing drugs ^b

^aExamples only; please refer to other sources for comprehensive listings of all potential drug-drug interactions. ^bPhenytoin, carbamazepine, phenobarbital. ^cExtended-release product available.

complication; its risk is highest in children <2 years old, especially those taking other antiseizure drugs or with inborn errors of metabolism.

Zonisamide, brivaracetam, tiagabine, gabapentin, perampanel, and lacosamide are additional drugs currently used for the treatment of focal seizures with or without evolution into generalized seizures. Phenobarbital and other barbiturate compounds were commonly used in the past as first-line therapy for many forms of epilepsy. However, the barbiturates frequently cause sedation in adults, hyperactivity in children, and other more subtle cognitive changes; thus, their use should be limited to situations in which no other suitable treatment alternatives exist.

Antiseizure Drug Selection for Generalized Seizures
Lamotrigine, valproic acid, and levetiracetam are currently considered the best initial choice for the treatment of primary generalized, tonic-clonic seizures. Topiramate, zonisamide, perampanel, phenytoin, carbamazepine, and oxcarbazepine are suitable alternatives, although carbamazepine, oxcarbazepine, and phenytoin can worsen certain types of generalized seizures. Valproic acid is particularly effective in absence, myoclonic, and atonic seizures. It is therefore commonly used in patients with generalized epilepsy syndromes having mixed seizure types. However, levetiracetam, rather than valproic acid, is increasingly considered the initial drug of choice for women with epilepsies having mixed seizure types given the adverse effects of valproic acid for women of childbearing age. Lamotrigine is also an alternative to valproate, especially for absence epilepsies. Ethosuximide is a particularly effective drug for the treatment of uncomplicated absence seizures, but it is not useful for tonic-clonic or focal seizures. Periodic monitoring of blood cell counts is required since ethosuximide rarely causes bone marrow suppression.

INITIATION AND MONITORING OF THERAPY

Because the response to any antiseizure drug is unpredictable, patients should be carefully educated about the approach to therapy. The goal is to prevent seizures and minimize the side effects of treatment; determination of the optimal medication and the optimal dose typically involves trial and error. This process may take months or longer if the baseline seizure frequency is low. Most antiseizure drugs need to be introduced relatively slowly to minimize side effects. Patients should expect that minor side effects such as mild sedation, slight changes in cognition, or imbalance will typically resolve within a few days. Starting doses are usually the lowest value listed under the dosage column in Table 425-9. Subsequent increases should be made only after achieving a steady state with the previous dose (i.e., after an interval of five or more half-lives).

Monitoring of serum antiseizure drug levels can be very useful for establishing the initial dosing schedule. However, the published therapeutic ranges of serum drug concentrations are only an approximate guide for determining the proper dose for a given patient. The key determinants are the clinical measures of seizure frequency and presence of side effects, not the laboratory values. Conventional assays of serum drug levels measure the total drug (i.e., both free and protein bound). However, it is the concentration of free drug that reflects extracellular levels in the brain and correlates best with efficacy. Thus, patients with decreased levels of serum proteins (e.g., decreased serum albumin due to impaired liver or renal function) may have an increased ratio of free to bound drug, yet the concentration of free drug may be adequate for seizure control. These patients may have a “subtherapeutic” drug level, but the dose should be changed only if seizures remain uncontrolled, not just to achieve a “therapeutic” level. It is also useful to monitor free drug levels in such patients. In practice, other than during the initiation or modification of therapy, monitoring of antiseizure drug levels is most useful for documenting adherence, assessing clinical suspicion of toxicity, or establishing baseline serum concentrations prior to pregnancy, when clearance of many antiseizure drugs increases significantly.

If seizures continue despite gradual increases to the maximum tolerated dose and documented compliance, then it becomes necessary to switch to another antiseizure drug. This is usually done by maintaining the patient on the first drug while a second drug is added. The dose of the second drug should be adjusted to decrease seizure frequency without causing toxicity. Once this is achieved, the first drug can be gradually withdrawn (usually over weeks unless there is significant toxicity). The dose of the second drug is then further optimized based on seizure response and side effects. Monotherapy should be the goal whenever possible.

WHEN TO DISCONTINUE THERAPY

Overall, ~50–60% of patients who have their seizures completely controlled with antiseizure drugs can eventually discontinue therapy. The following patient profile yields the greatest chance of remaining seizure free after drug withdrawal: (1) complete medical control of seizures for 1–5 years; (2) single seizure type, with generalized seizures having a better prognosis than focal seizures; (3) normal neurologic examination, including intelligence; (4) no family history of epilepsy; and (5) normal EEG. The appropriate seizure-free interval is unknown and undoubtedly depends on the form of epilepsy and whether or not the causal factor is still present (e.g., resection of a brain tumor causing seizures). However, it seems reasonable to attempt withdrawal of therapy after 2 years in a patient who meets all of the above criteria, is motivated to discontinue the

medication, and clearly understands the potential risks and benefits. In most cases, it is preferable to reduce the dose of the drug gradually over 2–3 months. Most recurrences occur in the first 3 months after discontinuing therapy, and patients should be advised to avoid potentially dangerous situations such as driving or swimming during this period. Up to 20% of seizure-free patients who discontinue antiseizure medications but then have a recurrent seizure may not regain full control when these medications are resumed.

TREATMENT OF REFRACTORY EPILEPSY

Approximately one-third of patients with epilepsy do not respond to treatment with a single antiseizure drug, and it becomes necessary to try a combination of drugs to control seizures. Patients who have focal epilepsy related to an underlying structural lesion or those with multiple seizure types and developmental delay are particularly likely to require multiple drugs. There are currently no clear guidelines for rational polypharmacy, although in theory, a combination of drugs with different mechanisms of action may be most useful. In most cases, the initial combination therapy combines first-line drugs (i.e., carbamazepine, oxcarbazepine, lamotrigine, valproic acid, levetiracetam, and phenytoin). If these drugs are unsuccessful, then the addition of other drugs such as zonisamide, brivaracetam, topiramate, lacosamide, or tiagabine is indicated. Patients with myoclonic seizures resistant to valproic acid may benefit from the addition of levetiracetam, zonisamide, clonazepam, or clobazam, and those with absence seizures may respond to a combination of valproic acid and ethosuximide. The same principles concerning the monitoring of therapeutic response, toxicity, and serum levels for monotherapy apply to polypharmacy, and potential drug interactions need to be recognized. If there is no improvement, a third drug can be added while the first two are maintained. If there is a response, the less effective or less well tolerated of the first two drugs should be gradually withdrawn.

SURGICAL TREATMENT OF REFRACTORY EPILEPSY

Approximately 20–30% of patients with epilepsy continue to have seizures despite efforts to find an effective combination of antiseizure drugs. For some patients with focal epilepsy, surgery can be extremely effective in substantially reducing seizure frequency and even providing complete seizure control. Understanding the potential value of surgery is especially important when a patient's seizures are not controlled with initial treatment, as such patients often do not respond to subsequent medication trials. Rather than submitting the patient to years of unsuccessful medical therapy and the psychosocial trauma and increased mortality associated with ongoing seizures, the patient should have an efficient but relatively brief attempt at medical therapy and then be referred for surgical evaluation.

The most common surgical procedure for patients with temporal lobe epilepsy involves resection of the anteromedial temporal lobe (temporal lobectomy) or a more limited removal of the underlying hippocampus and amygdala (amygdalohippocampectomy). Focal seizures arising from extratemporal regions may be abolished by a focal neocortical resection with precise removal of an identified lesion (lesionectomy). Localized neocortical resection without a clear lesion identified on MRI is also possible when other tests (e.g., MEG, PET, SPECT) implicate a focal cortical region as a seizure onset zone. When the cortical region cannot be removed, multiple subpial transection, which disrupts intracortical connections, is sometimes used to prevent seizure spread. Hemispherectomy or multilobar resection is useful for some patients with severe seizures due to hemispheric abnormalities such as hemimegalencephaly or other dysplastic abnormalities, and corpus callosotomy has been shown to be effective for disabling tonic or atonic seizures, usually when they are part of a mixed-seizure syndrome (e.g., Lennox-Gastaut syndrome).

Presurgical evaluation is designed to identify the functional and structural basis of the patient's seizure disorder. Inpatient video-EEG monitoring is used to define the anatomic location of the seizure focus and to correlate the abnormal electrophysiologic activity with behavioral manifestations of the seizure. Routine scalp

or scalp-sphenoidal recordings and a high-resolution MRI scan are usually sufficient for localization of the epileptogenic focus, especially when the findings are concordant. Functional imaging studies such as SPECT, PET, and MEG are adjunctive tests that may help to reveal or verify the localization of an apparent epileptogenic region. Once the presumed location of the seizure onset is identified, additional studies, including neuropsychological testing, the intracarotid amobarbital test (Wada test), and functional MRI may be used to assess language and memory localization and to determine the possible functional consequences of surgical removal of the epileptogenic region. In some cases, standard noninvasive evaluation is not sufficient to localize the seizure onset zone, and invasive electrophysiologic monitoring, such as implanted depth or subdural electrodes, is required for more definitive localization. The exact extent of the resection to be undertaken can also be determined by performing cortical mapping at the time of the surgical procedure, allowing for a tailored resection. This involves electrocorticographic recordings made with electrodes on the surface of the brain to identify the extent of epileptiform disturbances. If the region to be resected is within or near brain regions suspected of having sensorimotor or language function, electrical cortical stimulation mapping is performed on the awake patient to determine the function of cortical regions in question in order to avoid resection of so-called eloquent cortex and thereby minimize postsurgical deficits.

Advances in presurgical evaluation and microsurgical techniques have led to a steady increase in the success of epilepsy surgery. Clinically significant complications of surgery are <5%, and the use of functional mapping procedures has markedly reduced the neurologic sequelae due to removal or sectioning of brain tissue. For example, ~70% of well-selected patients treated with temporal lobectomy will become seizure free, and another 15–25% will have at least a 90% reduction in seizure frequency. Marked improvement is also usually seen in patients treated with hemispherectomy for catastrophic seizure disorders due to large hemispheric abnormalities. Postoperatively, patients generally need to remain on antiseizure drug therapy, but the marked reduction of seizures following resective surgery can have a very beneficial effect on quality of life. Recently, catheter-based stereotactic laser thermal ablation has been developed as a less invasive means for destroying the seizure focus in select patients.

Not all medically refractory patients are suitable candidates for resective surgery or laser ablation. For example, some patients have seizures arising from more than one brain region or from a single "eloquent" region that mediates a critical function (e.g., vision, movement, language), such that the potential harm from removal is unacceptably high. In these patients, implanted neurostimulation devices that deliver electrical energy to the brain to reduce seizures represent palliative treatment options. Vagus nerve stimulation (VNS) involves an extracranial device that works through scheduled intermittent ("open loop") stimulation of the left vagus nerve. Efficacy of VNS is limited, and side effects related to recurrent laryngeal nerve activation (e.g., hoarseness, throat pain, dyspnea) can be significant and dose-limiting. By contrast, responsive neurostimulation (RNS) involves an implanted device connected to two lead wires that are placed intracranially at the site(s) from where seizures arise. The neurostimulator detects the onset of a seizure (often before the seizure becomes clinically apparent) and delivers electrical stimulation—typically imperceptible—directly to the brain to reduce seizures over time, a form of "closed loop" neurostimulation. RNS is the only device that provides chronic EEG, which has a growing number of clinical applications, such as quantifying the lateralization of seizures arising from both sides of the brain, characterizing clinical spells, assessing effects of medications and other therapeutic interventions, and revealing cyclical patterns of epileptic brain activity that may help anticipate future events. A third modality, thalamic deep brain stimulation (DBS), involves open loop stimulation of deep, bilateral cerebral structures, the anterior thalamic nuclei, which are key nodes in limbic circuits mediating certain types of seizures. Whereas precise seizure localization is necessary for RNS, it is not required for VNS or DBS.

Long-term clinical trials of all three neurostimulation devices demonstrate significant reductions in frequency with outcomes improving over time, but only a minority of patients treated with these devices achieve seizure freedom (e.g., ~15% with RNS). Furthermore, no head-to-head device trials exist to establish relative superiority, so choice of a device is guided by patient-specific factors and by the strengths and limitations of each technology.

■ STATUS EPILEPTICUS

Status epilepticus refers to continuous seizures or repetitive, discrete seizures with impaired consciousness in the interictal period. Status epilepticus has numerous subtypes, including generalized convulsive status epilepticus (GCSE) (e.g., persistent, generalized electrographic seizures, coma, and tonic-clonic movements) and nonconvulsive status epilepticus (e.g., persistent absence seizures or focal seizures with confusion or partially impaired consciousness, and minimal motor abnormalities). The duration of seizure activity sufficient to meet the definition of status epilepticus has traditionally been specified as 15–30 min. However, a more practical definition is to consider status epilepticus as a situation in which the duration of seizures prompts the acute use of anticonvulsant therapy. For GCSE, this is typically when seizures last beyond 5 min.

GCSE is an emergency and must be treated immediately, because cardiorespiratory dysfunction, hyperthermia, and metabolic derangements can develop as a consequence of prolonged seizures, and these can lead to irreversible neuronal injury. Furthermore, CNS injury can occur even when the patient is paralyzed with neuromuscular blockade but continues to have electrographic seizures. The most common causes of GCSE are anticonvulsant withdrawal or noncompliance, metabolic disturbances, drug toxicity, CNS infection, CNS tumors, refractory epilepsy, and head trauma.

GCSE is obvious when the patient is having overt seizures. However, after 30–45 min of uninterrupted seizures, the signs may become increasingly subtle. Patients may have mild clonic movements of only the fingers or fine, rapid movements of the eyes. There may be paroxysmal episodes of tachycardia, hypertension, and pupillary dilation. In such cases, the EEG may be the only method of establishing the diagnosis. Thus, if the patient stops having overt seizures, yet remains comatose, an EEG should be performed to rule out ongoing status epilepticus. This is obviously also essential when a patient with GCSE has been paralyzed with neuromuscular blockade in the process of protecting the airway.

The first steps in the management of a patient in GCSE are to attend to any acute cardiorespiratory problems or hyperthermia, perform a brief medical and neurologic examination, establish venous access, and send samples for laboratory studies to identify metabolic abnormalities. Anticonvulsant therapy should then begin without delay; a treatment approach is shown in Fig. 425-5.

The treatment of nonconvulsive status epilepticus is thought to be less urgent than GCSE, because the ongoing seizures are not accompanied by the severe metabolic disturbances seen with GCSE. However, evidence suggests that nonconvulsive status epilepticus, especially that caused by ongoing, focal seizure activity, is associated with cellular injury in the region of the seizure focus; therefore, this condition should be treated as promptly as possible using the general approach described for GCSE.

BEYOND SEIZURES: OTHER MANAGEMENT ISSUES

■ EPILEPSY COMORBIDITIES

The adverse effects of epilepsy often go beyond clinical seizures. Many people with epilepsy feel completely normal between seizures and live

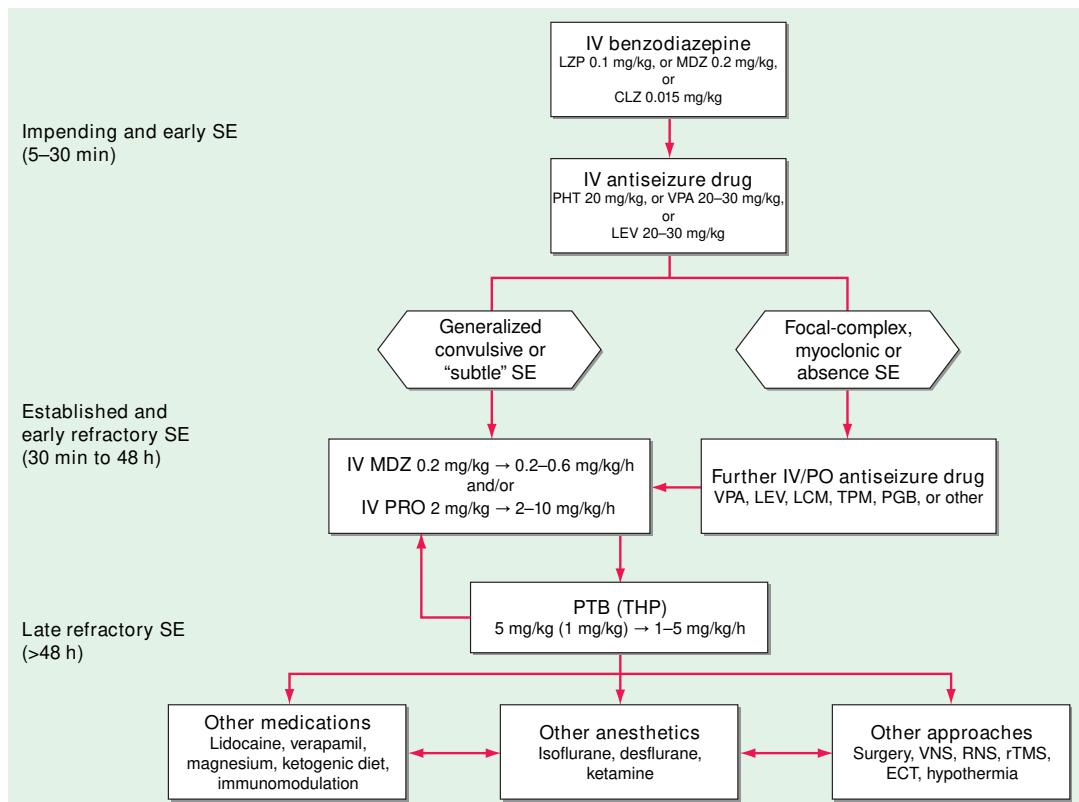


FIGURE 425-5 Pharmacologic treatment of generalized tonic-clonic status epilepticus (SE) in adults. CLZ, clonazepam; ECT, electroconvulsive therapy; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; PGB, pregabalin; PHT, phenytoin or fosphenytoin; PRO, propofol; PTB, pentobarbital; RNS, responsive neurostimulation; rTMS, repetitive transcranial magnetic stimulation; THP, thiopental; TPM, topiramate; VNS, vagus nerve stimulation; VPA, valproic acid. (Data from AO Rossetti, DH Lowenstein: Management of refractory status epilepticus in adults: still more questions than answers. *Lancet Neurol* 10:922, 2011.)

highly successful and productive lives. However, a significant proportion of patients suffer from varying degrees of cognitive dysfunction, including psychiatric disease, and it has become increasingly clear that the network dysfunction underlying epilepsy can have effects well beyond the occurrence of seizures. For example, patients with seizures secondary to developmental abnormalities or acquired brain injury may have impaired cognitive function and other neurologic deficits due to abnormal brain structure. Frequent interictal EEG abnormalities are associated with subtle dysfunction of memory and attention. Patients with many seizures, especially those emanating from the temporal lobe, often note an impairment of short-term memory that may progress over time.

The psychiatric problems associated with epilepsy include depression, anxiety, and psychosis. This risk varies considerably depending on many factors, including the etiology, frequency, and severity of seizures and the patient's age and previous personal or family history of psychiatric disorder. Depression occurs in ~20% of patients, and the incidence of suicide is higher in people with epilepsy than in the general population. Depression should be treated through counseling and/or medication. The selective serotonin reuptake inhibitors (SSRIs) typically have minimal effect on seizures, whereas tricyclic antidepressants may lower the seizure threshold. Anxiety can be a seizure symptom, and anxious or psychotic behavior can occur during a postictal delirium. Postictal psychosis is a rare phenomenon that typically occurs after a period of increased seizure frequency. There is usually a brief lucid interval lasting up to a week, followed by days to weeks of agitated, psychotic behavior. The psychosis usually resolves spontaneously but frequently will require short-term treatment with antipsychotic or anxiolytic medications.

■ MORTALITY OF EPILEPSY

People with epilepsy have a risk of death that is roughly two to three times greater than expected in a matched population without epilepsy. Most of the increased mortality is due to the underlying etiology of epilepsy (e.g., tumors or strokes in older adults). However, a significant number of patients die from accidents, status epilepticus, and a syndrome known as *sudden unexpected death in epilepsy* (SUDEP), which usually affects young people with convulsive seizures and tends to occur at night. The cause of SUDEP is unknown; it may result from brainstem-mediated effects of seizures on pulmonary, cardiac, and arousal functions. Recent studies suggest that, in some cases, a genetic mutation may be the cause of both epilepsy and a cardiac conduction defect that gives rise to sudden death.

■ PSYCHOSOCIAL ISSUES

There continues to be a cultural stigma about epilepsy, although it is slowly declining in societies with effective health education programs. Many people with epilepsy harbor fear of progressive cognitive decline or dying during a seizure. These issues need to be carefully addressed by educating the patient about epilepsy and by ensuring that family members, teachers, fellow employees, and other associates are equally well informed. A useful source of educational material is the website www.epilepsy.com.

■ EMPLOYMENT, DRIVING, AND OTHER ACTIVITIES

Many patients with epilepsy face difficulty in obtaining or maintaining employment, even when their seizures are well controlled. Federal and state legislation is designed to prevent employers from discriminating against people with epilepsy, and patients should be encouraged to understand and claim their legal rights. Patients in these circumstances also benefit greatly from the assistance of health providers who act as strong patient advocates.

Loss of driving privileges is one of the most disruptive social consequences of epilepsy. Physicians should be very clear about local regulations concerning driving and epilepsy, because the laws vary considerably among states and countries. In all cases, it is the physician's responsibility to warn patients of the danger imposed on themselves and others while driving if their seizures are uncontrolled (unless the seizures are not associated with impairment of consciousness or motor control). In general, most states allow patients to drive after a

seizure-free interval (on or off medications) of between 3 months and 2 years.

Patients with incompletely controlled seizures must also contend with the risk of being in other situations where an impairment of consciousness or loss of motor control could lead to major injury or death. Thus, depending on the type and frequency of seizures, many patients need to be instructed to avoid working at heights or with machinery or to have someone close by for activities such as bathing and swimming.

SPECIAL ISSUES RELATED TO WOMEN AND EPILEPSY

■ CATAMENIAL EPILEPSY

Some women experience a marked increase in seizure frequency around the time of menses. This is believed to be mediated by either the effects of estrogen and progesterone on neuronal excitability or changes in antiseizure drug levels due to altered protein binding or metabolism. Some women with epilepsy may benefit from increases in antiseizure drug dosages during menses. Natural progestins or intramuscular medroxyprogesterone may be of benefit to a subset of women.

■ PREGNANCY

Most women with epilepsy who become pregnant will have an uncomplicated gestation and deliver a normal baby. However, epilepsy poses some important risks to a pregnancy. Seizure frequency during pregnancy will remain unchanged in ~50% of women, increase in ~30%, and decrease in ~20%. Changes in seizure frequency are attributed to endocrine effects on the CNS, variations in antiseizure drug pharmacokinetics (such as acceleration of hepatic drug metabolism or effects on plasma protein binding), and changes in medication compliance. It is useful to see patients at frequent intervals during pregnancy and monitor serum antiseizure drug levels. Measurement of the unbound drug concentrations may be useful if there is an increase in seizure frequency or worsening of side effects of antiseizure drugs.

The overall incidence of fetal abnormalities in children born to mothers with epilepsy is 5–6%, compared to 2–3% in healthy women. Part of the higher incidence is due to teratogenic effects of antiseizure drugs, and the risk increases with the number of medications used (e.g., 10–20% risk of malformations with three drugs) and possibly with higher doses. A meta-analysis of published pregnancy registries and cohorts found that the most common malformations were defects in the cardiovascular and musculoskeletal system (1.4–1.8%). Valproic acid is strongly associated with an increased risk of adverse fetal outcomes (7–20%). Findings from a large pregnancy registry suggest that, other than topiramate, the newer antiseizure drugs are far safer than valproic acid.

Because the potential harm of uncontrolled convulsive seizures on the mother and fetus is considered greater than the teratogenic effects of antiseizure drugs, it is currently recommended that pregnant women be maintained on effective drug therapy. When possible, it seems prudent to have the patient on monotherapy at the lowest effective dose, especially during the first trimester. For some women, however, the type and frequency of their seizures may allow for them to safely wean off antiseizure drugs prior to conception. Patients should also take folate (1–4 mg/d), because the antifolate effects of anticonvulsants are thought to play a role in the development of neural tube defects, although the benefits of this treatment remain unproved in this setting.

Enzyme-inducing drugs such as phenytoin, carbamazepine, oxcarbazepine, topiramate, phenobarbital, and primidone cause a transient and reversible deficiency of vitamin K-dependent clotting factors in ~50% of newborn infants. Although neonatal hemorrhage is uncommon, the mother should be treated with oral vitamin K (20 mg/d, phylloquinone) in the last 2 weeks of pregnancy, and the infant should receive intramuscular vitamin K (1 mg) at birth.

■ CONTRACEPTION

Special care should be taken when prescribing antiseizure medications for women who are taking oral contraceptive agents. Drugs such as

carbamazepine, phenytoin, phenobarbital, and topiramate can significantly decrease the efficacy of oral contraceptives via enzyme induction and other mechanisms. Patients should be advised to consider alternative forms of contraception, including intrauterine devices and other long-acting reversible contraceptives, or their oral contraceptive medications should be modified to offset the effects of the antiseizure medications.

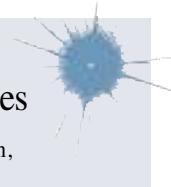
BREAST FEEDING

Antiseizure medications are excreted into breast milk to a variable degree. The ratio of drug concentration in breast milk relative to serum ranges from ~5% (valproic acid) to 300% (levetiracetam). Given the overall benefits of breast-feeding and the lack of evidence for long-term harm to the infant by being exposed to antiseizure drugs, mothers with epilepsy can be encouraged to breast-feed. This should be reconsidered, however, if there is any evidence of drug effects on the infant such as lethargy or poor feeding.

FURTHER READING

- C DK et al: Psychogenic non-epileptic seizures. *Curr Neurosci Rep* 17:71, 2017.
- C SB, S T: Evaluation of the patient with spells. *Continuum (Minneapolis Minn)* 17:984, 2011.
- C AZ, S JI: Management of adult onset seizures. *Mayo Clin Proc* 92:306, 2017.
- E CA et al: Epilepsy genetics: Clinical impacts and biological insights. *Lancet Neurol* 19:93, 2020.
- E PM C : A roadmap for precision medicine in the epilepsies. *Lancet Neurol* 14:1219, 2015.
- F RS et al: Operational classification of seizure types by the International League Against Epilepsy: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58:522, 2017.
- G JR, S SU: New-onset seizure in adults and adolescents: A review. *JAMA* 316:2657, 2016.
- G A, K P: Drug development for refractory epilepsy: The past 25 years and beyond. *Seizure* 44:147, 2017.
- J N et al: Surgical treatment for epilepsy: The potential gap between evidence and practice. *Lancet Neurol* 15:982, 2016.
- K AM: Management of psychiatric and neurological comorbidities in epilepsy. *Nat Rev Neurol* 12:106, 2016.
- K MR et al: Comorbidities of epilepsy: Current concepts and future perspectives. *Lancet Neurol* 15:106, 2016.
- K A et al: Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 84:1705, 2015.
- K P, B MJ: Early identification of refractory epilepsy. *N Engl J Med* 342:314, 2000.
- L HJ et al: Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: A systematic review and individual participant data meta-analysis. *Lancet Neurol* 16:523, 2017.
- M MS, F RS: Neuromodulation: Science and practice in epilepsy: Vagus nerve stimulation, thalamic deep brain stimulation, and responsive neurostimulation. *Expert Rev Neurother* 19:17, 2019.
- M G RA et al: New techniques and progress in epilepsy surgery. *Curr Neurol Neurosci Rep* 16:65, 2016.
- P SI, P PB: Management of epilepsy during pregnancy: An update. *Ther Adv Neurol Disord* 9:118, 2016.
- P A et al: Advances in the development of biomarkers for epilepsy. *Lancet Neurol* 15:843, 2016.
- R VR et al: Cues for seizure timing. *Epilepsia* 62(Suppl 1):S15, 2021.

Wade S. Smith, S. Claiborne Johnston,
J. Claude Hemphill, III



Cerebrovascular diseases include some of the most common and devastating disorders: ischemic stroke and hemorrhagic stroke. Stroke is the second leading cause of death worldwide, with 6.2 million dying from stroke in 2015, an increase of 830,000 since the year 2000. In 2016, the lifetime global risk of stroke from age 25 years onward was 25%, an increase of 8.9% from 1990. Nearly 7 million Americans age 20 or older report having had a stroke, and the prevalence is estimated to rise to 3.4 million adults in the next decade, representing 4% of the entire adult population. Conversely, case-specific disability-adjusted life-years due to stroke are falling, likely due to better prevention and treatment, but overall disease burden will continue to climb as the population ages, and stroke is likely to remain the second most common disabling condition in individuals aged 50 or older worldwide.

A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus, the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. *Cerebral ischemia* is caused by a reduction in blood flow that lasts longer than several seconds. Neurologic symptoms are manifest within seconds because neurons lack glycogen, so energy failure is rapid. If the cessation of flow lasts for more than a few minutes, *infarction* or death of brain tissue results. When blood flow is quickly restored, brain tissue can recover fully and the patient's symptoms are only transient: this is called a *transient ischemic attack* (TIA). The definition of TIA requires that all neurologic signs and symptoms resolve within 24 h without evidence of brain infarction on brain imaging. Stroke has occurred if the neurologic signs and symptoms last for >24 h or brain infarction is demonstrated. A generalized reduction in cerebral blood flow due to systemic hypotension (e.g., cardiac arrhythmia, myocardial infarction, or hemorrhagic shock) usually produces syncope (*Chap. 21*). If low cerebral blood flow persists for a longer duration, then infarction in the border zones between the major cerebral artery distributions may develop. In more severe instances, *global hypoxia-ischemia* causes widespread brain injury; the constellation of cognitive sequelae that ensues is called *hypoxic-ischemic encephalopathy* (*Chap. 307*). *Focal ischemia* or infarction, conversely, is usually caused by thrombosis of the cerebral vessels themselves or by emboli from a proximal arterial source or the heart (*Chap. 427*). *Intracranial hemorrhage* is caused by bleeding directly into or around the brain; it produces neurologic symptoms by producing a mass effect on neural structures, from the toxic effects of blood itself, or by increasing intracranial pressure (*Chap. 428*).

APPROACH TO THE PATIENT

Cerebrovascular Disease

Rapid evaluation is essential for use of acute treatments such as thrombolysis or thrombectomy. However, patients with acute stroke often do not seek medical assistance on their own because they may lose the appreciation that something is wrong (anosognosia) or lack the knowledge that acute treatment is beneficial; it is often a family member or a bystander who calls for help. Therefore, patients and their family members should be counseled to call emergency medical services immediately if they experience or witness the sudden onset of any of the following: loss of sensory and/or motor function on one side of the body (nearly 85% of ischemic stroke patients have hemiparesis); change in vision, gait, or ability to speak

or understand; or a sudden, severe headache. The acronym FAST (facial weakness, arm weakness, speech abnormality, and time) is simple and helpful to teach to the lay public about the common physical symptoms of stroke and to underscore that treatments are highly time sensitive.

Other causes of sudden-onset neurologic symptoms that may mimic stroke include seizure, intracranial tumor, migraine, and metabolic encephalopathy. An adequate history from an observer that no convulsive activity occurred at the onset usually excludes seizure (Chap. 425), although ongoing complex partial seizures without tonic-clonic activity can on occasion mimic stroke. Tumors (Chap. 90) may present with acute neurologic symptoms due to hemorrhage, seizure, or hydrocephalus. Surprisingly, migraine (Chap. 430) can mimic stroke, even in patients without a significant migraine history. When migraine develops without head pain (*acephalic migraine*), the diagnosis can be especially difficult. Patients without any prior history of migraine may develop acephalic migraine even after age 65. A sensory disturbance is often prominent, and the sensory deficit, as well as any motor deficits, tends to migrate slowly across a limb, over minutes rather than seconds as with stroke. The diagnosis of migraine becomes more secure as the cortical disturbance begins to cross vascular boundaries or if classic visual symptoms are present such as scintillating scotoma. At times, it may be impossible to make the diagnosis of migraine until there have been multiple episodes with no residual symptoms or signs and no changes on brain magnetic resonance imaging (MRI). Metabolic encephalopathies typically produce fluctuating mental status changes without focal neurologic findings. However, in the setting of prior stroke or brain injury, a patient with fever or sepsis may manifest a recurrent hemiparesis, which clears rapidly when the infection is treated. The metabolic process serves to “unmask” a prior deficit.

Once the diagnosis of stroke is made, a brain imaging study is necessary to determine if the cause of stroke is ischemia or hemorrhage (Fig. 426-1). Computed tomography (CT) imaging of the brain is the standard imaging modality to detect the presence or

absence of intracranial hemorrhage (see “Imaging Studies,” below). If the stroke is ischemic, administration of recombinant tissue plasminogen activator (rtPA) or endovascular mechanical thrombectomy may be beneficial in restoring cerebral perfusion (Chap. 427). Medical management to reduce the risk of complications becomes the next priority, followed by plans for secondary prevention. For ischemic stroke, several strategies can reduce the risk of subsequent stroke in all patients, while other strategies are effective for patients with specific causes of stroke such as cardiac embolus and carotid atherosclerosis. For hemorrhagic stroke, aneurysmal subarachnoid hemorrhage (SAH) and hypertensive intracerebral hemorrhage are two important causes. The treatment and prevention of hypertensive intracerebral hemorrhage are discussed in Chap. 428. SAH is discussed in Chap. 429.

STROKE SYNDROMES

A careful history and neurologic examination can often localize the region of brain dysfunction; if this region corresponds to an arterial distribution, the possible causes responsible for the syndrome can be narrowed. This is of particular importance when the patient presents with a TIA and a normal examination. For example, if a patient develops language loss and a right homonymous hemianopia, a search for causes of left middle cerebral artery emboli should be performed. A finding of an isolated stenosis of the right internal carotid artery in that patient, for example, suggests an asymptomatic carotid stenosis, and the search for other causes of stroke should continue. The following sections describe the clinical findings of cerebral ischemia associated with cerebral vascular territories depicted in Figs. 426-2 through 426-11. Stroke syndromes are divided into (1) large-vessel stroke within the anterior circulation, (2) large-vessel stroke within the posterior circulation, and (3) small-vessel disease of either vascular bed.

Stroke within the Anterior Circulation The internal carotid artery and its branches compose the anterior circulation of the brain. These vessels can be occluded by intrinsic disease of the vessel (e.g., atherosclerosis or dissection) or by embolic occlusion from a proximal source as discussed above. Occlusion of each major intracranial vessel has distinct clinical manifestations.

MIDDLE CEREBRAL ARTERY Occlusion of the proximal middle cerebral artery (MCA) or one of its major branches is most often due to an embolus (artery-to-artery, cardiac, or of unknown source) rather than intracranial atherothrombosis. Atherosclerosis of the proximal MCA may cause distal emboli to the middle cerebral territory or, less commonly, may produce low-flow TIAs. Collateral formation via leptomeningeal vessels often prevents MCA stenosis from becoming symptomatic.

The cortical branches of the MCA supply the lateral surface of the hemisphere except for (1) the frontal pole and a strip along the superomedial border of the frontal and parietal lobes supplied by the anterior cerebral artery (ACA) and (2) the lower temporal and occipital pole convolutions supplied by the posterior cerebral artery (PCA) (Figs. 426-2–426-5).

The proximal MCA (M1 segment) gives rise to penetrating branches (termed *lenticulostriate arteries*) that supply the putamen, outer globus pallidus, posterior limb of the internal capsule, adjacent corona radiata, and most of the caudate nucleus (Fig. 426-2). In the sylvian fissure, the MCA in most patients divides into *superior* and *inferior* divisions (M2 branches). Branches of the inferior division supply the inferior parietal and temporal cortex, and those from the superior division supply the frontal and superior parietal cortex (Fig. 426-3).

If the entire MCA is occluded at its origin (blocking both its penetrating and cortical branches) and the distal collaterals are limited, the clinical findings are contralateral hemiplegia, hemianesthesia, homonymous hemianopia, and a day or two of gaze preference to the ipsilateral side. Dysarthria is common because of facial weakness. When the dominant hemisphere is involved, global aphasia is present also, and when the nondominant hemisphere is affected, anosognosia, constructional apraxia, and neglect are found (Chap. 30).

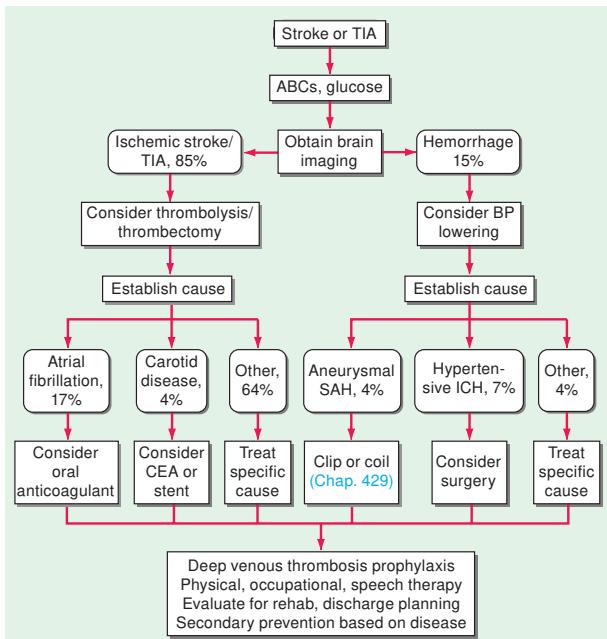


FIGURE 426-1 Medical management of stroke and TIA. Rounded boxes are diagnoses; rectangles are interventions. Numbers are percentages of stroke overall. ABCs, airway, breathing, circulation; BP, blood pressure; CEA, carotid endarterectomy; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

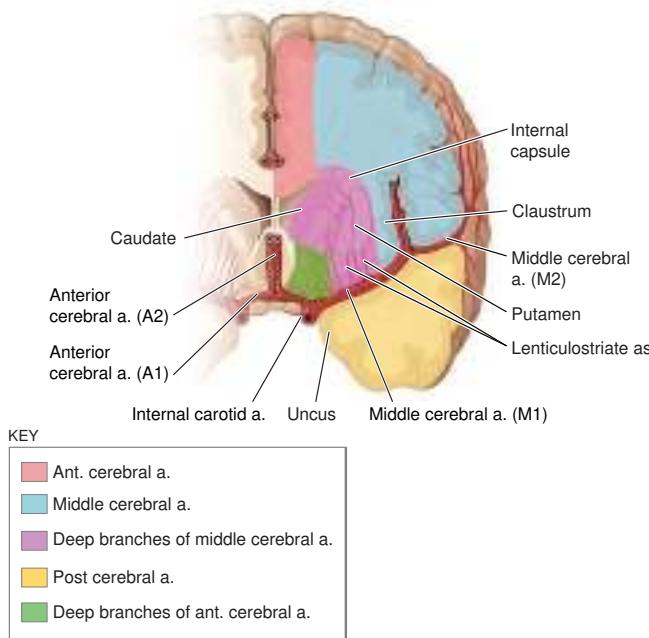


FIGURE 426-2 Diagram of a cerebral hemisphere in coronal section showing the territories of the major cerebral vessels that branch from the internal carotid arteries.

Complete MCA syndromes occur most often when an embolus occludes the stem of the artery. Cortical collateral blood flow and differing arterial configurations are probably responsible for the development of many partial syndromes. Partial syndromes may also be due to emboli that enter the proximal MCA without complete occlusion, occlude distal MCA branches, or fragment and move distally.

Partial syndromes due to embolic occlusion of a single branch include hand, or arm and hand, weakness alone (brachial syndrome) or facial weakness with nonfluent (Broca) aphasia (Chap. 30), with or without arm weakness (frontal opercular syndrome). A combination of sensory disturbance, motor weakness, and nonfluent aphasia suggests that an embolus has occluded the proximal superior division and infarcted large portions of the frontal and parietal cortices (Fig. 426-3). If a fluent (Wernicke's) aphasia occurs without weakness, the inferior division of the MCA supplying the posterior part (temporal cortex) of the dominant hemisphere is probably involved. Jargon speech and an inability to comprehend written and spoken language are prominent features, often accompanied by a contralateral, homonymous superior quadrantanopia. Hemineglect or spatial agnosia without weakness indicates that the inferior division of the MCA in the nondominant hemisphere is involved.

Occlusion of a lenticulostriate vessel produces small-vessel (lacunar) stroke within the internal capsule (Fig. 426-2). This produces pure motor stroke or sensory-motor stroke contralateral to the lesion. Ischemia within the genu of the internal capsule causes primarily facial weakness followed by arm and then leg

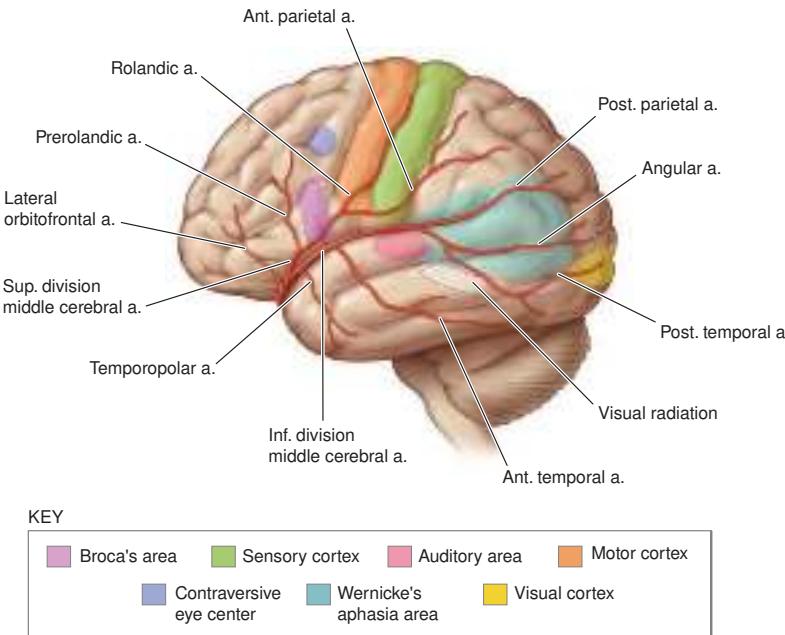


FIGURE 426-3 Diagram of a cerebral hemisphere, lateral aspect, showing the branches and distribution of the middle cerebral artery (MCA) and the principal regions of cerebral localization. Note the bifurcation of the MCA into a superior and inferior division.

Signs and symptoms: Structures involved

Paralysis of the contralateral face, arm, and leg; sensory impairment over the same area (pinprick, cotton touch, vibration, position, two-point discrimination, stereognosis, tactile localization, barognosia, cutaneoagnoia); *Somatic motor area for face and arm and the fibers descending from the leg area to enter the corona radiata and corresponding somatic sensory system*

Motor aphasia: Motor speech area of the dominant hemisphere

Central aphasia, word deafness, anomia, jargon speech, sensory aphagia, acalculia, alexia, finger agnosia, right-left confusion (the last four comprise the Gerstmann syndrome); Central, suprasylvian speech area and parietooccipital cortex of the dominant hemisphere

Conduction aphasia: Central speech area (parietal operculum)

Apraxagnosia of the nondominant hemisphere, anosognosia, hemiasomatognosia, unilateral neglect, agnosia for the left half of external space, dressing "apraxia," constructional "apraxia," distortion of visual coordinates, inaccurate localization in the half field, impaired ability to judge distance, upside-down reading, visual illusions (e.g., it may appear that another person walks through a table); *Nondominant parietal lobe (area corresponding to speech area in dominant hemisphere); loss of topographic memory is usually due to a nondominant lesion, occasionally to a dominant one*

Homonymous hemianopia (often homonymous inferior quadrantanopia); *Optic radiation deep to second temporal convolution*

Paralysis of conjugate gaze to the opposite side: *Frontal contraversive eye field or projecting fibers*

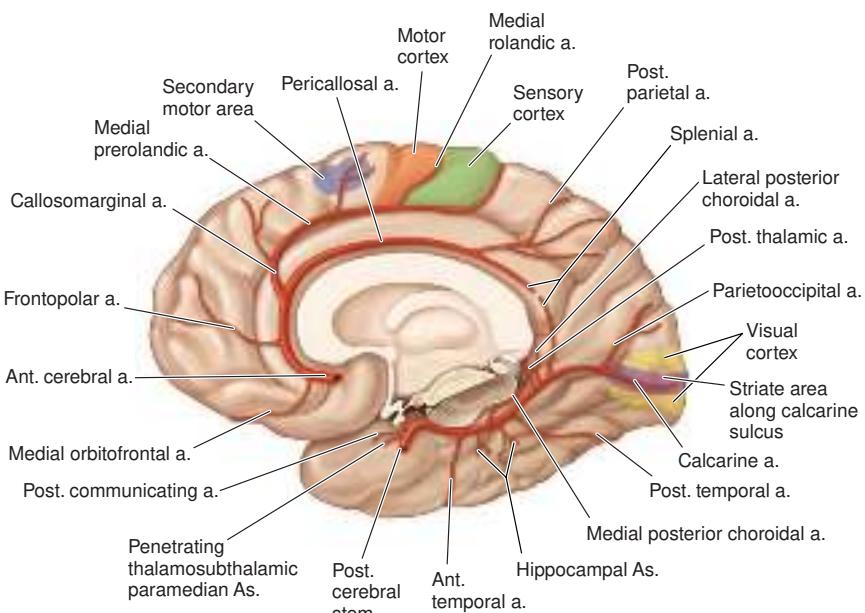


FIGURE 426-4 Diagram of a cerebral hemisphere, medial aspect, showing the branches and distribution of the anterior cerebral artery and the principal regions of cerebral localization.

Signs and symptoms: *Structures involved*

Paralysis of opposite foot and leg: *Motor leg area*

A lesser degree of paresis of opposite arm: *Arm area of cortex or fibers descending to corona radiata*

Cortical sensory loss over toes, foot, and leg: *Sensory area for foot and leg*

Urinary incontinence: *Sensorimotor area in paracentral lobule*

Contralateral grasp reflex, sucking reflex, gegenhalten (paratonic rigidity): *Medial surface of the posterior frontal lobe; likely supplemental motor area*

Abulia (akinetic mutism), slowness, delay, intermittent interruption, lack of spontaneity, whispering, reflex distraction to sights and sounds: *Uncertain localization—probably cingulate gyrus and medial inferior portion of frontal, parietal, and temporal lobes*

Impairment of gait and stance (gait apraxia): *Frontal cortex near leg motor area*

Dyspraxia of left limbs, tactile aphasia in left limbs: *Corpus callosum*

weakness as the ischemia moves posterior within the capsule. Alternatively, the contralateral hand may become ataxic, and dysarthria will be prominent (clumsy hand, dysarthria lacunar syndrome). Lacunar infarct affecting the globus pallidus and putamen often has few clinical signs, but parkinsonism and hemiballismus have been reported.

ANTERIOR CEREBRAL ARTERY The ACA is divided into two segments: the precommunal (A1) circle of Willis, or stem, which connects the internal carotid artery to the anterior communicating artery, and the postcommunal (A2) segment distal to the anterior communicating artery (Figs. 426-2 and 426-4). The A1 segment gives rise to several deep penetrating branches that supply the anterior limb of the internal capsule, the anterior perforate substance, amygdala, anterior hypothalamus, and the inferior part of the head of the caudate nucleus.

Occlusion of the proximal ACA is usually well tolerated because of collateral flow through the anterior communicating artery and collaterals through the MCA and PCA. Occlusion of a single A2 segment results in the contralateral symptoms noted in Fig. 426-4. If both A2 segments arise from a single anterior cerebral stem (contralateral A1 segment atresia), the occlusion may affect both hemispheres. Profound abulia (a delay in verbal and motor response) and bilateral pyramidal signs with paraparesis or quadriplegia and urinary incontinence result.

ANTERIOR CHOROIDAL ARTERY This artery arises from the internal carotid artery and supplies the posterior limb of the internal capsule and the white matter posterolateral to it, through which pass some of the geniculocalcarine fibers (Fig. 426-5). The complete syndrome of anterior choroidal artery occlusion consists of contralateral hemiplegia, hemianesthesia (hypesthesia), and homonymous hemianopia. However, because this territory is also supplied by penetrating vessels

of the proximal MCA and the posterior communicating and posterior choroidal arteries, minimal deficits may occur, and patients frequently recover substantially. Anterior choroidal strokes are usually the result of in situ thrombosis of the vessel, and the vessel is particularly vulnerable to iatrogenic occlusion during surgical clipping of aneurysms arising from the internal carotid artery.

INTERNAL CAROTID ARTERY The clinical picture of internal carotid occlusion varies depending on whether the cause of ischemia is propagated thrombus, embolism, or low flow. The cortex supplied by the MCA territory is affected most often. With a competent circle of Willis, occlusion may go unnoticed. If the thrombus propagates up the internal carotid artery into the MCA or embolizes it, symptoms are identical to proximal MCA occlusion (see above). Sometimes there is massive infarction of the entire deep white matter and cortical surface. When the origins of both the ACA and MCA are occluded at the top of the carotid artery, abulia or stupor occurs with hemiplegia, hemianesthesia, and aphasia or anosognosia. When the PCA arises from the internal carotid artery (a configuration called a *fetal PCA*), it may also become occluded and give rise to symptoms referable to its peripheral territory (Figs. 426-4 and 426-5).

In addition to supplying the ipsilateral brain, the internal carotid artery perfuses the optic nerve and retina via the ophthalmic artery. In ~25% of symptomatic internal carotid disease, recurrent transient monocular blindness (amaurosis fugax) warns of the lesion. Patients typically describe a horizontal shade that sweeps down or up across the field of vision. They may also complain that their vision was blurred in that eye or that the upper or lower half of vision disappeared. In most cases, these symptoms last only a few minutes. Rarely, ischemia or infarction of the ophthalmic artery or central retinal arteries occurs at the time of cerebral TIA or infarction.

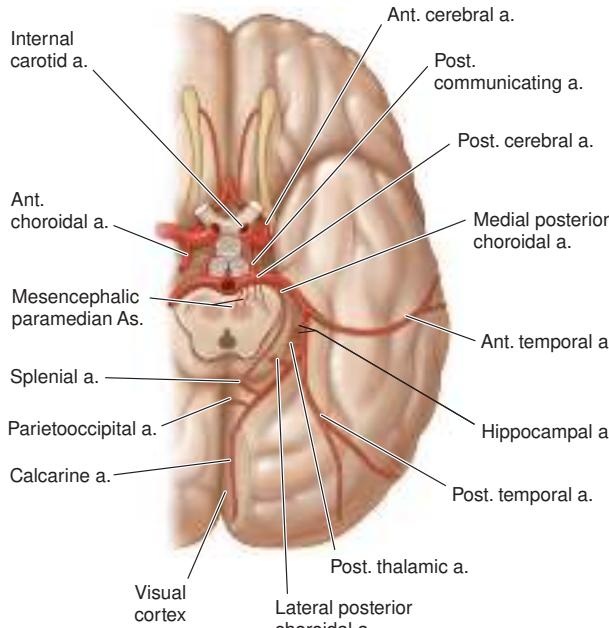


FIGURE 426-5 Inferior aspect of the brain with the branches and distribution of the posterior cerebral artery and the principal anatomic structures shown.

Signs and symptoms: Structures involved

Peripheral territory (see also Fig. 426-9). Homonymous hemianopia (often upper quadrantic): *Calcarine cortex or optic radiation nearby*. Bilateral homonymous hemianopia, cortical blindness, awareness or denial of blindness; tactile naming, achromatopsia (color blindness), failure to see to-and-fro movements, inability to perceive objects not centrally located, apraxia of ocular movements, inability to count or enumerate objects, tendency to run into things that the patient sees and tries to avoid: *Bilateral occipital lobe with possibly the parietal lobe involved*. Verbal dyslexia without agraphia, color anomia: *Dominant calcarine lesion and posterior part of corpus callosum*. Memory defect: *Hippocampal lesion bilaterally or on the dominant side only*. Topographic disorientation and prosopagnosia: *Usually with lesions of nondominant, calcarine, and lingual gyrus*. Simultanagnosia, hemispatial neglect: *Dominant visual cortex, contralateral hemisphere*. Unformed visual hallucinations, peduncular hallucinosis, metamorphopsia, teleopsia, illusory visual spread, palinopsia, distortion of outlines, central photophobia: *Calcarine cortex*. Complex hallucinations: *Usually nondominant hemisphere*.

Central territory. Thalamic syndrome: sensory loss (all modalities), spontaneous pain and dysesthesias, choreoathetosis, intention tremor, spasms of hand, mild hemiparesis: *Posteroventral nucleus of thalamus; involvement of the adjacent subthalamus body or its afferent tracts*. Thalamoperforate syndrome: crossed cerebellar ataxia with ipsilateral third nerve palsy (Claude's syndrome): *Dentatothalamic tract and issuing third nerve*. Weber's syndrome: third nerve palsy and contralateral hemiplegia: *Third nerve and cerebral peduncle*. Contralateral hemiplegia: *Cerebral peduncle*. Paralysis or paresis of vertical eye movement, skew deviation, sluggish pupillary responses to light, slight miosis and ptosis (retraction nystagmus and "tucking" of the eyelids may be associated): *Supranuclear fibers to third nerve, interstitial nucleus of Cajal, nucleus of Darkschewitsch, and posterior commissure*. Contralateral rhythmic, atactic action tremor; rhythmic postural or "holding" tremor (rugal tremor): *Dentatothalamic tract*.

A high-pitched prolonged carotid bruit fading into diastole is often associated with tightly stenotic lesions. As the stenosis grows tighter and flow distal to the stenosis becomes reduced, the bruit becomes fainter and may disappear when occlusion is imminent.

COMMON CAROTID ARTERY All symptoms and signs of internal carotid occlusion may also be present with occlusion of the common carotid artery. Jaw claudication may result from low flow in the external carotid branches. Bilateral common carotid artery occlusions at their origin may occur in Takayasu's arteritis (Chap. 363).

Stroke within the Posterior Circulation The posterior circulation is composed of the paired vertebral arteries, the basilar artery, and the paired PCAs. The vertebral arteries join to form the basilar artery at the pontomedullary junction. The basilar artery divides into two PCAs

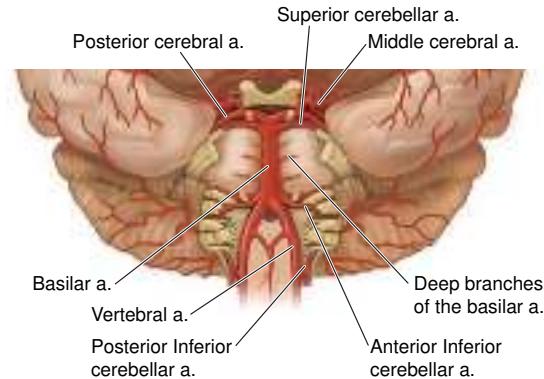


FIGURE 426-6 Diagram of the posterior circulation, showing the intracranial vertebral arteries forming the basilar artery that gives off the anterior inferior cerebellar, superior cerebellar, and posterior cerebral arteries. The posterior inferior cerebellar artery arises from each of the vertebral segments. The majority of brainstem blood flow arises from numerous deep branches of the basilar artery that penetrate directly into the brainstem.

in the interpeduncular fossa (Figs. 426-4–426-6). These major arteries give rise to long and short circumferential branches and to smaller deep penetrating branches that supply the cerebellum, medulla, pons, midbrain, subthalamus, thalamus, hippocampus, and medial temporal and occipital lobes. Occlusion of each vessel produces its own distinctive syndrome.

POSTERIOR CEREBRAL ARTERY In 75% of cases, both PCAs arise from the bifurcation of the basilar artery; in 20%, one has its origin from the ipsilateral internal carotid artery via the posterior communicating artery; in 5%, both originate from the respective ipsilateral internal carotid arteries (Figs. 426-4–426-6). The precommunal, or P1, segment of the true PCA is atretic in such cases.

PCA syndromes usually result from atheroma formation or emboli that lodge at the top of the basilar artery; posterior circulation disease may also be caused by dissection of either vertebral artery or fibromuscular dysplasia.

Two clinical syndromes are commonly observed with occlusion of the PCA: (1) *P1 syndrome*: midbrain, subthalamic, and thalamic signs, which are due to disease of the proximal P1 segment of the PCA or its penetrating branches (thalamogeniculate, Percheron, and posterior choroidal arteries); and (2) *P2 syndrome*: cortical temporal and occipital lobe signs, due to occlusion of the P2 segment distal to the junction of the PCA with the posterior communicating artery.

P1 SYNDROMES Infarction usually occurs in the ipsilateral subthalamus and medial thalamus and in the ipsilateral cerebral peduncle and midbrain (Figs. 426-5 and 426-11). A third nerve palsy with contralateral ataxia (Claude's syndrome) or with contralateral hemiplegia (Weber's syndrome) may result. The ataxia indicates involvement of the red nucleus or dentatorubrothalamic tract; the hemiplegia is localized to the cerebral peduncle (Fig. 426-11). If the subthalamic nucleus is involved, contralateral hemiballismus may occur. Occlusion of the artery of Percheron produces paresis of upward gaze and drowsiness and often abulia. Extensive infarction in the midbrain and subthalamus occurring with bilateral proximal PCA occlusion presents as coma, unreactive pupils, bilateral pyramidal signs, and decerebrate rigidity.

Occlusion of the penetrating branches of thalamic and thalamogeniculate arteries produces less extensive thalamic and thalamocapsular lacunar syndromes. The *thalamic Déjerine-Roussy syndrome* consists of contralateral hemisensory loss followed later by an agonizing, searing, or burning pain in the affected areas. It is persistent and responds poorly to analgesics. Anticonvulsants (carbamazepine or gabapentin) or tricyclic antidepressants may be beneficial.

P2 SYNDROMES (Figs. 426-4 and 426-5) Occlusion of the distal PCA causes infarction of the medial temporal and occipital lobes. Contralateral homonymous hemianopia without macula sparing is the usual

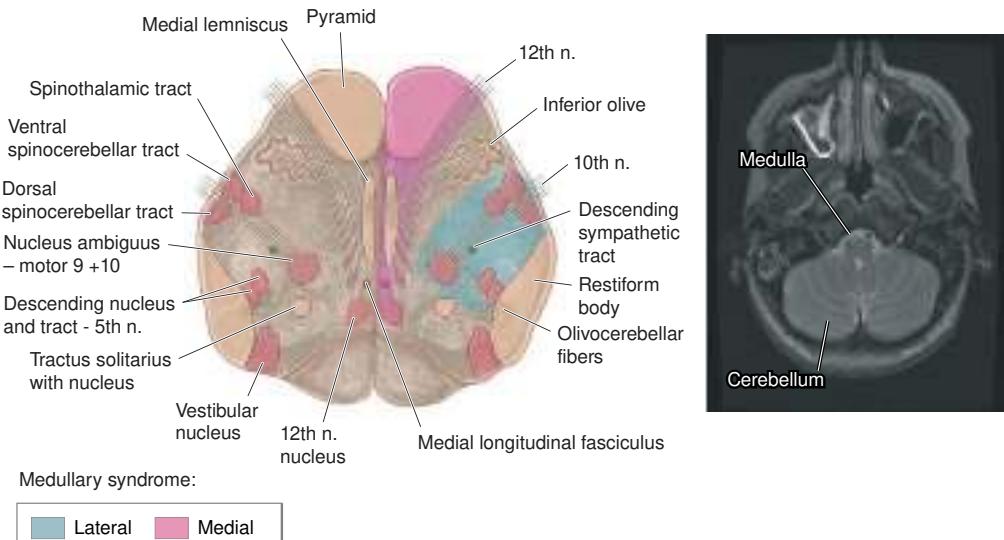


FIGURE 426-7 Axial section at the level of the medulla, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Note that in Figs. 426-7 through 426-11, all drawings are oriented with the dorsal surface at the bottom, matching the orientation of the brainstem that is commonly seen in all modern neuroimaging studies. Approximate regions involved in medial and lateral medullary stroke syndromes are shown.

Signs and symptoms: Structures involved

1. Medial medullary syndrome (occlusion of vertebral artery or of branch of vertebral or lower basilar artery)

On side of lesion

Paralysis with atrophy of one-half half the tongue: *Ipsilateral twelfth nerve*

On side opposite lesion

Paralysis of arm and leg, sparing face; impaired tactile and proprioceptive sense over one-half the body: *Contralateral pyramidal tract and medial lemniscus*

2. Lateral medullary syndrome (occlusion of any of five vessels may be responsible—vertebral, posterior inferior cerebellar, superior, middle, or inferior lateral medullary arteries)

On side of lesion

Pain, numbness, impaired sensation over one-half the face: *Descending tract and nucleus fifth nerve*

Ataxia of limbs, falling to side of lesion: *Uncertain—restiform body, cerebellar hemisphere, cerebellar fibers, spinocerebellar tract (?)*

Nystagmus, diplopia, oscillopsia, vertigo, nausea, vomiting: *Vestibular nucleus*

Horner's syndrome (miosis, ptosis, decreased sweating): *Descending sympathetic tract*

Dysphagia, hoarseness, paralysis of palate, paralysis of vocal cord, diminished gag reflex: *Issuing fibers ninth and tenth nerves*

Loss of taste: *Nucleus and tractus solitarius*

Numbness of ipsilateral arm, trunk, or leg: *Cuneate and gracile nuclei*

Weakness of lower face: *Genuflected upper motor neuron fibers to ipsilateral facial nucleus*

On side opposite lesion

Impaired pain and thermal sense over half the body, sometimes face: *Spinothalamic tract*

3. Total unilateral medullary syndrome (occlusion of vertebral artery): Combination of medial and lateral syndromes

4. Lateral pontomedullary syndrome (occlusion of vertebral artery): Combination of lateral medullary and lateral inferior pontine syndrome

5. Basilar artery syndrome (the syndrome of the lone vertebral artery is equivalent): A combination of the various brainstem syndromes plus those arising in the posterior cerebral artery distribution.

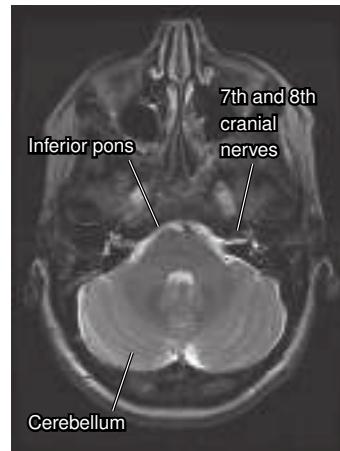
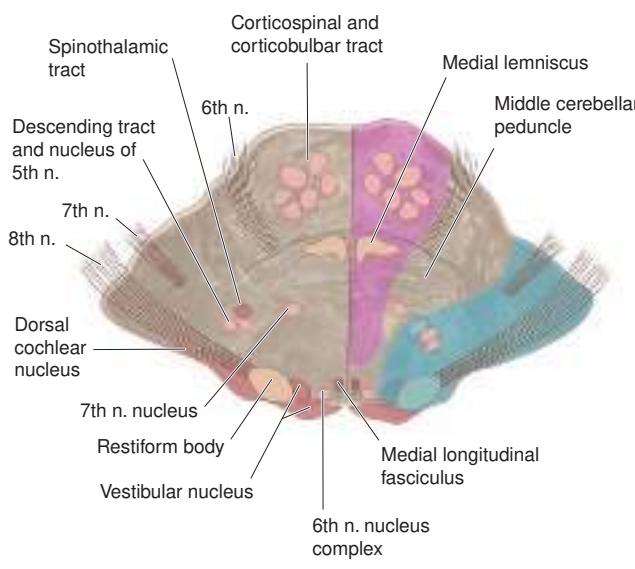
Bilateral long tract signs (sensory and motor; cerebellar and peripheral cranial nerve abnormalities): *Bilateral long tract; cerebellar and peripheral cranial nerves*

Paralysis or weakness of all extremities, plus all bulbar musculature: *Corticobulbar and corticospinal tracts bilaterally*

manifestation. (MCA strokes often produce hemianopia but typically spare the macula as calcarine cortex is perfused by the P2 segment). Occasionally, only the upper quadrant of visual field is involved or the macula vision is spared. If the visual association areas are spared and only the calcarine cortex is involved, the patient may be aware of visual defects. Medial temporal lobe and hippocampal involvement may cause an acute disturbance in memory, particularly if it occurs in the dominant hemisphere. The defect usually clears because memory has bilateral representation. If the dominant hemisphere is affected and the infarct extends to involve the splenium of the corpus callosum, the patient may demonstrate alexia without agraphia. Visual agnosia for faces, objects, mathematical symbols, and colors and anomia with paraphasic errors (amnestic aphasia) may also occur, even without callosal involvement. Occlusion of the PCA can produce *peduncular hallucinosis* (visual hallucinations of brightly colored scenes and objects).

Bilateral infarction in the distal PCAs produces cortical blindness (blindness with preserved pupillary light reaction). The patient is often unaware of the blindness or may even deny it (*Anton's syndrome*). Tiny

islands of vision may persist, and the patient may report that vision fluctuates as images are captured in the preserved portions. Rarely, only peripheral vision is lost and central vision is spared, resulting in “gun-barrel” vision. Bilateral visual association area lesions may result in *Balint's syndrome*, a disorder of the orderly visual scanning of the environment (Chap. 30), usually resulting from infarcts secondary to low flow in the “watershed” between the distal PCA and MCA territories, as occurs after cardiac arrest. Patients may experience persistence of a visual image for several minutes despite gazing at another scene (*pelinopsia*) or an inability to synthesize the whole of an image (*asimultanagnosia*). Embolic occlusion of the top of the basilar artery can produce any or all the central or peripheral territory symptoms. The hallmark is the sudden onset of bilateral signs, including ptosis, pupillary asymmetry or lack of reaction to light, and somnolence. Patients will often have posturing and myoclonic jerking that simulates seizure. Interrogation of the noncontrast CT scan for a hyperdense basilar artery sign (indicating thrombus in the basilar artery) or CT angiography (CTA) establishes this diagnosis. Physicians



Inferior pontine syndrome:



FIGURE 426-8 Axial section at the level of the inferior pons, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Approximate regions involved in medial and lateral inferior pontine stroke syndromes are shown.

Signs and symptoms: Structures involved

1. Medial inferior pontine syndrome (occlusion of paramedian branch of basilar artery)

On side of lesion

Paralysis of conjugate gaze to side of lesion (preservation of convergence): *Center for conjugate lateral gaze*

Nystagmus: *Vestibular nucleus*

Ataxia of limbs and gait: Likely *middle cerebellar peduncle*

Diplopia on lateral gaze: *Abducens nerve*

On side opposite lesion

Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract in lower pons*

Impaired tactile and proprioceptive sense over one-half of the body: *Medial lemniscus*

2. Lateral inferior pontine syndrome (occlusion of anterior inferior cerebellar artery)

On side of lesion

Horizontal and vertical nystagmus, vertigo, nausea, vomiting, oscillopsia: *Vestibular nerve or nucleus*

Facial paralysis: *Seventh nerve*

Paralysis of conjugate gaze to side of lesion: *Center for conjugate lateral gaze*

Deafness, tinnitus: *Auditory nerve or cochlear nucleus*

Ataxia: *Middle cerebellar peduncle and cerebellar hemisphere*

Impaired sensation over face: *Descending tract and nucleus fifth nerve*

On side opposite lesion

Impaired pain and thermal sense over one-half the body (may include face): *Spinothalamic tract*

should be suspicious of this rare but potentially treatable stroke syndrome in the setting of presumed new-onset seizure and cranial nerve deficits.

VERTEBRAL AND POSTERIOR INFERIOR CEREBELLAR ARTERIES The vertebral artery, which arises from the innominate artery on the right and the subclavian artery on the left, consists of four segments. The first (V1) extends from its origin to its entrance into the sixth or fifth transverse vertebral foramen. The second segment (V2) traverses the vertebral foramina from C6 to C2. The third (V3) passes through the transverse foramina and circles around the arch of the atlas to pierce the dura at the foramen magnum. The fourth (V4) segment courses upward to join the other vertebral artery to form the basilar artery (Fig. 426-6); only the fourth segment gives rise to branches that supply the brainstem and cerebellum. The posterior inferior cerebellar artery (PICA) in its proximal segment supplies the lateral medulla and, in its distal branches, the inferior surface of the cerebellum.

Atherothrombotic lesions have a predilection for V1 and V4 segments of the vertebral artery. The first segment may become diseased at the origin of the vessel and may produce posterior circulation emboli;

collateral flow from the contralateral vertebral artery or the ascending cervical, thyrocervical, or occipital arteries is usually sufficient to prevent low-flow TIAs or stroke. When one vertebral artery is atretic and an atherothrombotic lesion threatens the origin of the other, the collateral circulation, which may also include retrograde flow down the basilar artery, is often insufficient (Figs. 426-5 and 426-6). In this setting, low-flow TIAs may occur, consisting of syncope, vertigo, and alternating hemiplegia; this state also sets the stage for thrombosis. Disease of the distal fourth segment of the vertebral artery can promote thrombus formation manifest as embolism or with propagation as basilar artery thrombosis. Stenosis proximal to the origin of the PICA can threaten the lateral medulla and posterior inferior surface of the cerebellum.

If the subclavian artery is occluded proximal to the origin of the vertebral artery, there is a reversal in the direction of blood flow in the ipsilateral vertebral artery. Exercise of the ipsilateral arm may increase demand on vertebral flow, producing posterior circulation TIAs, or "subclavian steal."

Although atherosomatous disease rarely narrows the second and third segments of the vertebral artery, this region is subject to dissection,

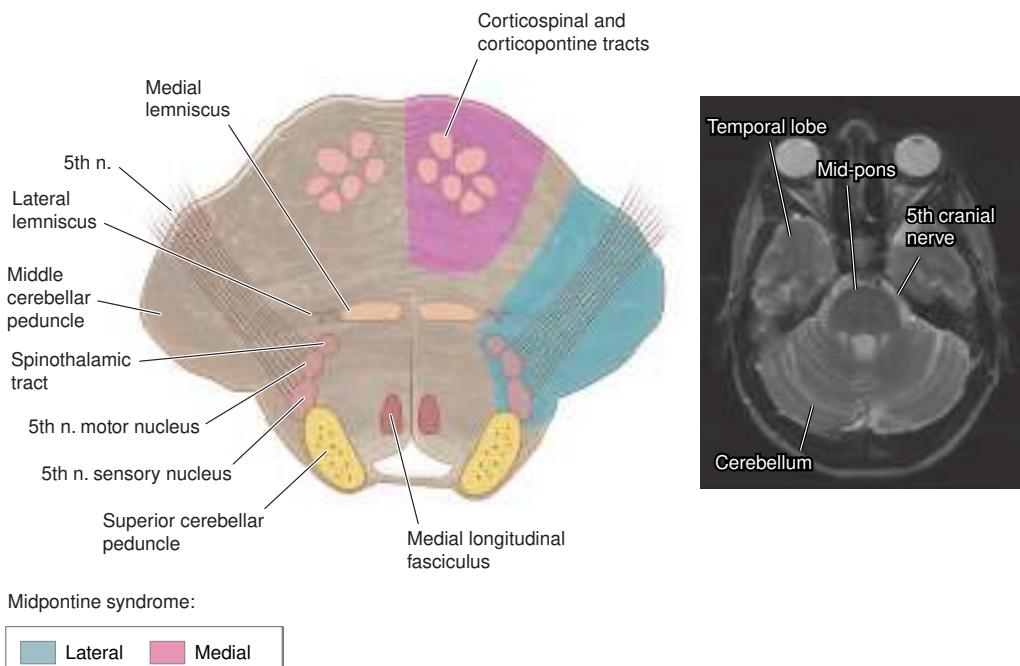


FIGURE 426-9 Axial section at the level of the midpons, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Approximate regions involved in medial and lateral midpontine stroke syndromes are shown.

Signs and symptoms: Structures involved

1. Medial midpontine syndrome (paramedian branch of midbasilar artery)

On side of lesion

Ataxia of limbs and gait (more prominent in bilateral involvement): *Pontine nuclei*

On side opposite lesion

Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract*

Variable impaired touch and proprioception when lesion extends posteriorly: *Medial lemniscus*

2. Lateral midpontine syndrome (short circumferential artery)

On side of lesion

Ataxia of limbs: *Middle cerebellar peduncle*

Paralysis of muscles of mastication: *Motor fibers or nucleus of fifth nerve*

Impaired sensation over side of face: *Sensory fibers or nucleus of fifth nerve*

On side opposite lesion

Impaired pain and thermal sense on limbs and trunk: *Spinothalamic tract*

fibromuscular dysplasia, and, rarely, encroachment by osteophytic spurs within the vertebral foramina.

Emolic occlusion or thrombosis of a V4 segment causes ischemia of the lateral medulla. The constellation of vertigo, numbness of the ipsilateral face and contralateral limbs, diplopia, hoarseness, dysarthria, dysphagia, and ipsilateral Horner's syndrome is called the *lateral medullary (or Wallenberg's) syndrome* (Fig. 426-7). Ipsilateral upper motor neuron facial weakness can also occur. Most cases result from ipsilateral vertebral artery occlusion; in the remainder, PICA occlusion is responsible. Occlusion of the medullary penetrating branches of the vertebral artery or PICA results in partial syndromes. *Hemiparesis is not a typical feature of vertebral artery occlusion; however, quadriparesis may result from occlusion of the anterior spinal artery.*

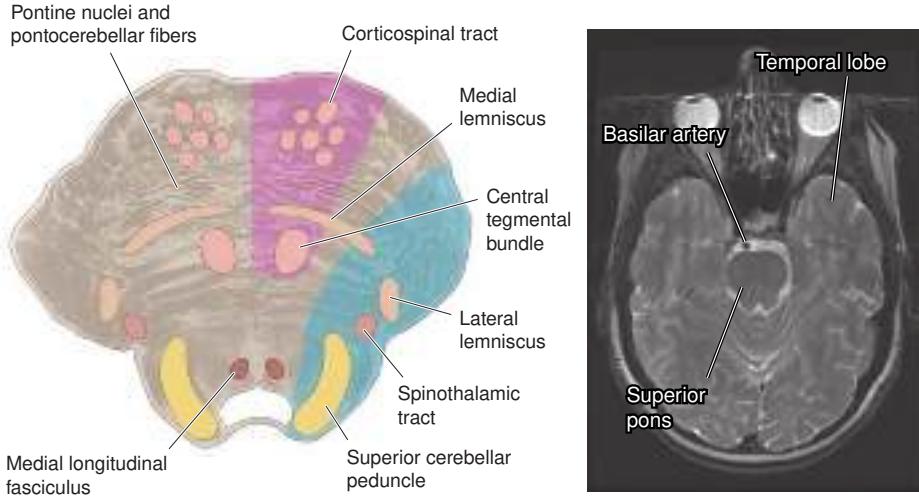
Rarely, a *medial medullary syndrome* occurs with infarction of the pyramid and contralateral hemiparesis of the arm and leg, sparing the face. If the medial lemniscus and emerging hypoglossal nerve fibers are involved, contralateral loss of joint position sense and ipsilateral tongue weakness occur.

Cerebellar infarction can lead to *respiratory arrest* due to brainstem herniation from cerebellar swelling, closure of the aqueduct of Silvius or fourth ventricle, followed by hydrocephalus and central herniation. This added downward displacement of the brainstem from hydrocephalus will exacerbate respiratory and hemodynamic instability. Drowsiness, Babinski signs, dysarthria, and bifacial weakness may be

absent, or present only briefly, before respiratory arrest ensues. Gait unsteadiness, headache, dizziness, nausea, and vomiting may be the only early symptoms and signs and should arouse suspicion of this impending complication, which may require neurosurgical decompression, often with an excellent outcome. Separating these symptoms from those of viral labyrinthitis can be a challenge, but headache, neck stiffness, and unilateral dysmetria favor stroke.

BASILAR ARTERY Branches of the basilar artery (Fig. 426-6) supply the base of the pons and superior cerebellum and fall into three groups: (1) paramedian, 7–10 in number, which supply a wedge of pons on either side of the midline; (2) short circumferential, 5–7 in number, that supply the lateral two-thirds of the pons and middle and superior cerebellar peduncles; and (3) bilateral long circumferential (superior cerebellar and anterior inferior cerebellar arteries), which course around the pons to supply the cerebellar hemispheres.

Atheromatous lesions can occur anywhere along the basilar trunk but are most frequent in the proximal basilar and distal vertebral segments. Typically, lesions occlude either the proximal basilar and one or both vertebral arteries. The clinical picture varies depending on the availability of retrograde collateral flow from the posterior communicating arteries. Rarely, dissection of a vertebral artery may involve the basilar artery and, depending on the location of true and false lumen, may produce multiple penetrating artery strokes.



Superior pontine syndrome:

Lateral Medial

FIGURE 426-10 Axial section at the level of the superior pons, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Approximate regions involved in medial and lateral superior pontine stroke syndromes are shown.

Signs and symptoms: *Structures involved*

1. Medial superior pontine syndrome (paramedian branches of upper basilar artery)

On side of lesion

Cerebellar ataxia (probably): *Superior and/or middle cerebellar peduncle*

Internuclear ophthalmoplegia: *Medial longitudinal fasciculus*

Myoclonic syndrome, palate, pharynx, vocal cords, respiratory apparatus, face, oculomotor apparatus, etc.: *Localization uncertain—central tegmental bundle, dentate projection, inferior olive/olivary nucleus*

On side opposite lesion

Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract*

Rarely touch, vibration, and position are affected: *Medial lemniscus*

2. Lateral superior pontine syndrome (syndrome of superior cerebellar artery)

On side of lesion

Ataxia of limbs and gait, falling to side of lesion: *Middle and superior cerebellar peduncles, superior surface of cerebellum, dentate nucleus*

Dizziness, nausea, vomiting; horizontal nystagmus: *Vestibular nucleus*

Paresis of conjugate gaze (ipsilateral): *Pontine contralateral gaze*

Skew deviation: *Uncertain*

Miosis, ptosis, decreased sweating over face (Horner's syndrome): *Descending sympathetic fibers*

Tremor: *Localization unclear—Dentate nucleus, superior cerebellar peduncle*

On side opposite lesion

Impaired pain and thermal sense on face, limbs, and trunk: *Spinothalamic tract*

Impaired touch, vibration, and position sense, more in leg than arm (there is a tendency to incongruity of pain and touch deficits): *Medial lemniscus (lateral portion)*

Although atherosclerosis occasionally occludes the distal portion of the basilar artery, emboli from the heart or proximal vertebral or basilar segments are more commonly responsible for “top of the basilar” syndromes.

Because the brainstem contains many structures in close apposition, a diversity of clinical syndromes may emerge with ischemia, reflecting involvement of the corticospinal and corticobulbar tracts, ascending sensory tracts, and cranial nerve nuclei (Figs. 426-7–426-11).

The symptoms of transient ischemia or infarction in the territory of the basilar artery often do not indicate whether the basilar artery itself or one of its branches is diseased, yet this distinction has important implications for therapy. *The picture of complete basilar occlusion, however, is easy to recognize as a constellation of bilateral long tract signs (sensory and motor) with signs of cranial nerve and cerebellar dysfunction.* Patients may have spontaneous posturing movements that are myoclonic in nature and simulate seizure activity. These movements are brief, repetitive, and multifocal and often confused with status epilepticus. CT or magnetic resonance angiography can rapidly detect basilar thrombosis, and rapid treatment (thrombectomy) can be lifesaving. A “locked-in” state of preserved consciousness with

quadriplegia and cranial nerve signs suggests complete pontine and lower midbrain infarction. The therapeutic goal is to identify *impending* basilar occlusion before devastating infarction occurs. A series of TIAs and a slowly progressive, fluctuating stroke are extremely significant, because they often herald an atherosclerotic occlusion of the distal vertebral or proximal basilar artery.

TIAs in the proximal basilar distribution may produce vertigo (often described by patients as “swimming,” “swaying,” “moving,” “unsteadiness,” or “light-headedness”). Other symptoms that warn of basilar thrombosis include diplopia, dysarthria, facial or circumoral numbness, and hemisensory symptoms. In general, symptoms of basilar branch TIAs affect one side of the brainstem, whereas symptoms of basilar artery TIAs usually affect both sides, although a “herald” hemiparesis has been emphasized as an initial symptom of basilar occlusion. Most often, TIAs, whether due to impending occlusion of the basilar artery or a basilar branch, are short lived (5–30 min) and repetitive, occurring several times a day. The pattern suggests intermittent reduction of flow. Although treatment with intravenous heparin or various combinations of antiplatelet agents has been used to prevent clot propagation, there is no specific

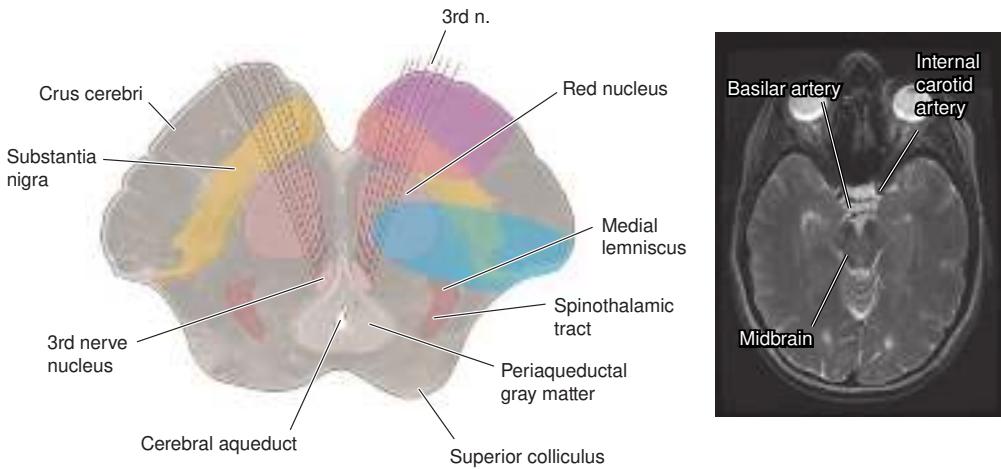


FIGURE 426-11 Axial section at the level of the midbrain, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Approximate regions involved in medial and lateral midbrain stroke syndromes are shown.

Signs and symptoms: *Structures involved*

1. Medial midbrain syndrome (paramedian branches of upper basilar and proximal posterior cerebral arteries)

On side of lesion

Eye "down and out" secondary to unopposed action of fourth and sixth cranial nerves, with dilated and unresponsive pupil: *Third nerve fibers*

On side opposite lesion

Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract descending in crus cerebri*

2. Lateral midbrain syndrome (syndrome of small penetrating arteries arising from posterior cerebral artery)

On side of lesion

Eye "down and out" secondary to unopposed action of fourth and sixth cranial nerves, with dilated and unresponsive pupil: *Third nerve fibers and/or third nerve nucleus*

On side opposite lesion

Hemiataxia, hyperkinesias, tremor: *Red nucleus, dentatorubrothalamic pathway*

evidence to support any one approach, and endovascular intervention is also an option.

Atherothrombotic occlusion of the basilar artery with infarction usually causes *bilateral* brainstem signs. A gaze paresis or internuclear ophthalmoplegia associated with ipsilateral hemiparesis may be the only manifestation of bilateral brainstem ischemia. More often, unequivocal signs of bilateral pontine disease are present. Complete basilar thrombosis carries a high mortality.

Occlusion of a branch of the basilar artery usually causes *unilateral* symptoms and signs involving motor, sensory, and cranial nerves. If symptoms remain unilateral, concern over pending basilar occlusion should be reduced.

Occlusion of the superior cerebellar artery results in severe ipsilateral cerebellar ataxia, nausea and vomiting, dysarthria, and contralateral loss of pain and temperature sensation over the extremities, body, and face (spino- and trigeminthalamic tract). Partial deafness, ataxic tremor of the ipsilateral upper extremity, Horner's syndrome, and palatal myoclonus may occur rarely. Partial syndromes occur frequently (Fig. 426-10). With large strokes, swelling and mass effects may compress the midbrain or produce hydrocephalus; these symptoms may evolve rapidly. Neurosurgical intervention may be lifesaving in such cases.

Occlusion of the anterior inferior cerebellar artery produces variable degrees of infarction because the size of this artery and the territory it supplies vary inversely with those of the PICA. The principal symptoms include (1) ipsilateral deafness, facial weakness, vertigo, nausea and vomiting, nystagmus, tinnitus, cerebellar ataxia, Horner's syndrome, and paresis of conjugate lateral gaze; and (2) contralateral loss of pain and temperature sensation. An occlusion close to the origin of the artery may cause corticospinal tract signs (Fig. 426-8).

Occlusion of one of the short circumferential branches of the basilar artery affects the lateral two-thirds of the pons and middle or superior cerebellar peduncle, whereas occlusion of one of the paramedian branches affects a wedge-shaped area on either side of the medial pons (Figs. 426-8–426-10).

IMAGING STUDIES

See also Chap. 423.

CT Scans CT radiographic images identify or exclude hemorrhage as the cause of stroke, and they identify extraparenchymal hemorrhages, neoplasms, abscesses, and other conditions masquerading as stroke. Brain CT scans obtained in the first several hours after an infarction generally show no abnormality, and the infarct may not be seen reliably for 24–48 h. CT may fail to show small ischemic strokes in the posterior fossa because of bone artifact; small infarcts on the cortical surface may also be missed.

Contrast-enhanced CT scans add specificity by showing contrast enhancement of subacute infarcts and allow visualization of venous structures. Coupled with multidetector scanners, CT angiography can be performed with administration of IV iodinated contrast allowing visualization of the cervical and intracranial arteries, intracranial veins, aortic arch, and even the coronary arteries in one imaging session. Carotid disease and intracranial vascular occlusions are readily identified with this method (see Fig. 427-2). After an IV bolus of contrast, deficits in brain perfusion produced by vascular occlusion can also be demonstrated (Fig. 426-12) and used to predict the region of infarcted brain and the brain at risk of further infarction (i.e., the ischemic penumbra, see "Pathophysiology of Ischemic Stroke" in *Chap. 427*). CT imaging is also sensitive for detecting SAH (although by itself does

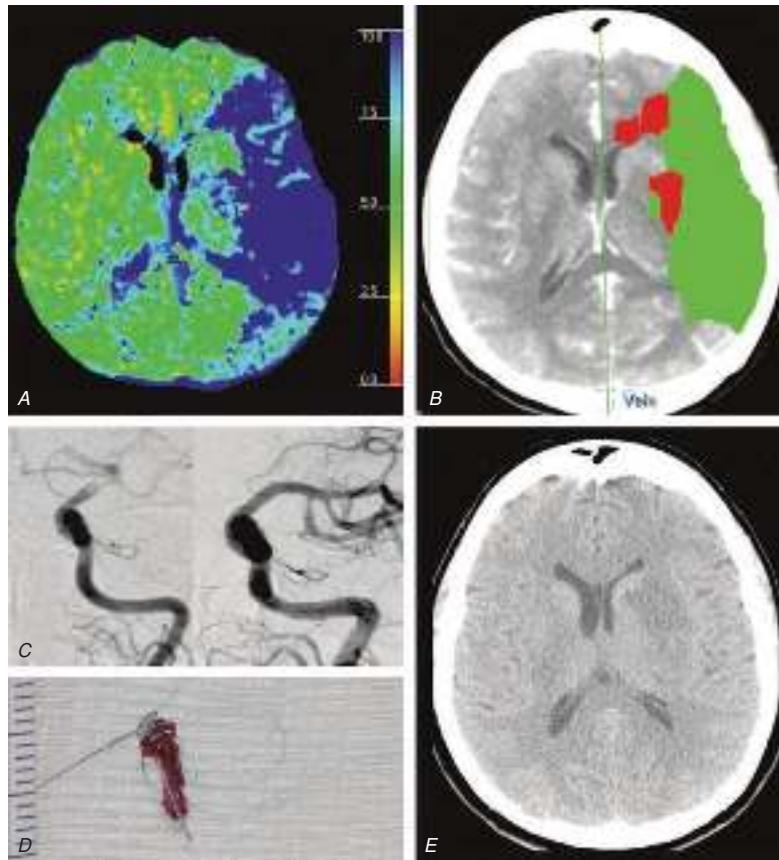


FIGURE 426-12 Acute left middle cerebral artery (MCA) stroke with right hemiplegia but preserved language. *A*, Computed tomography (CT) perfusion mean-transit time map showing delayed perfusion of the left MCA distribution (blue). *B*, Predicted region of infarct (red) and penumbra (green) based on CT perfusion data. *C*, Conventional angiogram showing occlusion of the left internal carotid–MCA bifurcation (*left panel*), and revascularization of the vessels following successful thrombectomy 8 h after stroke symptom onset (*right panel*). *D*, The clot removed with a thrombectomy device (L5, Concentric Medical, Inc.). *E*, CT scan of the brain 2 days later; note infarction in the region predicted in *B* but preservation of the penumbral region by successful revascularization.

not rule it out), and CTA can readily identify intracranial aneurysms (Chap. 429). Because of its speed and wide availability, noncontrast head CT is the imaging modality of choice in patients with acute stroke (Fig. 426-1), and CTA and CT perfusion imaging may also be useful and convenient adjuncts.

MRI

MRI reliably documents the extent and location of infarction in all areas of the brain, including the posterior fossa and cortical surface. It also identifies intracranial hemorrhage and other abnormalities and, using special sequences, can be as sensitive as CT for detecting acute intracerebral hemorrhage. MRI scanners with magnets of higher field strength produce more reliable and precise images. Diffusion-weighted imaging is more sensitive for early brain infarction than standard MR sequences or CT (Fig. 426-13), as is fluid-attenuated inversion recovery (FLAIR) imaging (Chap. 423). Using IV administration of gadolinium contrast, magnetic resonance (MR) perfusion studies can be performed. Brain regions showing poor perfusion but no abnormality on diffusion provide, compared to CT, an equivalent measure of the ischemic penumbra. MR angiography is highly sensitive for stenosis of extracranial internal carotid arteries and of large intracranial vessels. With higher degrees of stenosis, MR angiography tends to overestimate the degree of stenosis when compared to conventional x-ray angiography. MRI with fat saturation is an imaging sequence used to visualize extra- or intracranial arterial dissection. This sensitive technique images clotted blood within the dissected vessel wall. Iron-sensitive imaging (ISI) is helpful to detect cerebral microbleeds that may be present in cerebral amyloid angiopathy and other hemorrhagic disorders.

MRI is more expensive and time consuming than CT and less readily available. Claustrophobia and the logistics of imaging acutely critically ill patients also limit its application. Most acute stroke protocols use CT because of these limitations. However, MRI is useful outside the acute period by more clearly defining the extent of tissue injury and discriminating new from old regions of brain infarction. MRI may have utility in patients with TIA, because it is also more likely to identify new infarction, which is a strong predictor of subsequent stroke.

Cerebral Angiography Conventional x-ray cerebral angiography is the gold standard for identifying and quantifying atherosclerotic stenoses of the cerebral arteries and for identifying and characterizing other pathologies, including aneurysms, vasospasm, intraluminal thrombi, fibromuscular dysplasia, arteriovenous fistulae, vasculitis, and collateral channels of blood flow. Conventional angiography carries risks of arterial damage, groin hemorrhage, embolic stroke, and renal failure from contrast nephropathy, so it should be reserved for situations where less invasive means are inadequate. Acute stroke treatment with endovascular thrombectomy has proven effective in ischemic strokes caused by internal carotid terminus or MCA occlusions and has now part of routine clinical practice at centers that have this capability (see Chap. 427).

Ultrasound Techniques Stenosis at the origin of the internal carotid artery can be identified and quantified reliably by ultrasonography that combines a B-mode ultrasound image with a Doppler ultrasound assessment of flow velocity (“duplex” ultrasound). Transcranial Doppler (TCD) assessment of MCA, ACA, and PCA flow and of vertebrobasilar flow is also useful. This latter technique can detect

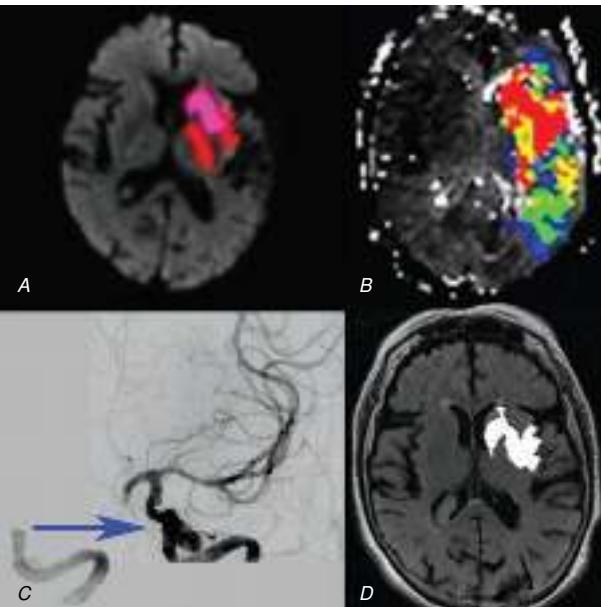


FIGURE 426-13 Magnetic resonance imaging (MRI) of acute stroke. *A*, MRI diffusion-weighted image (DWI) of an 82-year-old woman 2.5 h after onset of right-sided weakness and aphasia reveals restricted diffusion within the left basal ganglia and internal capsule (colored regions). *B*, Perfusion defect within the left hemisphere (colored signal) imaged after administration of an IV bolus of gadolinium contrast. The discrepancy between the region of poor perfusion shown in *B* and the diffusion deficit shown in *A* is called *diffusion-perfusion mismatch* and provides an estimate of the ischemic penumbra. Without specific therapy, the region of infarction will expand into much or all of the perfusion deficit. *C*, Cerebral angiogram of the left internal carotid artery in this patient before (left) and after (right) successful endovascular embolectomy. The occlusion is within the carotid terminus. *D*, Fluid-attenuated inversion recovery image obtained 3 days later showing a region of infarction (coded as white) that corresponds to the initial DWI image in *A*, but not the entire area at risk shown in *B*, suggesting that successful embolectomy saved a large region of brain tissue from infarction. (*Used with permission from Gregory Albers, MD, Stanford University.*)

stenotic lesions in the large intracranial arteries because such lesions increase systolic flow velocity. TCD can also detect microemboli from otherwise asymptomatic carotid plaques. In many cases, MR angiography combined with carotid and transcranial ultrasound studies eliminates the need for conventional x-ray angiography in evaluating vascular stenosis. Alternatively, CTA of the entire head and neck can be performed during the initial imaging of acute stroke. Because this images the entire arterial system relevant to stroke, with the exception of the heart, much of the clinician's stroke workup can be completed with this single imaging study.

Perfusion Techniques Both xenon techniques (principally xenon-CT) and positron emission tomography (PET) can quantify cerebral blood flow. These tools are generally used for research (Chap. 423) but can be useful for determining the significance of arterial stenosis and planning for revascularization surgery. Single-photon emission computed tomography (SPECT) and MR perfusion techniques report relative cerebral blood flow. As noted above, CT imaging is used as the initial imaging modality for acute stroke, and some centers combine both CTA and CT perfusion imaging together with the noncontrast CT scan. CT perfusion imaging increases the sensitivity for detecting ischemia and can measure the ischemic penumbra (Fig. 426-12). Alternatively, MR perfusion can be combined with MR diffusion imaging to identify the ischemic penumbra as the mismatch between these two imaging sequences (Fig. 426-13).

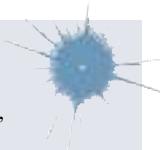
FURTHER READING

- B EJ et al: Heart disease and stroke statistics—2019 update: A report from the American Heart Association. *Circulation* 139:e56, 2019.

427

Ischemic Stroke

Wade S. Smith, S. Claiborne Johnston,
J. Claude Hemphill, III



The clinical diagnosis of stroke is discussed in Chap. 426. Once this diagnosis is made and either a noncontrast computed tomography (CT) scan or magnetic resonance imaging (MRI) scan has been performed, rapid reversal of ischemia is paramount. This chapter will focus on the stroke treatment timeline and subsequent secondary stroke prevention.

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

Acute occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies. The magnitude of flow reduction is a function of collateral blood flow, and this depends on individual vascular anatomy (which may be altered by disease), the site of occlusion, and systemic blood pressure. A decrease in cerebral blood flow to zero causes death of brain tissue within 4–10 min; values <16–18 mL/100 g tissue per minute cause infarction within an hour; and values <20 mL/100 g tissue per minute cause ischemia without infarction unless prolonged for several hours or days. If blood flow is restored to ischemic tissue before significant infarction develops, the patient may experience only transient symptoms, and the clinical syndrome is called a transient ischemic attack (TIA). Another important concept is the *ischemic penumbra*, defined as the ischemic but reversibly dysfunctional tissue surrounding a core area of infarction. The penumbra can be imaged by perfusion imaging using MRI or CT (see below and Figs. 426-12 and 426-13). The ischemic penumbra will eventually progress to infarction if no change in flow occurs, and hence, saving the ischemic penumbra is the goal of revascularization therapies.

Focal cerebral infarction occurs via two distinct pathways (Fig. 427-1): (1) a necrotic pathway in which cellular cytoskeletal breakdown is rapid, due principally to energy failure of the cell; and (2) an apoptotic pathway in which cells become programmed to die. Ischemia produces necrosis by starving neurons of glucose and oxygen, which in turn results in failure of mitochondria to produce ATP. Without ATP, membrane ion pumps stop functioning and neurons depolarize, allowing intracellular calcium to rise. Cellular depolarization also causes glutamate release from synaptic terminals; excess extracellular glutamate produces neurotoxicity by activating postsynaptic glutamate receptors that increase neuronal calcium influx. Ischemia also injures or destroys axons, dendrites, and glia within brain tissue. Free radicals are produced by degradation of membrane lipids and mitochondrial dysfunction. Free radicals cause catalytic destruction of membranes and likely damage other vital functions of cells. Lesser degrees of ischemia, as are seen within the ischemic penumbra, favor apoptotic cellular death, causing cells to die days to weeks later. Fever dramatically worsens brain injury during ischemia, as does hyperglycemia (glucose >11.1 mmol/L [200 mg/dL]), so it is reasonable to suppress fever and prevent hyperglycemia as much as possible. The value of induced mild hypothermia to improve stroke outcomes is the subject of continuing clinical research.

TREATMENT

Acute Ischemic Stroke (Fig. 427-2)

After the clinical diagnosis of stroke is made (Chap. 426), an orderly process of evaluation and treatment should follow. The first goal

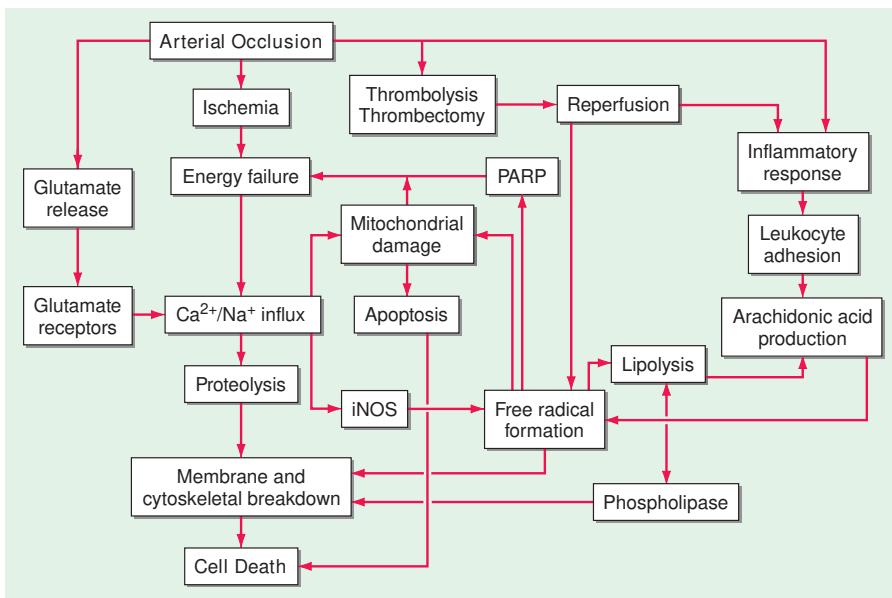


FIGURE 427-1 Major steps in the cascade of cerebral ischemia. See text for details. iNOS, inducible nitric oxide synthase; PARP, poly-A ribose polymerase.

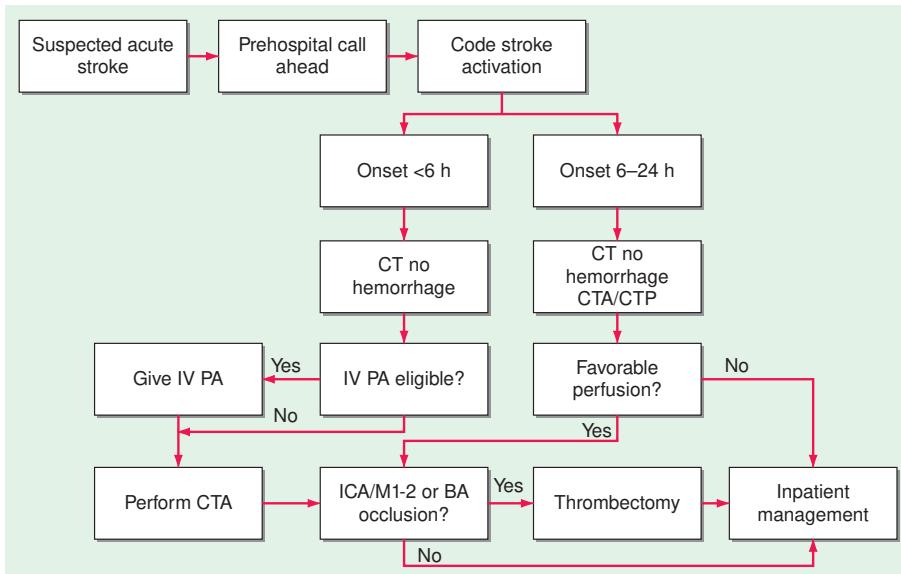


FIGURE 427-2 Management of acute stroke (pathway followed by the authors). For suspected stroke identified by prehospital professionals, we encourage calling ahead to the destination hospital. This allows early “stroke code” activation to prepare for an emergent computed tomography (CT) on arrival. For patients with onset <6 h from last time seen normal, we expedite a noncontrast head CT scan, and if free of hemorrhage and the patient is IV plasminogen activator (PA) eligible, this is administered in the CT scanner. (For IV tissue PA [tPA], the bolus is given and infusion initiated; for tenecteplase, the full dose is given as a bolus.) Then CT angiography (CTA) from left atrium to skull vertex is performed to identify an eligible target lesion for thrombectomy. For a patient presenting in the 6- to 24-h time window, PA is not considered, and the decision to perform thrombectomy is based on perfusion imaging.

Priorities of Acute Stroke Consultation: Once stroke is suspected, the first priorities are to assess airway and blood pressure, followed by establishing the time last seen normal. Patients with disabling neurologic deficits (particularly with National Institutes of Health Stroke Scale >5) may be eligible for thrombolytic or endovascular therapy. Based on the onset time, we follow the protocol shown in the figure. Following acute treatments, if any, we proceed with establishing the cause of the ischemic stroke. If atrial fibrillation is established or newly discovered, we favor use of apixaban 5 mg twice daily (or a reduced dose of 2.5 mg twice daily for impaired glomerular filtration rate) lifelong. If atrial fibrillation is not detected, we obtain a transthoracic echocardiogram to assess left atrial size and/or any valvular lesions. With large left atria and a clear embolic stroke, we favor use of an oral anticoagulant while obtaining ambulatory 30-day electrocardiogram monitoring. If we identify significant internal carotid stenosis, we refer for carotid endarterectomy during the same hospitalization regardless of infarct size. For all else, we use the dual antiplatelet agents aspirin (81 mg) and ticagrelor (180-mg load, followed by 90 mg twice daily) daily for 30 days then discontinue ticagrelor and continue aspirin at 81 mg daily. We prefer ticagrelor to clopidogrel, which is also proven in these settings, because it is not affected by common polymorphisms of CYP2C19 that limit efficacy of clopidogrel in significant proportions of patients, particularly those of Asian descent. If the CTA revealed significant intracranial atherosclerosis or other precranial vessel stenosis within the vascular territory of the infarct (lumen caliber reduced by >50%) we continue dual antiplatelet agents for at least 3 months, then convert to a single agent. Unless contraindicated, all patients receive atorvastatin 80 mg, with goal low-density lipoprotein level of <70 mg/dL unless the stroke has a nonatherothrombotic cause. Patients who are statin intolerant can receive PCSK9 inhibitors. Blood pressure control should target systolic blood pressure <120 mmHg long term, but we allow permissive hypertension for the first few weeks to help with collateral flow to the brain. BA, basilar artery; CTP, computed tomography perfusion; ICA, internal carotid artery; IV, intravenous; M1, middle cerebral artery first division; M2, middle cerebral artery second division; PA, plasminogen activator.

is to prevent or reverse brain injury. Attend to the patient's airway, breathing, and circulation (ABCs), and treat hypoglycemia or hyperglycemia if identified by finger stick testing. Perform an emergency noncontrast head CT scan to differentiate between ischemic stroke and hemorrhagic stroke (*Chap. 428*); there are no reliable clinical findings that conclusively separate ischemia from hemorrhage, although a more depressed level of consciousness, higher initial blood pressure, or worsening of symptoms after onset favor hemorrhage, and a deficit that is maximal at onset, or remits, suggests ischemia. Treatments designed to reverse or lessen the amount of tissue infarction and improve clinical outcome fall within six categories: (1) medical support, (2) IV thrombolysis, (3) endovascular revascularization, (4) antithrombotic treatment, (5) neuroprotection, and (6) stroke centers and rehabilitation.

MEDICAL SUPPORT

When ischemic stroke occurs, the immediate goal is to optimize cerebral perfusion in the surrounding ischemic penumbra. Attention is also directed toward preventing the common complications of bedridden patients—*infections* (pneumonia, urinary, and skin) and deep-venous thrombosis (DVT) with pulmonary embolism. Subcutaneous heparin (unfractionated and low-molecular-weight) is safe and can be used concomitantly. Use of pneumatic compression stockings is of proven benefit in reducing risk of DVT and is a safe alternative to heparin.

Because collateral blood flow within the ischemic brain may be blood pressure dependent, there is controversy about whether blood pressure should be lowered acutely. Blood pressure should be reduced if it exceeds 220/120 mmHg, if there is malignant hypertension (*Chap. 277*) or concomitant myocardial ischemia, or if blood pressure is >185/110 mmHg and thrombolytic therapy is anticipated. When faced with the competing demands of myocardium and brain, lowering the heart rate with a β_1 -adrenergic blocker (such as esmolol) can be a first step to decrease cardiac work and maintain blood pressure. Routine lowering of blood pressure below the limits listed above has the potential to worsen outcomes. Fever is detrimental and should be treated with antipyretics and surface cooling. Serum glucose should be monitored and kept <10.0 mmol/L (180 mg/dL), and above at least 3.3 mmol/L (60 mg/dL); a more intensive glucose control strategy does not improve outcome.

Between 5 and 10% of patients develop enough cerebral edema to cause obtundation and brain herniation. Edema peaks on the second or third day but can cause mass effect for ~10 days. The larger the infarct, the greater the likelihood that clinically significant edema will develop. Water restriction and IV mannitol may be used to raise the serum osmolarity, but hypovolemia should be avoided because this may contribute to hypotension and worsening infarction. Combined analysis of three randomized European trials of hemicraniectomy (craniotomy and temporary removal of part of the skull) shows that hemicraniectomy reduces mortality by 50%, and the clinical outcomes of survivors are significantly improved. Older patients (age >60 years) benefit less but still significantly. The size of the diffusion-weighted imaging volume of brain infarction during the acute stroke is a predictor of future deterioration requiring hemicraniectomy.

Special vigilance is warranted for patients with cerebellar infarction. These strokes may mimic labyrinthitis because of prominent vertigo and vomiting; the presence of head or neck pain should alert the physician to consider cerebellar stroke due to vertebral artery dissection. Even small amounts of cerebellar edema can acutely increase intracranial pressure (ICP) by obstructing cerebrospinal fluid (CSF) flow leading to hydrocephalus or by directly compressing the brainstem. The resulting brainstem compression can manifest as coma and respiratory arrest and require emergency surgical decompression. Suboccipital decompression is recommended in patients with cerebellar infarcts who demonstrate neurologic deterioration and should be performed before significant brainstem compression occurs.

INTRAVENOUS THROMBOLYSIS

The National Institute of Neurological Disorders and Stroke (NINDS) Recombinant Tissue Plasminogen Activator (rtPA) Stroke Study showed a clear benefit for IV rtPA in selected patients with acute stroke. The NINDS study used IV rtPA (0.9 mg/kg to a 90-mg maximum; 10% as a bolus, then the remainder over 60 min) versus placebo in ischemic stroke within 3 h of onset. One-half of the patients were treated within 90 min. Symptomatic intracranial hemorrhage occurred in 6.4% of patients on rtPA and 0.6% on placebo. In the rtPA group, there was a significant 12% absolute increase in the number of patients with only minimal disability (32% on placebo and 44% on rtPA) and a nonsignificant 4% reduction in mortality (21% on placebo and 17% on rtPA). Thus, despite an increased incidence of symptomatic intracranial hemorrhage, treatment with IV rtPA within 3 h of the onset of ischemic stroke improved clinical outcome.

Three subsequent trials of IV rtPA did not confirm this benefit, perhaps because of the dose of rtPA used, the timing of its delivery, and small sample size. When data from all randomized IV rtPA trials were combined, however, efficacy was confirmed in the <3-h time window, and efficacy likely extended to 4.5 h and possibly to 6 h. Based on these combined results, the European Cooperative Acute Stroke Study (ECASS) III explored the safety and efficacy of rtPA in the 3- to 4.5-h time window. Unlike the NINDS study, patients aged >80 years and diabetic patients with a previous stroke were excluded. In this 821-patient randomized study, efficacy was again confirmed, although the treatment effect was less robust than in the 0- to 3-h time window. In the rtPA group, 52.4% of patients achieved a good outcome at 90 days, compared to 45.2% of the placebo group (odds ratio [OR] 1.34, $p = .04$). The symptomatic intracranial hemorrhage rate was 2.4% in the rtPA group and 0.2% in the placebo group ($p = .008$).

Based on these data, rtPA is approved in the 3- to 4.5-h window in Europe and Canada but is still only approved for 0–3 h in the United States. A dose of 0.6 mg/kg is typically used in Japan and other Asian countries based on observation of >600 patients given this lower dose and observing similar outcomes to historical controls and a lower rate of intracranial hemorrhage. This dose also mitigates concerns that patients of Asian descent have a higher propensity to bleed from most antithrombotic and thrombolytic medications. Use of IV rtPA is a central component of primary stroke centers (see below). It represents the first treatment proven to improve clinical outcomes in ischemic stroke and is cost-effective and cost-saving. The time of stroke onset is defined as the time the patient's symptoms were witnessed to begin or the time the patient was last seen as normal. Patients who awaken with stroke have the onset defined as when they went to bed. Advanced neuroimaging techniques (see *Chap. 426*) may help to select patients beyond the 4.5-h window who will benefit from thrombolysis. Two trials using MRI selection beyond 4.5 h have shown clinical benefit from IV rtPA. Patients with minor stroke (nondisabling deficit and National Institutes of Health Stroke Scale [NIHSS] 0–5) appear to respond to acute aspirin as well as IV rtPA. *Table 427-1* summarizes eligibility criteria and instructions for administration of IV rtPA.

The plasminogen activator tenecteplase (0.25 mg/kg IV bolus over 5 s), although not directly tested against IV rtPA, is being used by some centers because it is given without need for a 1-h infusion. This may improve the efficiency of transferring patients from primary to comprehensive stroke centers for thrombectomy because the IV infusion required for IV rtPA is not required for tenecteplase, thus obviating need for critical care transport. Several trials using tenecteplase prior to endovascular therapy have found it to be safe.

ENDOVASCULAR REVASCULARIZATION

Ischemic stroke from large-vessel intracranial occlusion results in high rates of mortality and morbidity. Occlusions in such large vessels (middle cerebral artery [MCA], intracranial internal carotid artery, and the basilar artery) generally involve a large clot volume and often fail to open with IV rtPA alone.

TABLE 427-1 Administration of Intravenous Recombinant Tissue Plasminogen Activator (rtPA) for Acute Ischemic Stroke (AIS)^a

INDICATION	CONTRAINDICATION
Clinical diagnosis of stroke	Sustained BP >185/110 mmHg despite treatment
Onset of symptoms to time of drug administration ≤4.5 h ^b	Bleeding diathesis
CT scan showing no hemorrhage or edema of >1/3 of the MCA territory	Recent head injury or intracerebral hemorrhage
Age ≥18 years	Major surgery in preceding 14 days Gastrointestinal bleeding in preceding 21 days Recent myocardial infarction
Administration of rtPA	
IV access with two peripheral IV lines (avoid arterial or central line placement)	
Review eligibility for rtPA	
Administer 0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h ^c	
Frequent cuff BP monitoring	
No other antithrombotic treatment for 24 h	
For decline in neurologic status or uncontrolled BP, stop infusion, give cryoprecipitate, and reimage brain emergently	
Avoid urethral catheterization for ≥2 h	

^aSee Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing. ^bDepending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions. ^cA dose of 0.6 mg/kg is commonly used in Asia (Japan and China) based on randomized data indicating less hemorrhage and similar efficacy using this lower dose.

Abbreviations: BP, blood pressure; CT, computed tomography; MCA, middle cerebral artery.

Endovascular mechanical thrombectomy has been studied as an alternative or adjunctive treatment of acute stroke in patients who are ineligible for, or have contraindications to, thrombolytics or in those who failed to achieve vascular recanalization with IV thrombolytics (see Fig. 426-12). In 2015, the results of six randomized trials were published, all demonstrating that endovascular therapy improved clinical outcomes for internal carotid and MCA occlusions proven by CT angiography (CTA), under 6 h from stroke onset, with or without pretreatment with IV tissue plasminogen activator (tPA). One study concluded that patients were home nearly 2 months earlier if they received endovascular therapy. A combined meta-analysis of all patients in these trials confirmed a large benefit with endovascular therapy (odds ratio [OR], 2.49; 95% confidence interval [CI], 1.76–3.53; $p <.001$). The percentage of patients who achieved modified Rankin scores of 0–2 (normal or symptomatic but independent) was 46% in the endovascular group and 26.5% in the medical arm. A more recent meta-analysis reveals a mortality benefit as well with thrombectomy. As with IV rtPA treatment, clinical outcome is dependent on time to effective therapy. The odds of a good outcome exceed 3 if groin puncture occurs within 2 h of symptom onset but is only 2 if 8 h elapse. Over 80% of patients who had vessel opening within 1 h of arrival to the emergency department had a good outcome, whereas only one-third had a good outcome if 6 h elapsed.

The outcomes from endovascular therapy are likely improved with IV rtPA treatment prior to thrombectomy if the patient is eligible for rtPA and it is safe to administer. Recent data support replacing IV rtPA with IV tenecteplase because its simple bolus administration makes transporting the patient to an endovascular center less cumbersome.

Extending the time window beyond 6 h appears to be effective if the patient has specific imaging findings demonstrating good vascular collaterals (CT perfusion or magnetic resonance [MR] perfusion techniques, see Chap. 426) and can be treated within 24 h. The Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial reported good outcomes more frequently with endovascular

therapy than with medical care alone (47 vs 13%, $p <.0001$). The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE-3) trial confirmed these results (45 vs 17%, $p <.001$) if treated up to 16 h from stroke onset. Nonrandomized data of thrombectomy for basilar occlusion have found this treatment to be safe up to 24 h from symptom onset and associated with lower 3-month Rankin scores.

Now that endovascular stroke therapy is proven to be effective, the creation of comprehensive stroke centers designed to rapidly identify and treat patients with large-vessel cerebral ischemia is a major focus internationally. Creating geographic systems of care whereby stroke patients are first evaluated at primary stroke centers (which can administer IV rtPA or tenecteplase) then transferred to comprehensive centers if needed, or directly triaged to comprehensive centers based on field assessment, appears to be an effective strategy to improve outcomes.

ANTITHROMBOTIC TREATMENT

Platelet Inhibition Aspirin is the only antiplatelet agent that has been proven to be effective for the acute treatment of ischemic stroke; there are several antiplatelet agents proven for the secondary prevention of stroke (see below). Two large trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), found that the use of aspirin within 48 h of stroke onset reduced both stroke recurrence risk and mortality minimally. Among 19,435 patients in IST, those allocated to aspirin, 300 mg/d, had slightly fewer deaths within 14 days (9.0 vs 9.4%), significantly fewer recurrent ischemic strokes (2.8 vs 3.9%), no excess of hemorrhagic strokes (0.9 vs 0.8%), and a trend toward a reduction in death or dependence at 6 months (61.2 vs 63.5%). In CAST, 21,106 patients with ischemic stroke received 160 mg/d of aspirin or a placebo for up to 4 weeks. There were very small reductions in the aspirin group in early mortality (3.3 vs 3.9%), recurrent ischemic strokes (1.6 vs 2.1%), and dependency at discharge or death (30.5 vs 31.6%). These trials demonstrate that the use of aspirin in the treatment of AIS is safe and produces a small net benefit. For every 1000 acute strokes treated with aspirin, ~9 deaths or nonfatal stroke recurrences will be prevented in the first few weeks and ~13 fewer patients will be dead or dependent at 6 months. Combining aspirin with clopidogrel or with ticagrelor following minor stroke or TIA is effective at preventing second stroke (see below).

Anticoagulation Numerous clinical trials have failed to demonstrate any benefit of routine anticoagulation in the primary treatment of atherothrombotic cerebral ischemia and have also shown an increase in the risk of brain and systemic hemorrhage. Therefore, the routine use of heparin or other anticoagulants for patients with atherothrombotic stroke is not warranted. Heparin and oral anticoagulation are likely no more effective than aspirin for stroke associated with arterial dissection. However, there may be benefit of anticoagulation for halting progression of dural sinus thrombosis.

NEUROPROTECTION

Neuroprotection is the concept of providing a treatment that prolongs the brain's tolerance to ischemia. Drugs that block the excitatory amino acid pathways have been shown to protect neurons and glia in animals, but despite multiple human trials, they have not yet been proven to be beneficial. Hypothermia is a powerful neuroprotective treatment in patients with cardiac arrest (Chap. 307) and is neuroprotective in animal models of stroke, but it has not been adequately studied in patients with ischemic stroke and is associated with an increase in pneumonia rates that could adversely impact stroke outcomes. Hypothermia combined with hemisectomy is no more effective than hemisectomy with euthermia.

STROKE CENTERS AND REHABILITATION

Patient care in stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality. Use of clinical pathways and staff dedicated to the stroke patient can improve care. This includes use of standardized stroke order sets. Stroke teams

that provide emergency 24-h evaluation of acute stroke patients for acute medical management and consideration of thrombolysis or endovascular treatments are essential components of primary and comprehensive stroke centers, respectively.

Proper rehabilitation of the stroke patient includes early physical, occupational, and speech therapy. It is directed toward educating the patient and family about the patient's neurologic deficit, preventing the complications of immobility (e.g., pneumonia, DVT and pulmonary embolism, pressure sores of the skin, and muscle contractures), and providing encouragement and instruction in overcoming the deficit. Use of pneumatic compression stockings is of proven benefit in reducing risk of DVT and is a safe alternative to heparin. The goal of rehabilitation is to return the patient home and to maximize recovery by providing a safe, progressive regimen suited to the individual patient. Additionally, the use of constrained movement therapy (immobilizing the unaffected side) has been shown to improve hemiparesis following stroke, even years after the stroke, suggesting that physical therapy can recruit unused neural pathways. Controversy exists regarding whether selective serotonin uptake inhibitors improve motor recovery but they may be helpful in preventing poststroke depression. Newer robotic therapies appear promising as well. The human nervous system is more adaptable than previously thought, and developing physical and pharmacologic strategies to enhance long-term neural recovery is an active area of research.

■ ETIOLOGY OF ISCHEMIC STROKE

(Fig. 427-3 and Table 427-2) Although the initial management of AIS often does not depend on the etiology, establishing a cause is essential to reduce the risk of recurrence. Focus should be on atrial fibrillation and carotid atherosclerosis, because these etiologies have proven secondary prevention strategies. The clinical presentation and examination findings often establish the cause of stroke or narrow the possibilities to a few. Judicious use of laboratory testing and imaging studies completes the initial evaluation. Nevertheless, nearly 30% of strokes remain unexplained despite extensive evaluation.

Clinical examination should focus on the peripheral and cervical vascular system (measuring blood pressure), the heart (dysrhythmia, murmurs), extremities (peripheral emboli), and retina (effects of hypertension and cholesterol emboli [Hollenhorst plaques]). A complete neurologic examination is performed to localize the anatomic site of stroke (Chap. 426). An imaging study of the brain is nearly always indicated and is required for patients being considered for thrombolysis; it may be combined with CT- or MRI-based angiography to visualize the vasculature of the neck and intracranial vessels (see "Imaging Studies," Chap. 426). A chest x-ray, electrocardiogram (ECG), urinalysis, complete blood count, erythrocyte sedimentation rate (ESR), serum electrolytes, blood urea nitrogen (BUN), creatinine, blood glucose, serum lipid profile, prothrombin time (PT), and partial thromboplastin time (PTT) are often useful and should be considered in all patients. An ECG, and subsequent cardiac telemetry, may demonstrate arrhythmias or reveal evidence of recent myocardial infarction (MI). Of all these studies, only brain imaging is necessary prior to IV rtPA; the results of other studies should not delay the rapid administration of IV rtPA if the patient is eligible.

Cardioembolic Stroke Cardioembolism is responsible for ~20% of all ischemic strokes. Stroke caused by heart disease is primarily due to embolism of thrombotic material forming on the atrial or ventricular wall or the left heart valves. These thrombi then detach and embolize into the arterial circulation. The thrombus may fragment or lyse quickly, producing only a TIA. Alternatively, the arterial occlusion may last longer, producing stroke. Embolic strokes tend to occur suddenly with maximum neurologic deficit present at onset. With reperfusion following more prolonged ischemia, petechial hemorrhages can occur within the ischemic territory. These are usually of no clinical significance and should be distinguished from frank intracranial hemorrhage into a region of ischemic stroke where the mass effect from the hemorrhage can cause a significant decline in neurologic function.

Emboi from the heart most often lodge in the intracranial internal carotid artery, the MCA, the posterior cerebral artery (PCA), or one of their branches; infrequently, the anterior cerebral artery (ACA) is

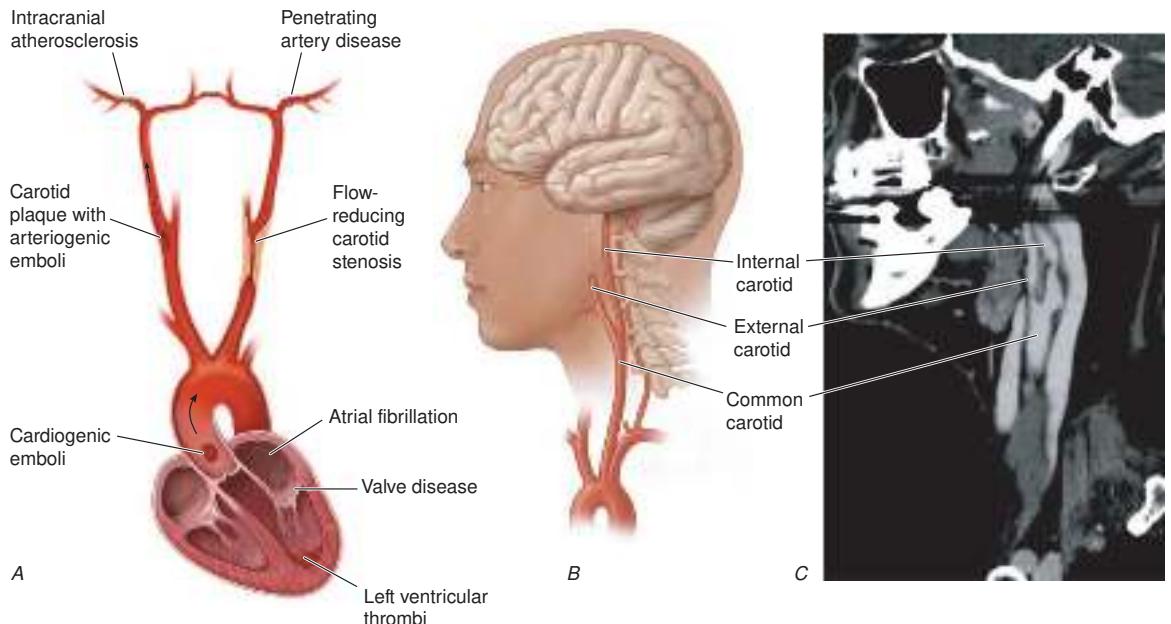


FIGURE 427-3 Pathophysiology of ischemic stroke. **A.** Diagram illustrating the three major mechanisms that underlie ischemic stroke: (1) occlusion of an intracranial vessel by an embolus (e.g., cardiogenic sources such as atrial fibrillation or artery-to-artery emboli from carotid atherosclerotic plaque), often affecting the large intracranial vessels; (2) in situ thrombosis of an intracranial vessel, typically affecting the small penetrating arteries that arise from the major intracranial arteries; (3) hypoperfusion caused by flow-limiting stenosis of a major extracranial (e.g., internal carotid) or intracranial vessel, often producing "watershed" ischemia. **B.** and **C.** Diagram and reformatted computed tomography angiogram of the common, internal, and external carotid arteries. High-grade stenosis of the internal carotid artery, which may be associated with either cerebral emboli or flow-limiting ischemia, was identified in this patient.

TABLE 427-2 Causes of Ischemic Stroke

COMMON CAUSES	UNCOMMON CAUSES
Thrombosis	Hypercoagulable disorders
Lacunar stroke (small vessel)	Protein C deficiency ^a
Large-vessel thrombosis	Protein S deficiency ^a
Dehydration	Antithrombin III deficiency ^a
Embolic occlusion	Antiphospholipid syndrome
Artery-to-artery	Factor V Leiden mutation ^a
Carotid bifurcation	Prothrombin G20210 mutation ^a
Aortic arch	Systemic malignancy
Arterial dissection	Sickle cell anemia
Cardioembolic	β Thalassemia
Atrial fibrillation	Polycythemia vera
Mural thrombus	Systemic lupus erythematosus
Myocardial infarction	Homocysteinemia
Dilated cardiomyopathy	Thrombotic thrombocytopenic purpura
Valvular lesions	Disseminated intravascular coagulation
Mitral stenosis	Dysproteinemias ^a
Mechanical valve	Nephrotic syndrome ^a
Bacterial endocarditis	Inflammatory bowel disease ^a
Paradoxical embolus	Oral contraceptives
Atrial septal defect	COVID-19 infection
Patent foramen ovale	Venous sinus thrombosis ^b
Atrial septal aneurysm	Fibromuscular dysplasia
Spontaneous echo contrast	Vasculitis
Stimulant drugs: cocaine, amphetamine	Systemic vasculitis (PAN, granulomatosis with polyangiitis [Wegener's], Takayasu's, giant cell arteritis)
	Primary CNS vasculitis
	Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster)
	Noninflammatory vasculopathy
	Reversible vasoconstriction syndrome
	Fabry's disease
	Angiocentric lymphoma
Cardiogenic	
	Mitral valve calcification
	Atrial myxoma
	Intracardiac tumor
	Marantic endocarditis
	Libman-Sacks endocarditis
	Subarachnoid hemorrhage vasospasm
	Moyamoya disease
	Eclampsia

^aChiefly cause venous sinus thrombosis. ^bMay be associated with any hypercoagulable disorder.

Abbreviations: CNS, central nervous system; PAN, polyarteritis nodosa.

involved. Emboli large enough to occlude the stem of the MCA (3–4 mm) or internal carotid terminus lead to large infarcts that involve both deep gray and white matter and some portions of the cortical surface and its underlying white matter. A smaller embolus may occlude a small cortical or penetrating arterial branch. The location and size of an infarct within a vascular territory depend on the extent of the collateral circulation.

The most significant cause of cardioembolic stroke in most of the world is nonrheumatic (often called nonvalvular) atrial fibrillation. MI, prosthetic valves, rheumatic heart disease, and ischemic cardiomyopathy are other considerations (Table 427-2). Cardiac disorders causing brain embolism are discussed in the chapters on heart diseases, but a few pertinent aspects are highlighted here.

Nonrheumatic atrial fibrillation is the most common cause of cerebral embolism overall. The presumed stroke mechanism is thrombus formation in the fibrillating atrium or atrial appendage, with subsequent embolization. Patients with atrial fibrillation have an average annual risk of stroke of ~5%. The risk of stroke can be estimated by calculating the CHA₂DS₂-VASc score (Table 427-3). Left atrial enlargement is an additional risk factor for formation of atrial thrombi. Rheumatic heart disease usually causes ischemic stroke when there is prominent mitral stenosis or atrial fibrillation. Recent MI may be a source of emboli, especially when transmural and involving the anteroapical ventricular wall, and prophylactic anticoagulation following MI with left ventricular thrombus has been shown to reduce ischemic stroke risk. Mitral valve prolapse is not usually a source of emboli unless the prolapse is severe.

Paradoxical embolization occurs when venous thrombi migrate to the arterial circulation, usually via a patent foramen ovale (PFO) or atrial septal defect. Bubble-contrast echocardiography (IV injection of agitated saline coupled with either transthoracic or transesophageal echocardiography) can demonstrate a right-to-left cardiac shunt, revealing the conduit for paradoxical embolization. Alternatively, a right-to-left shunt is implied if immediately following IV injection of agitated saline, the ultrasound signature of bubbles is observed during transcranial Doppler insonation of the MCA; pulmonary arteriovenous malformations should be considered if this test is positive yet an echocardiogram fails to reveal an intracardiac shunt. Both techniques are highly sensitive for detection of right-to-left shunts. Besides venous clot, fat and tumor emboli, bacterial endocarditis, IV air, and amniotic fluid emboli at childbirth may occasionally be responsible for paradoxical embolization. The importance of a PFO as a cause of stroke is debated, particularly because they are present in ~15% of the general population. The presence of a venous source of embolus, most commonly a deep-venous thrombus, may provide confirmation of the importance of a PFO with an accompanying right-to-left shunt in a particular case. Meta-analysis of three recent randomized trials reported a hazard ratio of 0.41 for recurrent stroke (about a 1% per year absolute reduction) using percutaneous occlusion devices in patients with no other explanation for their stroke. Guidelines now endorse PFO closure with percutaneous devices after consultation with a neurologist and a cardiologist. This is the practice followed by the authors.

Bacterial endocarditis can be a source of valvular vegetations that give rise to septic emboli. The appearance of multifocal symptoms and signs in a patient with stroke makes bacterial endocarditis more likely. Infarcts of microscopic size occur, and large septic infarcts may evolve into brain abscesses or cause hemorrhage into the infarct, which generally precludes use of anticoagulation or thrombolytics. Mycotic aneurysms caused by septic emboli may also present as subarachnoid hemorrhage (SAH) or intracerebral hemorrhage.

Artery-to-Artery Embolic Stroke Thrombus formation on atherosclerotic plaques may embolize to intracranial arteries producing an artery-to-artery embolic stroke. Less commonly, a diseased vessel may acutely thrombose. Unlike the myocardial vessels, artery-to-artery embolism, rather than local thrombosis, appears to be the dominant vascular mechanism causing large-vessel brain ischemia. Any diseased vessel may be an embolic source, including the aortic arch, common carotid, internal carotid, vertebral, and basilar arteries.

CAROTID ATHEROSCLEROSIS Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurcation and proximal internal carotid artery; the carotid siphon (portion within the cavernous sinus) is also vulnerable to atherosclerosis. Male gender, older age, smoking, hypertension, diabetes, and hypercholesterolemia are risk factors for carotid disease, as they are for stroke in general (Table 427-4). Carotid atherosclerosis produces an estimated 10% of ischemic stroke. For further discussion of the pathogenesis of atherosclerosis, see Chap. 237.

Carotid disease can be classified by whether the stenosis is symptomatic or asymptomatic and by the degree of stenosis (percent narrowing of the narrowest segment compared to a nondiseased segment). Symptomatic carotid disease implies that the patient has experienced

TABLE 427-3 Recommendations on Chronic Use of Antithrombotics for Various Cardiac Conditions

CONDITION	RECOMMENDATION
Nonvalvular atrial fibrillation	Calculate CHA ₂ DS ₂ -VASC score ^a Aspirin or no antithrombotic Aspirin or OAC OAC
Rheumatic mitral valve disease	OAC OAC plus aspirin
Mitral valve prolapse	No therapy Aspirin OAC
Mitral annular calcification	Aspirin OAC OAC
Aortic valve calcification	No therapy Aspirin
Aortic arch mobile atheroma	Aspirin or OAC
Patent foramen ovale	Aspirin or closure with device OAC
Mechanical heart valve	VKA INR 2.5, range 2–3 VKA INR 3.0, range 2.5–3.5 VKA INR 3.0, range 2.5–3.5 Aspirin plus VKA INR 3.0, range 2.5–3.5 Add aspirin and/or increase INR: prior target was 2.5, increase to 3.0, range 2.5–3.5; prior target was 3.0, increase to 3.5, range 3–4
Bioprosthetic valve	Aspirin
Infective endocarditis	Avoid antithrombotic agents
Nonbacterial thrombotic endocarditis	Full-dose, unfractionated heparin or SC LMWH, or Xa inhibitor

^aCHA₂DS₂-VASC score is calculated as follows: 1 point for congestive heart failure, 1 point for hypertension, 2 points for age ≥ 75 years, 1 point for diabetes mellitus, 2 points for stroke or TIA, 1 point for vascular disease (prior myocardial infarction, peripheral vascular disease, or aortic plaque), 1 point for age 65–74 years, 1 point for female sex category; sum of points is the total CHA₂DS₂-VASC score.

Note: Dose of aspirin is 50–325 mg/d; target INR for VKA is between 2 and 3 unless otherwise specified.

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant (VKA, thrombin inhibitor, or oral factor Xa inhibitors); TIA, transient ischemic attack; VKA, vitamin K antagonist.

Sources: Data from DE Singer et al: Chest 133:546S, 2008; DN Salem et al: Chest 133:593S, 2008; CT January et al: JACC 64:2246, 2014.

a stroke or TIA within the vascular distribution of the artery, and it is associated with a greater risk of subsequent stroke than asymptomatic stenosis, in which the patient is symptom free and the stenosis is detected through screening. Greater degrees of arterial narrowing are generally associated with a higher risk of stroke, except that those with near occlusions are at lower risk of stroke.

OTHER CAUSES OF ARTERY TO ARTERY EMBOLIC STROKE *Intracranial atherosclerosis* produces stroke either by an embolic mechanism or by in situ thrombosis of a diseased vessel. It is more common in patients of Asian and African-American descent. Recurrent stroke risk is ~15% per year, similar to untreated symptomatic carotid atherosclerosis.

Dissection of the internal carotid or vertebral arteries or even vessels beyond the circle of Willis is a common source of embolic stroke in young (age <60 years) patients. The dissection is usually painful and precedes the stroke by several hours or days. Extracranial dissections do not cause hemorrhage, presumably because of the tough adventitia of these vessels. Intracranial dissections, conversely, may produce SAH because the adventitia of intracranial vessels is thin and pseudoaneurysms may form, requiring urgent treatment to prevent rerupture. Treating asymptomatic pseudoaneurysms following extracranial dissection is likely not necessary. The cause of dissection is usually unknown, and recurrence is rare. Ehlers-Danlos type IV, Marfan's disease, cystic medial necrosis, and fibromuscular dysplasia are associated with dissections. Trauma (usually a motor vehicle accident or a sports injury) can cause carotid and vertebral artery dissections. Spinal manipulative therapy is associated with vertebral artery dissection and stroke. Most dissections heal spontaneously, and stroke or TIA is uncommon beyond 2 weeks. One trial showed no difference in stroke prevention with aspirin compared to anticoagulation, with a low recurrent stroke rate of 2%.

■ SMALL VESSEL STROKE

The term *lacunar infarction* refers to infarction following atherothrombotic or lipohyalinotic occlusion of a small artery in the brain. The term *small-vessel stroke* denotes occlusion of such a small penetrating artery and is now the preferred term. Small-vessel strokes account for ~20% of all strokes.

Pathophysiology The MCA stem, the arteries comprising the circle of Willis (A1 segment, anterior and posterior communicating arteries, and P1 segment), and the basilar and vertebral arteries all give rise to 30- to 300- μm branches that penetrate the deep gray and white matter of the cerebrum or brainstem (Fig. 427-4). Each of these small branches can occlude either by atherothrombotic disease at its origin or by the development of lipohyalinotic thickening. Thrombosis of these vessels causes small infarcts that are referred to as *lacunes* (Latin for “lake” of fluid noted at autopsy). These infarcts range in size from 3 mm to 2 cm in diameter. Hypertension and age are the principal risk factors.

Clinical Manifestations The most common small-vessel stroke syndromes are the following: (1) *pure motor hemiparesis* from an infarct in the posterior limb of the internal capsule or the pons; the face, arm, and leg are almost always involved; (2) *pure sensory stroke* from an infarct in the ventral thalamus; (3) *ataxic hemiparesis* from an infarct in the ventral pons or internal capsule; (4) and *dysarthria and a clumsy hand* or arm due to infarction in the ventral pons or in the genu of the internal capsule.

Transient symptoms (small-vessel TIAs) may herald a small-vessel infarct; they may occur several times a day and last only a few minutes. Recovery from small-vessel strokes tends to be more rapid and complete than recovery from large-vessel strokes; in some cases, however, there is severe permanent disability.

A large-vessel source (either thrombosis or embolism) may manifest initially as a small-vessel infarction. Therefore, the search for embolic sources (carotid and heart) should not be completely abandoned in the evaluation of these patients. Secondary prevention of small-vessel stroke involves risk factor modification, specifically reduction in blood pressure (see “Treatment: Primary and Secondary Prevention of Stroke and TIA,” below).

TABLE 427-4 Risk Factors for Stroke

RISK FACTOR	RELATIVE RISK	RELATIVE RISK REDUCTION WITH TREATMENT	NUMBER NEEDED TO TREAT ^a	
			PRIMARY PREVENTION	SECONDARY PREVENTION
Hypertension	2–5	38%	100–300	50–100
Atrial fibrillation	1.8–2.9	68% warfarin, 21% aspirin	20–83	13
Diabetes	1.8–6	No proven effect		
Smoking	1.8	50% at 1 year, baseline risk at 5 years postcessation		
Hyperlipidemia	1.8–2.6	16–30%	560	230
Asymptomatic carotid stenosis	2.0	53%	85	N/A
Symptomatic carotid stenosis (70–99%)		65% at 2 years	N/A	12
Symptomatic carotid stenosis (50–69%)		29% at 5 years	N/A	77

^aNumber needed to treat to prevent one stroke annually. Prevention of other cardiovascular outcomes is not considered here.

Abbreviation: N/A, not applicable.

LESS COMMON CAUSES OF STROKE

(Table 427-2) *Hypercoagulable disorders* (Chap. 65) primarily increase the risk of cortical vein or cerebral venous sinus thrombosis. Systemic lupus erythematosus with Libman-Sacks endocarditis can be a cause

of embolic stroke. These conditions overlap with the antiphospholipid syndrome (Chap. 357), which probably requires long-term anticoagulation to prevent further stroke. Homocysteinemia may cause arterial thromboses as well; this disorder is caused by various mutations in the homocysteine pathways and responds to different forms of cobalamin depending on the mutation. Disseminated intravascular coagulopathy can cause both venous and arterial occlusive events; COVID-19 infection may predispose for acute ischemic stroke due to large-vessel occlusion.

Venous sinus thrombosis of the lateral or sagittal sinus or of small cortical veins (cortical vein thrombosis) occurs as a complication of oral contraceptive use, pregnancy and the postpartum period, inflammatory bowel disease, intracranial infections (meningitis), and dehydration. It is also seen in patients with laboratory-confirmed thrombophilia including antiphospholipid syndrome, polycythemia, sickle cell anemia, deficiencies of proteins C and S, factor V Leiden mutation (resistance to activated protein C), antithrombin III deficiency, homocysteinemia, and the prothrombin G20210 mutation. Women who take oral contraceptives and have the prothrombin G20210 mutation may be at particularly high risk for sinus thrombosis. Patients present with headache and may also have focal neurologic signs (especially paraparesis) and seizures. Often, CT imaging is normal unless an intracranial venous hemorrhage has occurred, but the venous sinus occlusion is readily visualized using MR or CT venography or conventional x-ray angiography. With greater degrees of sinus thrombosis, the patient may develop signs of increased ICP and coma. Intravenous heparin, regardless of the presence of intracranial hemorrhage, reduces morbidity and mortality, and the long-term outcome is generally good. Heparin prevents further thrombosis and reduces venous hypertension and ischemia. If an underlying hypercoagulable state is not found, many physicians treat with oral anticoagulants for 3–6 months and then convert to aspirin, depending on the degree of resolution of the venous sinus thrombus. Anticoagulation is often continued indefinitely if thrombophilia is diagnosed.

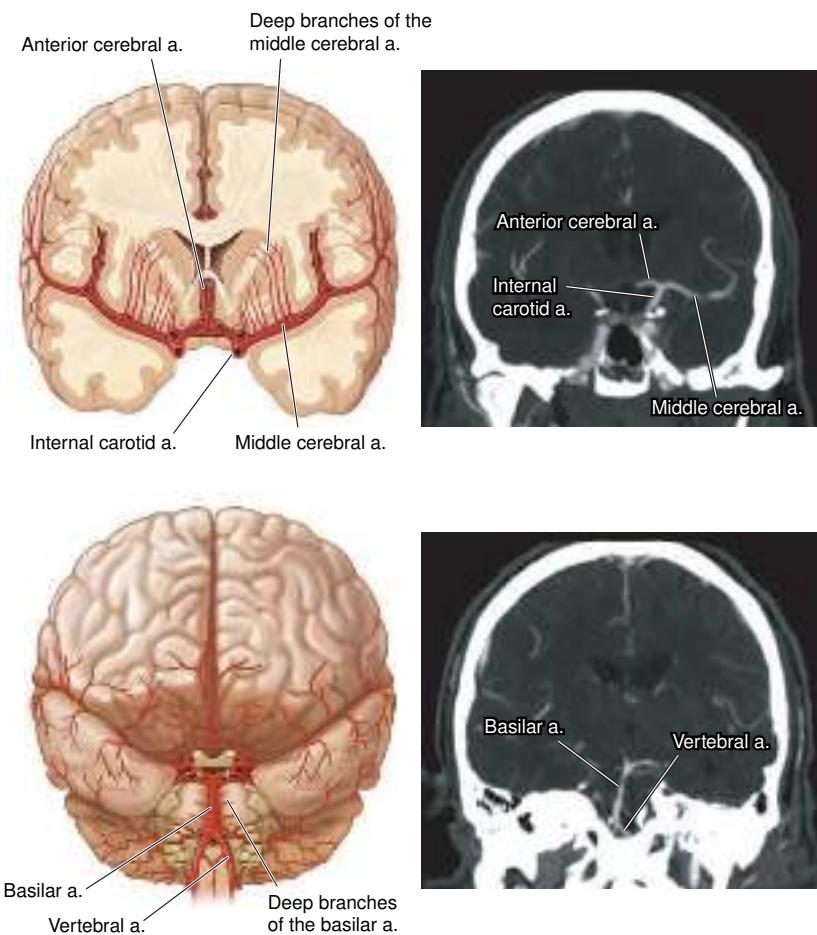


FIGURE 427-4 Diagrams and reformatted computed tomography (CT) angiograms in the coronal section illustrating the deep penetrating arteries involved in small-vessel strokes. In the anterior circulation, small penetrating arteries called *lenticulostriates* arise from the proximal portion of the anterior and middle cerebral arteries and supply deep subcortical structures (*upper panels*). In the posterior circulation, similar arteries arise directly from the vertebral and basilar arteries to supply the brainstem (*lower panels*). Occlusion of a single penetrating artery gives rise to a discrete area of infarct (pathologically termed a “lacune,” or lake). Note that these vessels are too small to be visualized on CT angiography.

Sickle cell anemia (SS disease) is a common cause of stroke in children. A subset of homozygous carriers of this hemoglobin mutation develop stroke in childhood, and this may be predicted by documenting high-velocity blood flow within the MCAs using transcranial Doppler ultrasonography. In children who are identified to have high velocities, treatment with aggressive exchange transfusion dramatically reduces risk of stroke, and if exchange transfusion is ceased, their stroke rate increases again along with MCA velocities.

Fibromuscular dysplasia (Chap. 281) affects the cervical arteries and occurs mainly in women. The carotid or vertebral arteries show multiple rings of segmental narrowing alternating with dilatation. Vascular occlusion is usually incomplete. The process is often asymptomatic but occasionally is associated with an audible bruit, TIAs, or stroke. Involvement of the renal arteries is common and may cause hypertension. The cause and natural history of fibromuscular dysplasia are unknown. TIA or stroke generally occurs only when the artery is severely narrowed or dissects. Anticoagulation or antiplatelet therapy may be helpful.

Temporal (giant cell) arteritis (Chap. 363) is a relatively common affliction of elderly individuals in which the external carotid system, particularly the temporal arteries, undergoes subacute granulomatous inflammation with giant cells. Occlusion of posterior ciliary arteries derived from the ophthalmic artery results in blindness in one or both eyes and can be prevented with glucocorticoids. It rarely causes stroke because the internal carotid artery is usually not inflamed. Idiopathic giant cell arteritis involving the great vessels arising from the aortic arch (*Takayasu's arteritis*) may cause carotid or vertebral thrombosis; it is rare in the Western Hemisphere.

Necrotizing (or granulomatous) arteritis (Chap. 363), occurring alone or in association with generalized polyarteritis nodosa or granulomatosis with polyangiitis (Wegener's), involves the distal small branches (<2 mm diameter) of the main intracranial arteries and produces small ischemic infarcts in the brain, optic nerve, and spinal cord. The CSF often shows pleocytosis, and the protein level is elevated. *Primary central nervous system vasculitis* is rare; small or medium-sized vessels are usually affected, without apparent systemic vasculitis. The differential diagnosis includes other inflammatory vasculopathies including infection (tuberculous, fungal), sarcoidosis, angiocentric lymphoma, carcinomatous meningitis, and noninflammatory causes such as atherosclerosis, emboli, connective tissue disease, vasospasm, migraine-associated vasculopathy, and drug-associated causes. Some cases develop in the postpartum period and are self-limited.

Patients with any form of vasculopathy may present with insidious progression of combined white and gray matter infarctions, prominent headache, and cognitive decline. Brain biopsy or high-resolution conventional x-ray angiography is usually required to make the diagnosis (Fig. 427-5). A lumbar puncture (elevated white blood cells, elevated

IgG index, bands on electrophoresis) can provide support for an inflammatory etiology of a neurovascular problem. When inflammation is confirmed, aggressive immunosuppression with glucocorticoids, and often cyclophosphamide, is usually necessary to prevent progression; a diligent investigation for infectious causes such as tuberculosis is essential prior to immunosuppression. With prompt recognition and treatment, many patients can make an excellent recovery.

Drugs, in particular amphetamines and perhaps cocaine, may cause stroke on the basis of acute hypertension or drug-induced vasculopathy. This vasculopathy is commonly due to vasospasm or atherosclerosis, but cases of inflammatory vasculitis have also been reported. No data exist on the value of any treatment, but cessation of stimulants is prudent. Phenylpropanolamine has been linked with intracranial hemorrhage, as has cocaine and methamphetamine, perhaps related to a drug-induced vasculopathy. *Moyamoya disease* is a poorly understood occlusive disease involving large intracranial arteries, especially the distal internal carotid artery and the stem of the MCA and ACA. Vascular inflammation is absent. The lenticulostriate arteries develop a rich collateral circulation around the occlusive lesion, which gives the impression of a "puff of smoke" (*moyamoya* in Japanese) on conventional x-ray angiography. Other collaterals include transdural anastomoses between the cortical surface branches of the meningeal and scalp arteries. The disease occurs mainly in Asian children or young adults, but the appearance may be identical in adults who have atherosclerosis, particularly in association with diabetes. Intracranial hemorrhage may result from rupture of the moyamoya collaterals; thus, anticoagulation is risky. Progressive occlusion of large surface arteries can occur, producing large-artery distribution strokes. Surgical bypass of extracranial carotid arteries to the dura or MCAs may prevent stroke and hemorrhage.

Posterior reversible encephalopathy syndrome (PRES) can occur with head injury, seizure, migraine, sympathomimetic drug use, and eclampsia and in the postpartum period. The pathophysiology is uncertain but likely involves a hyperperfusion state where blood pressure exceeds the upper limit of cerebral autoregulation resulting in cerebral edema (Chap. 307). Patients complain of headache and manifest fluctuating neurologic symptoms and signs, especially visual symptoms. Sometimes cerebral infarction ensues, but typically, the clinical and imaging findings reverse completely. MRI findings are characteristic with the edema present within the occipital lobes but can be generalized and do not respect any single vascular territory. A closely related *reversible cerebral vasoconstriction syndrome* (RCVS) typically presents with sudden, severe headache closely mimicking SAH. Patients may experience ischemic infarction and intracerebral hemorrhage and typically have new-onset, severe hypertension. Conventional x-ray angiography reveals changes in the vascular caliber throughout the hemispheres resembling vasculitis, but the process is noninflammatory. Oral calcium channel blockers may be effective in producing remission, and recurrence is rare.

Leukoaraiosis, or *periventricular white matter disease*, is the result of multiple small-vessel infarcts within the subcortical white matter. It is readily seen on CT or MRI scans as areas of white matter injury surrounding the ventricles and within the corona radiata. The pathophysiologic basis of the disease is lipohyalinosis of small penetrating arteries within the white matter, likely produced by chronic hypertension. Patients with periventricular white matter disease may develop a subcortical dementia syndrome, and it is likely that this common form of dementia may be delayed or prevented with antihypertensive medications (Chap. 433).

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is an inherited disorder that presents as small-vessel strokes, progressive dementia, and extensive symmetric white matter changes often including the anterior temporal lobes visualized by MRI. Approximately 40% of patients have migraine with aura, often manifest as transient motor or sensory deficits. Onset is usually in the fourth or fifth decade of life. This autosomal dominant condition is caused by one of several mutations in *Notch-3*, a member of a highly conserved gene family characterized by epidermal growth factor repeats in its extracellular domain. Other monogenic ischemic

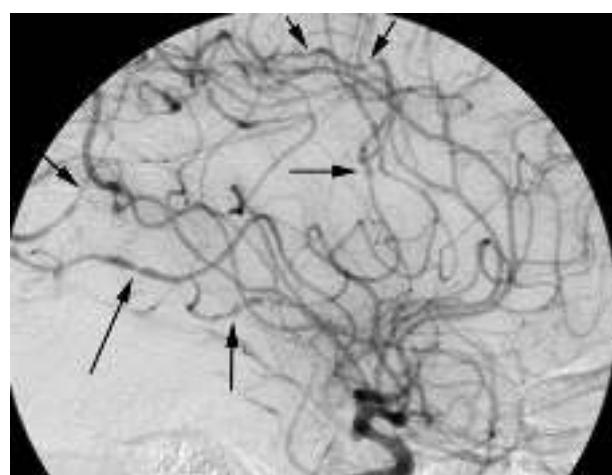


FIGURE 427-5 Cerebral angiogram from a 32-year-old male with central nervous system vasculopathy. Dramatic beading (arrows) typical of vasculopathy is seen.

stroke syndromes include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS). Fabry's disease also produces both a large-vessel arteriopathy and small-vessel infarctions. The *COL4A1* mutation is associated with multiple small-vessel strokes with hemorrhagic transformation.

■ TRANSIENT ISCHEMIC ATTACKS

TIA are episodes of stroke symptoms that last only briefly; the standard definition of duration is <24 h, but most TIAs last <1 h. If a relevant brain infarction is identified on brain imaging, the clinical entity is now classified as stroke regardless of the duration of symptoms. A normal brain imaging study following a TIA does not rule out TIA; rather, the clinical syndrome is diagnostic. The causes of TIA are similar to the causes of ischemic stroke, but because TIAs may herald stroke, they are an important risk factor that should be considered separately and urgently. TIAs may arise from emboli to the brain or from *in situ* thrombosis of an intracranial vessel. With a TIA, the occluded blood vessel reopens and neurologic function is restored.

The risk of stroke after a TIA is ~10–15% in the first 3 months, with most events occurring in the first 2 days. This risk can be directly estimated using the well-validated ABCD² score (Table 427-5). Therefore, urgent evaluation and treatment are justified. Because etiologies for stroke and TIA are identical, evaluation for TIA should parallel that of stroke.

TREATMENT

Transient Ischemic Attack

The improvement characteristic of TIA is a contraindication to thrombolysis. However, because the risk of subsequent stroke in the first few hours and days following TIA is high, some physicians admit the patient to the hospital so a plasminogen activator can be rapidly administered if symptoms return. The combination of aspirin and clopidogrel was found to prevent stroke following TIA better than aspirin alone in a large Chinese randomized trial and the National Institutes of Health (NIH)-sponsored trial (POINT

study). Failure to respond to the combination of aspirin and clopidogrel is linked to carriage of a common CYP2C19 polymorphism that leads to poor metabolism of clopidogrel into its active form. This mutation is common, particularly in Asians. Recently, ticagrelor, 180-mg loading dose and then 90 mg twice daily, was tested in combination with aspirin compared to aspirin alone, and this also showed benefit in preventing stroke; this dual antiplatelet regimen may be favored because of the lack of genetic heterogeneity in platelet inhibition.

Primary and Secondary Prevention of Stroke and TIA

GENERAL PRINCIPLES

Many medical and surgical interventions, as well as lifestyle modifications, are available for preventing stroke. Some of these can be widely applied because of their low cost and minimal risk; others are expensive and carry substantial risk but may be valuable for selected high-risk patients. Identification and control of modifiable risk factors, and especially hypertension, is the best strategy to reduce the burden of stroke, and the total number of strokes could be reduced substantially by these means (Table 427-4).

ATHEROSCLEROSIS RISK FACTORS

The relationship of various factors to the risk of atherosclerosis is described in Chaps. 237 and 238. Older age, diabetes mellitus, hypertension, tobacco smoking, abnormal blood cholesterol (particularly, low high-density lipoprotein [HDL] and/or elevated low-density lipoprotein [LDL]), lipoprotein (a) excess, and other factors are either proven or probable risk factors for ischemic stroke, largely by their link to atherosclerosis. Risk of stroke is much greater in those with prior stroke or TIA. Many cardiac conditions predispose to stroke, including atrial fibrillation and recent MI. Oral contraceptives and hormone replacement therapy increase stroke risk, and although rare, certain inherited and acquired hypercoagulable states predispose to stroke.

Hypertension is the most significant of the risk factors; in general, all hypertension should be treated to a target of <130/80 mmHg. Recent data (the Systolic Blood Pressure Intervention Trial—SPRINT) suggest that lowering systolic blood pressure <120 mmHg reduces stroke and heart attack by 43% compared to systolic blood pressure <140 mmHg, without an increased risk of syncope or falls. The presence of known cerebrovascular disease is not a contraindication to treatment aimed at achieving normotension. Data are particularly strong in support of thiazide diuretics and angiotensin-converting enzyme inhibitors.

Several trials have confirmed that statin drugs reduce the risk of stroke even in patients without elevated LDL or low HDL. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed benefit in secondary stroke reduction for patients with recent stroke or TIA who were prescribed atorvastatin, 80 mg/d. The primary prevention trial, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), found that patients with low LDL (<130 mg/dL) caused by elevated C-reactive protein benefitted by daily use of this statin. Primary stroke occurrence was reduced by 51% (hazard ratio, 0.49; $p = .004$), and there was no increase in the rates of intracranial hemorrhage. Meta-analysis has also supported a primary treatment effect for statins given acutely for ischemic stroke. A serum LDL <70 mg/dL lowers recurrent stroke risk better than an LDL of 90–110 mg/dL. Therefore, a statin should be considered in all patients with prior ischemic stroke. Tobacco smoking should be discouraged in all patients (Chap. 454). The use of pioglitazone (an agonist of peroxisome proliferator-activated receptor gamma) in patients with type 2 diabetes and previous stroke does not lower stroke, MI, or vascular death rates but is effective in lowering vascular events in patients with stroke and prediabetes or insulin resistance alone. Diabetes prevention is likely the most effective strategy for primary and secondary stroke prevention.

TABLE 427-5 Risk of Stroke Following Transient Ischemic Attack: The ABCD² Score

CLINICAL FACTOR	SCORE
A: Age ≥60 years	1
B: SBP >140 mmHg or DBP >90 mmHg	1
C: Clinical symptoms	
Unilateral weakness	2
Speech disturbance without weakness	1
D: Duration	
>60 min	2
10–59 min	1
D: Diabetes (oral medications or insulin)	1
TOTAL SCORE	SUM EACH CATEGORY
ABCD ² Score Total	3-Month Rate of Stroke (%) ^a
0	0
1	2
2	3
3	3
4	8
5	12
6	17
7	22

^aData ranges are from five cohorts.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Source: Data from SC Johnston et al: Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 369:283, 2007.

ANTIPLATELET AGENTS FOR STROKE PREVENTION

Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting the formation of intraarterial platelet aggregates. These can form on diseased arteries, induce thrombus formation, and occlude or embolize into the distal circulation. Aspirin, clopidogrel, the combination of aspirin plus extended-release dipyridamole, and recently ticagrelor are the antiplatelet agents most commonly used for this purpose. Ticagrelor has not been found to be better than aspirin for stroke prevention except in combination with aspirin following TIA.

Aspirin is the most widely studied antiplatelet agent. Aspirin acetylates platelet cyclooxygenase, which irreversibly inhibits the formation in platelets of thromboxane A₂, a platelet aggregating and vasoconstricting prostaglandin. This effect is permanent and lasts for the usual 8-day life of the platelet. Paradoxically, aspirin also inhibits the formation in endothelial cells of prostacyclin, an antiaggregating and vasodilating prostaglandin. This effect is transient. As soon as aspirin is cleared from the blood, the nucleated endothelial cells again produce prostacyclin. Aspirin in low doses given once daily inhibits the production of thromboxane A₂ in platelets without substantially inhibiting prostacyclin formation. Higher doses of aspirin have not been proven to be more effective than lower doses.

Clopidogrel and ticagrelor block the adenosine diphosphate (ADP) receptor on platelets and thus prevent the cascade resulting in activation of the glycoprotein IIb/IIIa receptor that leads to fibrinogen binding to the platelet and consequent platelet aggregation. Clopidogrel can cause rash and, in rare instances, thrombotic thrombocytopenic purpura. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, which led to U.S. Food and Drug Administration (FDA) approval, found that it was only marginally more effective than aspirin in reducing risk of stroke. The Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial was a large multicenter, randomized, double-blind study that compared clopidogrel in combination with aspirin to clopidogrel alone in the secondary prevention of TIA or stroke. The MATCH trial found no difference in TIA or stroke prevention with this combination but did show a small but significant increase in major bleeding complications (3 vs 1%). In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, which included a subgroup of patients with prior stroke or TIA along with other groups at high risk of cardiovascular events, there was no benefit of clopidogrel combined with aspirin compared to aspirin alone. Lastly, the SPS3 trial looked at the long-term combination of clopidogrel and aspirin versus clopidogrel alone in small-vessel stroke and found no improvement in stroke prevention and a significant increase in both hemorrhage and death. Thus, the long-term use of clopidogrel in combination with aspirin is not recommended for stroke prevention.

The short-term combination of clopidogrel with aspirin may be effective in preventing second stroke, however. A large trial of Chinese patients enrolled within 24 h of TIA or minor ischemic stroke found that a clopidogrel-aspirin regimen (clopidogrel 300 mg load then 75 mg/d with aspirin 75 mg for the first 21 days) was superior to aspirin (75 mg/d) alone, with 90-day stroke risk decreased from 11.7 to 8.2% ($p < .001$) and no increase in major hemorrhage. This benefit was limited to those not carrying the CYP2C19 polymorphism associated with clopidogrel hypometabolism. An international NIH-sponsored trial demonstrated similar results; therefore, the combination of aspirin and clopidogrel should be administered for TIA or minor ischemic stroke for the first 21–90 days before switching to monotherapy.

A recent study of oral ticagrelor plus aspirin versus aspirin alone has shown similar benefits in secondary stroke reduction and carries the likely advantage that ticagrelor's antiplatelet effect is not genetically variable, as is the case with clopidogrel.

Dipyridamole is an antiplatelet agent that inhibits the uptake of adenosine by a variety of cells, including those of the vascular endothelium. The accumulated adenosine is an inhibitor of

aggregation. At least in part through its effects on platelet and vessel wall phosphodiesterases, dipyridamole also potentiates the antiaggregatory effects of prostacyclin and nitric oxide produced by the endothelium and acts by inhibiting platelet phosphodiesterase, which is responsible for the breakdown of cyclic AMP. The resulting elevation in cyclic AMP inhibits aggregation of platelets. Dipyridamole is erratically absorbed depending on stomach pH, but a newer formulation combines timed-release dipyridamole, 200 mg, with aspirin, 25 mg, and has better oral bioavailability. This combination drug was studied in three trials. The European Stroke Prevention Study (ESPS) II showed efficacy of both 50 mg/d of aspirin and extended-release dipyridamole in preventing stroke and a significantly better risk reduction when the two agents were combined. The open-label ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) trial confirmed the ESPS-II results. After 3.5 years of follow-up, 13% of patients on aspirin and dipyridamole and 16% on aspirin alone (hazard ratio, 0.80; 95% CI, 0.66–0.98) met the primary outcome of death from all vascular causes. In the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial, the combination of extended-release dipyridamole and aspirin was compared directly with clopidogrel with and without the angiotensin receptor blocker telmisartan; there were no differences in the rates of second stroke (9% each) or degree of disability in patients with median follow-up of 2.4 years. Telmisartan also had no effect on these outcomes. This suggests that these antiplatelet regimens are similar and raises questions about default prescription of agents to block the angiotensin pathway in all stroke patients. The principal side effect of dipyridamole is headache. The combination capsule of extended-release dipyridamole and aspirin is approved for prevention of stroke.

Many large clinical trials have demonstrated clearly that most antiplatelet agents reduce the risk of all important vascular atherothrombotic events (i.e., ischemic stroke, MI, and death due to all vascular causes) in patients at risk for these events. The overall *relative* reduction in risk of nonfatal stroke is ~25–30% and of all vascular events is ~25%. The *absolute* reduction varies considerably, depending on the patient's risk. Individuals at very low risk for stroke seem to experience the same relative reduction, but their risks may be so low that the “benefit” is meaningless. Conversely, individuals with a 10–15% risk of vascular events per year experience a reduction to ~7.5–11%.

Aspirin is inexpensive, can be given in low doses, and could be recommended for all adults to prevent both stroke and MI. However, it causes epigastric discomfort, gastric ulceration, and gastrointestinal hemorrhage, which may be asymptomatic or life threatening. Consequently, not every 40- or 50-year-old should be advised to take aspirin regularly because the risk of atherothrombotic stroke is extremely low and is outweighed by the risk of adverse side effects. Conversely, every patient who has experienced an atherothrombotic stroke or TIA and has no contraindication to antiplatelet therapy (or indication for anticoagulation) should be taking an antiplatelet agent regularly because the average annual risk of another stroke is 8–10%; another few percent will experience an MI or vascular death. Clearly, the likelihood of benefit far outweighs the risks of treatment.

The choice of antiplatelet agent and dose must balance the risk of stroke, the expected benefit, and the risk and cost of treatment. However, there are no definitive data, and opinions vary. Many authorities believe low-dose (30–75 mg/d) and high-dose (650–1300 mg/d) aspirin are about equally effective. Some advocate very low doses to avoid adverse effects, and still others advocate very high doses to be sure the benefit is maximal. Most physicians in North America recommend 81–325 mg/d, whereas most Europeans recommend 50–100 mg. Clopidogrel and extended-release dipyridamole plus aspirin are being increasingly recommended as first-line drugs for secondary prevention. Similarly, the choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are more effective than aspirin but the cost is higher, and this is likely to affect long-term patient adherence. The use of platelet aggregation

studies in individual patients taking aspirin is controversial because of limited data.

In our practices, when considering antithrombotic therapy for secondary stroke prevention for noncardioembolic strokes and TIAs, we prescribe aspirin 81 mg/d in aspirin-naïve patients after an initial load of 325 mg. We add either clopidogrel (600-mg load, then 75 mg daily) or ticagrelor (180-mg load, then 90 mg twice daily) for TIA or minor stroke (NIHSS <5) for 21–30 days, followed by monotherapy with aspirin alone at 81 mg daily. We treat stroke due to intracranial atherosclerosis with aspirin 81 mg plus clopidogrel 75 mg daily for 3 months, after which time treatment is continued with aspirin alone.

ANTICOAGULATION THERAPY AND EMBOLIC STROKE PREVENTION

Several trials have shown that anticoagulation (international normalized ratio [INR] range, 2–3) in patients with chronic nonvalvular (nonrheumatic) atrial fibrillation (NVAF) prevents cerebral embolism and stroke and is safe. For primary prevention and for patients who have experienced stroke or TIA, anticoagulation with a vitamin K antagonist (VKA) reduces the risk by ~67%, which clearly outweighs the 1–3% risk per year of a major bleeding complication. VKAs are difficult to dose, their effects vary with dietary intake of vitamin K, and they require frequent blood monitoring of the PTT/INR. Several newer oral anticoagulants (OACs) have recently been shown to be more convenient and efficacious for stroke prevention in NVAF. A randomized trial compared the oral thrombin inhibitor dabigatran to VKAs in a noninferiority trial to prevent stroke or systemic embolization in NVAF. Two doses of dabigatran were used: 110 mg/d and 150 mg/d. Both dose tiers of dabigatran were noninferior to VKAs in preventing second stroke and systemic embolization, and the higher dose tier was superior (relative risk, 0.66; 95% CI, 0.53–0.82; $p <.001$) and the rate of major bleeding was lower in the lower dose tier of dabigatran compared to VKAs. Dabigatran requires no blood monitoring to titrate the dose, and its effect is independent of oral intake of vitamin K. Newer oral factor Xa inhibitors have also been found to be equivalent or safer and more effective than VKAs in NVAF stroke prevention. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, patients were randomized between apixaban, 5 mg twice daily, and dose-adjusted warfarin (INR 2–3). The combined endpoint of ischemic or hemorrhagic stroke or system embolism occurred in 1.27% of patients in the apixaban group and in 1.6% in the warfarin group ($p <.001$ for noninferiority and $p <.01$ for superiority). Major bleeding was 1% less, favoring apixaban ($p <.001$). Similar results were obtained in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF). In this trial, patients with NVAF were randomized to rivaroxaban versus warfarin: 1.7% of the factor Xa group and 2.2% of the warfarin group reached the endpoint of stroke and systemic embolism ($p <.001$ for noninferiority); intracranial hemorrhage was also lower with rivaroxaban. Finally, the factor Xa inhibitor edoxaban was also found to be noninferior to warfarin. Thus, oral factor Xa inhibitors are at least a suitable alternative to VKAs, for both primary and secondary prevention, and likely are superior both in efficacy and perhaps compliance. Recent FDA approval of a reversal agent for the Xa inhibitors apixaban and rivaroxaban (andexanet alfa) provides an antidote in the case of major bleeding. Idarucizumab has been available for reversal of dabigatran. Randomized trials have not demonstrated the superiority of anticoagulants over antiplatelet medications for strokes that appear embolic without a clear source. However, subgroup analyses of these patients who also have moderate or severe left atrial enlargement do show benefit of OACs over aspirin, and a randomized trial to address this strategy further is underway.

For patients who cannot take anticoagulant medications, clopidogrel plus aspirin was compared to aspirin alone in the Atrial

Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-A). Clopidogrel combined with aspirin was more effective than aspirin alone in preventing vascular events, principally stroke, but increased the risk of major bleeding (relative risk, 1.57; $p <.001$). Left atrial appendage occlusion followed by antiplatelet therapy was found to be noninferior to oral Xa inhibitors in patients at moderate to high risk of bleeding in a single trial. If confirmed, this may be a safer strategy than management with aspirin alone for these patients at high risk of atrial fibrillation-related stroke.

The decision to use anticoagulation for primary prevention is based primarily on risk factors (Table 427-3). The history of a TIA or stroke tips the balance in favor of anticoagulation regardless of other risk factors. Intermittent atrial fibrillation carries the same risk of stroke as chronic atrial fibrillation, and several ambulatory studies of seemingly “cryptogenic” stroke have found evidence of intermittent atrial fibrillation in nearly 20% of patients monitored for a few weeks. Interrogation of implanted pacemakers also confirms an association between subclinical atrial fibrillation and stroke risk. Therefore, for patients with otherwise cryptogenic embolic stroke (no evidence of any other cause for stroke), ambulatory monitoring for 3–4 weeks is a reasonable strategy to determine the best prophylactic therapy.

Because of the high annual stroke risk in untreated rheumatic heart disease with atrial fibrillation, primary prophylaxis against stroke has not been studied in a double-blind fashion. These patients generally should receive long-term anticoagulation. Dabigatran and the oral Xa inhibitors have not been studied in this population.

Anticoagulation also reduces the risk of embolism in acute MI. Most clinicians recommend a 3-month course of anticoagulation when there is anterior Q-wave infarction, substantial left ventricular dysfunction, congestive heart failure, mural thrombosis, or atrial fibrillation. OACs are recommended long term if atrial fibrillation persists.

Stroke secondary to thromboembolism is one of the most serious complications of prosthetic heart valve implantation. The intensity of anticoagulation and/or antiplatelet therapy is dictated by the type of prosthetic valve and its location. Dabigatran may be less effective than warfarin, and the oral Xa inhibitors have not been studied in this population.

If the embolic source cannot be eliminated, anticoagulation should in most cases be continued indefinitely. Many neurologists recommend combining antiplatelet agents with anticoagulants for patients who “fail” anticoagulation (i.e., have another stroke or TIA), but the evidence basis for this is lacking.

It is our practice to prescribe apixaban 5 mg twice daily for nonvalvular atrial fibrillation with CHADS₂-VASc score of ≥2, aspirin 81 mg plus clopidogrel 75 mg daily for patients who cannot take oral anticoagulation, and VKAs for valvular atrial fibrillation or mechanical heart valve.

ANTICOAGULATION THERAPY AND NONCARDIOGENIC STROKE

Data do not support the use of long-term VKAs for preventing atherothrombotic stroke for either intracranial or extracranial cerebrovascular disease. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) found no benefit of warfarin sodium (INR 1.4–2.8) over aspirin, 325 mg, for secondary prevention of stroke but did find a slightly higher bleeding rate in the warfarin group; a European study confirmed this finding. The Warfarin and Aspirin for Symptomatic Intracranial Disease (WASID) study (see below) demonstrated no benefit of warfarin (INR 2–3) over aspirin in patients with symptomatic intracranial atherosclerosis and found a higher rate of bleeding complications. The first of several trials testing factor Xa medications for prevention of embolic stroke of unknown source failed to show benefit compared to treatment with antiplatelet medications. The oral factor Xa inhibitor apixaban was found to be noninferior to subcutaneous dalteparin for patients with cancer

and venous thromboembolism; many oncologists are using Xa inhibitors to prevent second stroke in patients with malignancy.

It is our practice to prescribe aspirin for secondary stroke prevention in noncardiogenic cerebral embolism except for stroke associated with cancer (apixaban 5 mg twice daily) and the antiphospholipid syndrome (warfarin with target INR 2–3).

TREATMENT

Carotid Atherosclerosis

Carotid atherosclerosis can be removed surgically (endarterectomy) or mitigated with endovascular stenting with or without balloon angioplasty. Anticoagulation has not been directly compared with antiplatelet therapy for carotid disease.

SURGICAL THERAPY

Symptomatic carotid stenosis was studied in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST). Both showed a substantial benefit for surgery in patients with stenosis of $\geq 70\%$. In NASCET, the average cumulative ipsilateral stroke risk at 2 years was 26% for patients treated medically and 9% for those receiving the same medical treatment plus a carotid endarterectomy. This 17% *absolute* reduction in the surgical group is a 65% *relative* risk reduction favoring surgery (Table 427-4). NASCET also showed a significant, although less robust, benefit for patients with 50–70% stenosis. ECST found harm for patients with stenosis $<30\%$ treated surgically.

A patient's risk of stroke and possible benefit from surgery are related to the presence of retinal versus hemispheric symptoms, degree of arterial stenosis, extent of associated medical conditions (of note, NASCET and ECST excluded "high-risk" patients with significant cardiac, pulmonary, or renal disease), institutional surgical morbidity and mortality, timing of surgery relative to symptoms, and other factors. A recent meta-analysis of the NASCET and ECST trials demonstrated that endarterectomy is most beneficial when performed within 2 weeks of symptom onset. In addition, benefit is more pronounced in patients >75 years, and men appear to benefit more than women.

In summary, a patient with recent symptomatic hemispheric ischemia, high-grade stenosis in the appropriate internal carotid artery, and an institutional perioperative morbidity and mortality rate of $\leq 6\%$ generally should undergo carotid endarterectomy. If the perioperative stroke rate is $>6\%$ for any particular surgeon, however, the benefits of carotid endarterectomy are questionable.

The indications for surgical treatment of *asymptomatic carotid disease* have been clarified by the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST). ACAS randomized asymptomatic patients with $\geq 60\%$ stenosis to medical treatment with aspirin or the same medical treatment plus carotid endarterectomy. The surgical group had a risk over 5 years for ipsilateral stroke (and any perioperative stroke or death) of 5.1%, compared to a risk in the medical group of 11%. Although this demonstrates a 53% *relative* risk reduction, the *absolute* risk reduction is only 5.9% over 5 years, or 1.2% annually (Table 427-4). Nearly one-half of the strokes in the surgery group were caused by preoperative angiograms. ACST randomized asymptomatic patients with $>60\%$ carotid stenosis to endarterectomy or medical therapy. The 5-year risk of stroke in the surgical group (including perioperative stroke or death) was 6.4%, compared to 11.8% in the medically treated group (46% *relative* risk reduction and 5.4% *absolute* risk reduction).

In both ACAS and ACST, the perioperative complication rate was higher in women, perhaps negating any benefit in the reduction of stroke risk within 5 years. It is possible that with longer follow-up, a clear benefit in women will emerge. At present, carotid endarterectomy in asymptomatic women remains particularly controversial.

In summary, the natural history of asymptomatic stenosis is an $\sim 2\%$ per year stroke rate, whereas symptomatic patients experience

a 13% per year risk of stroke. Whether to recommend carotid revascularization for an asymptomatic patient is somewhat controversial and depends on many factors, including patient preference, degree of stenosis, age, gender, and comorbidities. Medical therapy for reduction of atherosclerosis risk factors, including cholesterol-lowering agents and antiplatelet medications, is generally recommended for patients with asymptomatic carotid stenosis. As with atrial fibrillation, it is imperative to counsel the patient about TIAs so that therapy can be revised if symptoms develop.

ENDOVASCULAR THERAPY

Balloon angioplasty coupled with stenting is being used with increasing frequency to open stenotic carotid arteries and maintain their patency. These techniques can treat carotid stenosis not only at the bifurcation but also near the skull base and in the intracranial segments. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized high-risk patients (defined as patients with clinically significant coronary or pulmonary disease, contralateral carotid occlusion, restenosis after endarterectomy, contralateral laryngeal-nerve palsy, prior radical neck surgery or radiation, or age >80) with symptomatic carotid stenosis $>50\%$ or asymptomatic stenosis $>80\%$ to either stenting combined with a distal emboli-protection device or endarterectomy. The risk of death, stroke, or MI within 30 days and ipsilateral stroke or death within 1 year was 12.2% in the stenting group and 20.1% in the endarterectomy group ($p = .055$), suggesting that stenting is at the very least comparable to endarterectomy as a treatment option for this patient group at high risk of surgery. However, the outcomes with both interventions may not have been better than leaving the carotid stenoses untreated, particularly for the asymptomatic patients, and much of the benefit seen in the stenting group was due to a reduction in periprocedure MI. Two randomized trials comparing stents to endarterectomy in lower-risk patients have been published. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) enrolled patients with either asymptomatic or symptomatic stenosis. The 30-day risk of stroke was 4.1% in the stent group and 2.3% in the surgical group, but the 30-day risk of MI was 1.1% in the stent group and 2.3% in the surgery group, suggesting relative equivalence of risk between the procedures. At median follow-up of 2.5 years, the combined endpoint of stroke, MI, and death was the same (7.2% stent vs 6.8% surgery) and remained so at 10-year follow-up. The rate of restenosis at 2 years was also similar in both groups. The International Carotid Stenting Study (ICSS) randomized symptomatic patients to stents versus endarterectomy and found a different result: at 120 days, the incidence of stroke, MI, or death was 8.5% in the stenting group versus 5.2% in the endarterectomy group ($p = .006$). At median follow-up of 5 years, these differences were no longer significant except a small increase in nondisabling stroke in the stenting group but no change in the average disability. In meta-analysis, carotid endarterectomy (CEA) is less morbid in older patients (aged ≥ 70) than is stenting. Investigation is ongoing in asymptomatic patients to compare medical therapy to stenting and CEA. This will likely answer how well medical patients do with more modern medical therapy (statins, close blood pressure control, and lifestyle modification).

BYPASS SURGERY

Extracranial-to-intracranial (EC-IC) bypass surgery has been proven ineffective for atherosclerotic stenoses that are inaccessible to conventional CEA. In patients with recent stroke, an associated carotid occlusion, and evidence of inadequate perfusion of the brain as measured with positron emission tomography, no benefit from EC-IC bypass was found in a trial stopped for futility.

PATENT FORAMEN OVALE (PFO)

In patients with PFO and/or atrial septal aneurysm with an embolic stroke and no other cause identified, three randomized trials using various endovascular closure devices individually and in meta-analysis report a significant (1% per year) reduction in second

stroke compared to antiplatelet agents. If the neurological opinion is that no other source of stroke is identified and consultation with a cardiologist knowledgeable about PFO closure supports intervention, we recommend endovascular PFO closure.

INTRACRANIAL ATHEROSCLEROSIS

The WASID trial randomized patients with symptomatic stenosis (50–99%) of a major intracranial vessel to either high-dose aspirin (1300 mg/d) or warfarin (target INR, 2.0–3.0), with a combined primary endpoint of ischemic stroke, brain hemorrhage, or death from vascular cause other than stroke. The trial was terminated early because of an increased risk of adverse events related to warfarin anticoagulation. With a mean follow-up of 1.8 years, the primary endpoint was seen in 22.1% of patients in the aspirin group and 21.8% of the warfarin group. Death from any cause was seen in 4.3% of the aspirin group and 9.7% of the warfarin group; 3.2% of patients on aspirin experienced major hemorrhage, compared to 8.3% of patients taking warfarin.

Intracranial stenting of intracranial atherosclerosis was found to be dramatically harmful compared to aspirin in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRISS) trial. This trial enrolled newly symptomatic TIA or minor stroke patients with associated 70–99% intracranial stenosis to primary stenting with a self-expanding stent or to medical management. Both groups received clopidogrel, aspirin, statin, and aggressive control of blood pressure. The endpoint of stroke or death occurred in 14.7% of the stented group and 5.8% of the medically treated groups ($p = .002$). This low rate of second stroke was significantly lower than in the WASID trial and suggests that aggressive medical management had a marked influence on secondary stroke risk. A concomitant study of balloon-expandable stenting was halted early at 125 patients because of the negative SAMMPRISS results and due to harm. Therefore, routine use of intracranial stenting is harmful, and medical therapy is superior for intracranial atherosclerosis.

Dural Sinus Thrombosis. Limited evidence exists to support short-term use of anticoagulants, regardless of the presence of intracranial hemorrhage, for venous infarction following sinus thrombosis. The long-term outcome for most patients, even those with intracerebral hemorrhage, is excellent.

FURTHER READING

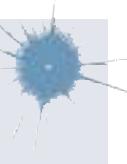
- G M et al: Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* 387:1723, 2016.
- G JC et al: Prospective, multicenter, controlled trial of mobile stroke units. *N Engl J Med* 385:971, 2021.
- J CT et al: 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 74:104, 2019.
- L SC et al: Prognosis of carotid dissecting aneurysms: Results from CADISS and a systematic review. *Neurology* 88:646, 2017.
- O P et al: Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 75:3122, 2020.
- P WJ et al: Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 50:e344, 2019.
- S JL et al: Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA* 316:1279, 2016.
- S R G et al: A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 373:2103, 2015.
- T MT et al: Evidence-based guidelines for the management of large hemispheric infarction: A statement for health care professionals

from the Neurocritical Care Society and the German Society for Neuro-intensive Care and Emergency Medicine. *Neurocrit Care* 22:146, 2015.

428

Intracranial Hemorrhage

Wade S. Smith, J. Claude Hemphill, III,
S. Claiborne Johnston



Intracranial hemorrhage is a form of stroke (see Chap. 426). Compared to ischemic stroke, patients with intracranial hemorrhage are more likely to present with headache; however, brain imaging is required to distinguish these entities. CT imaging of the head is highly sensitive and specific for intracranial hemorrhage and determines the location(s) of bleeding. Hemorrhages are classified by their location and the underlying vascular pathology. Hemorrhage directly into the brain parenchyma, also known as intracerebral hemorrhage (ICH), and arteriovenous malformations (AVMs) of the brain will be considered here. Other categories of hemorrhage include bleeding into subdural and epidural spaces, usually caused by trauma (Chap 443), and subarachnoid hemorrhage due to trauma or the rupture of an intracranial aneurysm (Chap. 429).

DIAGNOSIS

Intracranial hemorrhage is often identified on noncontrast CT imaging of the brain during the acute evaluation of stroke. Because CT is more widely available and may be logically easier to perform than MRI, CT imaging is generally the preferred method for acute stroke evaluation (Fig. 428-1). The location of the hemorrhage narrows the differential diagnosis to a few entities. Table 428-1 lists the causes and anatomic spaces involved in hemorrhages.

EMERGENCY MANAGEMENT

Close attention should be paid to airway management because a reduction in the level of consciousness is common and often progressive. The initial blood pressure should be maintained until the results of the

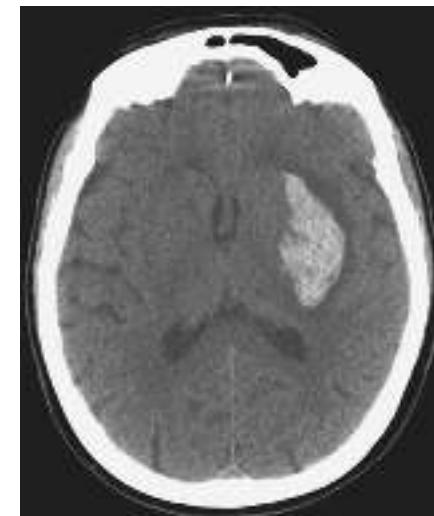


FIGURE 428-1 Hypertensive hemorrhage. Transaxial noncontrast computed tomography scan through the region of the basal ganglia reveals a hematoma involving the left putamen in a patient with rapidly progressive onset of right hemiparesis.

TABLE 428-1 Causes of Intracranial Hemorrhage

CAUSE	LOCATION	COMMENTS
Head trauma	Intraparenchymal: frontal lobes, anterior temporal lobes; subarachnoid; extra-axial (subdural, epidural)	Coup and contrecoup injury during brain deceleration
Hypertensive hemorrhage	Putamen, globus pallidus, thalamus, cerebellar hemisphere, pons	Chronic hypertension produces hemorrhage from small (~30–100 µm) vessels in these regions
Transformation of prior ischemic infarction	Basal ganglion, subcortical regions, lobar	Occurs in 1–6% of ischemic strokes with predilection for large hemispheric infarctions
Metastatic brain tumor	Lobar	Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma
Coagulopathy	Any	Risk for ongoing hematoma expansion
Drug	Any, lobar, subarachnoid	Cocaine, amphetamine
Arteriovenous malformation	Lobar, intraventricular, subarachnoid	Risk is ~2–3% per year for bleeding if previously unruptured
Aneurysm	Subarachnoid, intraparenchymal, rarely subdural	Mycotic and nonmycotic forms of aneurysms
Amyloid angiopathy	Lobar	Degenerative disease of intracranial vessels; associated with dementia, rare in patients <60 years
Cavernous angioma	Intraparenchymal	Multiple cavernous angiomas linked to mutations in <i>KRIT1</i> , <i>CCM2</i> , and <i>PDCD10</i> genes
Dural arteriovenous fistula	Lobar, subarachnoid	Produces bleeding by venous hypertension
Dural sinus thrombosis	Along sagittal sinus, posterior temporal/inferior parietal	Sagittal sinus thrombosis can cause hemispheric parasagittal hemorrhage with edema; vein of Labbé occlusion from transverse sinus occlusion produces posterior temporal/inferior parietal hemorrhage
Capillary telangiectasias	Usually brainstem	Rare cause of hemorrhage

CT scan are reviewed and demonstrate ICH. In theory, a higher blood pressure should promote hematoma expansion, but it remains unclear if lowering of blood pressure reduces hematoma growth. Recent clinical trials have shown that systolic blood pressure (SBP) can be safely lowered acutely and rapidly to <140 mmHg in patients with spontaneous ICH whose initial SBP was 150–220 mmHg. The INTERACT2 trial was a large phase 3 clinical trial to address the effect of acute blood pressure lowering on ICH functional outcome. INTERACT2 randomized patients with spontaneous ICH within 6 h of onset and a baseline SBP of 150–220 mmHg to two different SBP targets (<140 and <180 mmHg). In those with the target SBP <140 mmHg, 52% had an outcome of death or major disability at 90 days compared with 55.6% of those with a target SBP <180 mmHg ($p = .06$). There was a significant shift to improved outcomes in the lower blood pressure arm, whereas both groups had a similar mortality. ATACH2 was a similarly designed clinical trial that assessed the same blood pressure targets but demonstrated no difference in outcome between groups. Current U.S. and European guidelines emphasize that blood pressure lowering to a target SBP is likely safe and possibly beneficial. However, these guidelines were completed prior to publication of the ATACH2 results; thus, the specific optimal target remains a point of debate. It is unclear whether these clinical trial results apply to patients who have higher SBP on

presentation or who are deeply comatose with possible elevated intracranial pressure (ICP). In patients who have ICP monitors in place, current recommendations are that maintaining the cerebral perfusion pressure (mean arterial pressure [MAP] minus ICP) at 50–70 mmHg is reasonable, depending on the individual patient's cerebral autoregulation status (Chap. 307). Blood pressure should be lowered with nonvasodilating IV drugs such as nicardipine, labetalol, or esmolol. Patients with cerebellar hemorrhages with depressed mental status or radiographic evidence of hydrocephalus should undergo urgent neurosurgical evaluation; these patients require close monitoring because they can deteriorate rapidly. Based on the clinical examination and CT findings, further imaging studies may be necessary, including MRI or conventional x-ray angiography. Stuporous or comatose patients with clinical and imaging signs of herniation are generally treated presumptively for elevated ICP with tracheal intubation and sedation, administration of osmotic diuretics such as mannitol or hypertonic saline, and elevation of the head of the bed while surgical consultation is obtained (Chap. 307). Reversal of coagulopathy and consideration of surgical evacuation of the hematoma (detailed below) are two other principal aspects of initial emergency management.

■ INTRACEREBRAL HEMORRHAGE

ICH accounts for ~10% of all strokes, and ~35–45% of patients die within the first month. Incidence rates are particularly high in Asians and blacks. Hypertension, coagulopathy, sympathomimetic drugs (cocaine, methamphetamine), and cerebral amyloid angiopathy (CAA) cause most of these hemorrhages. Advanced age, heavy alcohol, and low-dose aspirin use in those without symptomatic cardiovascular disease increase the risk, and cocaine or methamphetamine use is one of the most important causes in the young.

Hypertensive ICH • PATHOPHYSIOLOGY Hypertensive ICH usually results from spontaneous rupture of a small penetrating artery deep in the brain. The most common sites are the basal ganglia (especially the putamen), thalamus, cerebellum, and pons. The small arteries in these areas seem most prone to hypertension-induced vascular injury. When hemorrhages occur in other brain areas or in nonhypertensive patients, greater consideration should be given to other causes such as hemorrhagic disorders, neoplasms, vascular malformations, vasculitis, and CAA. The hemorrhage may be small, or a large clot may form and compress adjacent tissue, causing herniation and death. Blood may also dissect into the ventricular space, which substantially increases morbidity and may cause hydrocephalus.

Most hypertensive ICHs initially develop over 30–90 min, whereas those associated with anticoagulant therapy may evolve for as long as 24–48 h. It is now recognized that about a third of patients even with no coagulopathy may have significant hematoma expansion with the first day. Within 48 h, macrophages begin to phagocytize the hemorrhage at its outer surface. After 1–6 months, the hemorrhage is generally resolved to a slitlike cavity lined with a glial scar and hemosiderin-laden macrophages.

CLINICAL MANIFESTATIONS ICH generally presents as the abrupt onset of a focal neurologic deficit. Seizures are uncommon. Although clinical symptoms may be maximal at onset, more commonly, the focal deficit worsens over 30–90 min and is associated with a diminishing level of consciousness and signs of increased ICP such as headache and vomiting.

The putamen is the most common site for hypertensive hemorrhage, and the adjacent internal capsule is usually damaged (Fig. 428-1). Contralateral hemiparesis is therefore the sentinel sign. When mild, the face sags on one side over 5–30 min, speech becomes slurred, the arm and leg gradually weaken, and the eyes deviate away from the side of the hemiparesis. The paralysis may worsen until the affected limbs become flaccid or extend rigidly. When hemorrhages are large, drowsiness gives way to stupor as signs of upper brainstem compression appear. Coma ensues, accompanied by deep, irregular, or intermittent respiration, a dilated and fixed ipsilateral pupil, and decerebrate rigidity. In milder cases, edema in adjacent brain tissue may cause progressive deterioration over 12–72 h.

Thalamic hemorrhages also produce a contralateral hemiplegia or hemiparesis from pressure on, or dissection into, the adjacent internal capsule. A prominent sensory deficit involving all modalities is usually present. Aphasia, often with preserved verbal repetition, may occur after hemorrhage into the dominant thalamus, and constructional apraxia or mutism occurs in some cases of nondominant hemorrhage. There may also be a homonymous visual field defect. Thalamic hemorrhages cause several typical ocular disturbances by extension inferiorly into the upper midbrain. These include deviation of the eyes downward and inward so that they appear to be looking at the nose, unequal pupils with absence of light reaction, skew deviation with the eye opposite the hemorrhage displaced downward and medially, ipsilateral Horner's syndrome, absence of convergence, paralysis of vertical gaze, and retraction nystagmus. Patients may later develop a chronic, contralateral pain syndrome (Déjérine-Roussy syndrome).

In pontine hemorrhages, deep coma with quadriplegia often occurs over a few minutes. Typically, there is prominent decerebrate rigidity and "pinpoint" (1 mm) pupils that react to light. There is impairment of reflex horizontal eye movements evoked by head turning (doll's-head or oculocephalic maneuver) or by irrigation of the ears with ice water (Chap. 28). Hyperpnea, severe hypertension, and hyperhidrosis are common. Most patients with deep coma from pontine hemorrhage ultimately die or develop a locked-in state, but small hemorrhages are compatible with survival and significant recovery.

Cerebellar hemorrhages usually develop over several hours and are characterized by occipital headache, repeated vomiting, and ataxia of gait. In mild cases, there may be no other neurologic signs except for gait ataxia. Dizziness or vertigo may be prominent. There is often paresis of conjugate lateral gaze toward the side of the hemorrhage, forced deviation of the eyes to the opposite side, or an ipsilateral sixth nerve palsy. Less frequent ocular signs include blepharospasm, involuntary closure of one eye, ocular bobbing, and skew deviation. Dysarthria and dysphagia may occur. As the hours pass, the patient often becomes stuporous and then comatose from brainstem compression or obstructive hydrocephalus; immediate surgical evacuation before severe brainstem compression occurs may be lifesaving. Hydrocephalus from fourth ventricle compression can be relieved by external ventricular drainage; however, in this situation, definitive hematoma evacuation is recommended rather than treatment with ventricular drainage alone. If the deep cerebellar nuclei are spared, full recovery is common.

Lobar Hemorrhage The major neurologic deficit with an occipital hemorrhage is hemianopsia; with a left temporal hemorrhage, aphasia and delirium; with a parietal hemorrhage, hemisensory loss; and with frontal hemorrhage, arm weakness. Large hemorrhages may be associated with stupor or coma if they compress the thalamus or midbrain. Most patients with lobar hemorrhages have focal headaches, and more than one-half vomit or are drowsy. Stiff neck and seizures are uncommon.

Other Causes of ICH CAA is a disease of the elderly in which arteriolar degeneration occurs and amyloid is deposited in the walls of the cerebral arteries. Amyloid angiopathy causes both single and recurrent lobar hemorrhages and is probably the most common cause of lobar hemorrhage in the elderly. It accounts for some intracranial hemorrhages associated with IV thrombolysis given for myocardial infarction. This disorder can be suspected in patients who present with multiple hemorrhages (and infarcts) over several months or years or in patients with "microbleeds" in the cortex, seen on brain MRI sequences sensitive for hemosiderin (iron-sensitive imaging), but it is definitively diagnosed by pathologic demonstration of Congo red staining of amyloid in cerebral vessels. The ε2 and ε4 allelic variations of the apolipoprotein E gene are associated with increased risk of recurrent lobar hemorrhage and may therefore be markers of amyloid angiopathy. Positron emission tomography imaging can image amyloid-beta deposits in CAA using specific antibody labels and may be helpful in diagnosing CAA noninvasively. Although cerebral biopsy is the most definitive method of diagnosis, evidence of inflammation on lumbar puncture should prompt consideration of CAA-associated vasculitis

as an underlying cause, and oral glucocorticoids may be beneficial. Noninflammatory CAA has no specific treatment. Oral anticoagulants are typically avoided.

Cocaine and methamphetamine are frequent causes of stroke in young (age <45 years) patients. ICH, ischemic stroke, and subarachnoid hemorrhage (SAH) are all associated with stimulant use. Angiographic findings vary from completely normal arteries to large-vessel occlusion or stenosis, vasospasm, or changes consistent with vasculopathy. The mechanism of sympathomimetic-related stroke is not known, but cocaine enhances sympathetic activity causing acute, sometimes severe, hypertension, and this may lead to hemorrhage. Slightly more than one-half of stimulant-related intracranial hemorrhages are intracerebral and the rest are subarachnoid. In cases of SAH, a saccular aneurysm is usually identified. Presumably, acute hypertension causes aneurysmal rupture.

Head injury often causes intracranial bleeding. The common sites are intraparenchymal (especially temporal and inferior frontal lobes) and into the subarachnoid, subdural, and epidural spaces. Trauma must be considered in any patient with an unexplained acute neurologic deficit (hemiparesis, stupor, or confusion), particularly if the deficit occurred in the context of a fall (Chap. 443).

Intracranial hemorrhages associated with *anticoagulant therapy* can occur at any location; they are often lobar or subdural. Anticoagulant-related ICHs may continue to evolve over 24–48 h, especially if coagulopathy is insufficiently reversed. Coagulopathy and thrombocytopenia should be reversed rapidly, as discussed below. ICH associated with *hematologic disorders* (leukemia, aplastic anemia, thrombocytopenic purpura) can occur at any site and may present as multiple ICHs. Skin and mucous membrane bleeding may be evident and offers a diagnostic clue.

Hemorrhage into a *brain tumor* may be the first manifestation of neoplasm. Choriocarcinoma, malignant melanoma, renal cell carcinoma, and bronchogenic carcinoma are among the most common metastatic tumors associated with ICH. Glioblastoma multiforme in adults and medulloblastoma in children may also have areas of ICH.

Hypertensive encephalopathy is a complication of malignant hypertension. In this acute syndrome, severe hypertension is associated with headache, nausea, vomiting, convulsions, confusion, stupor, and coma. Focal or lateralizing neurologic signs, either transitory or permanent, may occur but are infrequent and therefore suggest some other vascular disease (hemorrhage, embolism, or atherosclerotic thrombosis). There are retinal hemorrhages, exudates, papilledema (hypertensive retinopathy), and evidence of renal and cardiac disease. In most cases, ICP and CSF protein levels are elevated. MRI brain imaging shows a pattern of typically posterior (occipital > frontal) brain edema that is reversible and termed *reversible posterior leukoencephalopathy*. The hypertension may be essential or due to chronic renal disease, acute glomerulonephritis, acute toxemia of pregnancy, pheochromocytoma, or other causes. Lowering the blood pressure reverses the process, but stroke can occur, especially if blood pressure is lowered too rapidly. Neuropathologic examination reveals multifocal to diffuse cerebral edema and hemorrhages of various sizes from petechial to massive. Microscopically, there is necrosis of arterioles, minute cerebral infarcts, and hemorrhages. The term *hypertensive encephalopathy* should be reserved for this syndrome and not for chronic recurrent headaches, dizziness, recurrent transient ischemic attacks, or small strokes that often occur in association with high blood pressure. Distinguishing hypertensive encephalopathy with ICH from hypertensive ICH is important since aggressive lowering of SBP to 140–180 mmHg acutely is usually considered in hypertensive ICH, but less aggressive measures should be used in hypertensive encephalopathy. Having no alteration in mental status or other prodrome prior to the ICH favors hypertensive ICH as the disease.

Primary intraventricular hemorrhage is rare and should prompt investigation for an underlying vascular anomaly. Sometimes bleeding begins within the periventricular substance of the brain and dissests into the ventricular system without leaving signs of intraparenchymal hemorrhage. Alternatively, bleeding can arise from periependymal veins. Vasculitis, usually polyarteritis nodosa or lupus

erythematosus, can produce hemorrhage in any region of the central nervous system; most hemorrhages are associated with hypertension, but the arteritis itself may cause bleeding by disrupting the vessel wall. Nearly one-half of patients with primary intraventricular hemorrhage have identifiable bleeding sources seen using conventional angiography.

Venous sinus thrombosis (Chap. 427) causes cortical vein hypertension, cerebral edema, and venous infarction. This may progress to cause ICH surrounding the region of the occluded cerebral venous sinus or within the drainage region of the vein of Labbé, producing a posterior temporal inferior parietal hematoma. Despite the presence of hemorrhage, IV anticoagulation is helpful to reduce the venous hypertension and limit venous ischemia and further ICH.

Sepsis can cause small petechial hemorrhages throughout the cerebral white matter. *Moyamoya disease* (Chap. 427), mainly an occlusive arterial disease that causes ischemic symptoms, may on occasion produce ICH, particularly in the young. Hemorrhages into the spinal cord are usually the result of an AVM, cavernous malformation, or metastatic tumor. *Epidural spinal hemorrhage* produces a rapidly evolving syndrome of spinal cord or nerve root compression (Chap. 442). Spinal hemorrhages usually present with sudden back pain and some manifestation of myelopathy.

Laboratory and Imaging Evaluation Patients should have routine blood chemistries and hematologic studies. Specific attention to the platelet count, prothrombin time, partial thromboplastin time, and international normalized ratio is important to identify coagulopathy. CT imaging reliably detects acute focal hemorrhages in the supratentorial space. Rarely, very small pontine or medullary hemorrhages may not be well delineated because of motion and bone-induced artifact that obscure structures in the posterior fossa. After the first 2 weeks, x-ray attenuation values of clotted blood diminish until they become isodense with surrounding brain. Mass effect and edema may remain. In some cases, a surrounding rim of contrast enhancement appears after 2–4 weeks and may persist for months. MRI, although more sensitive for delineating posterior fossa lesions, is generally not necessary for primary diagnosis. Images of flowing blood on MRI scan may identify AVMs as the cause of the hemorrhage. MRI, CT angiography (CTA), and conventional x-ray angiography are used when the cause of intracranial hemorrhage is uncertain, particularly if the patient is young or not hypertensive and the hematoma is not in one of the usual sites for hypertensive hemorrhage. CTA or postcontrast CT imaging may reveal one or more small areas of enhancement within a hematoma; this “spot sign” is thought to represent ongoing bleeding. The presence of a spot sign is associated with an increased risk of hematoma expansion, increased mortality, and lower likelihood of favorable functional outcome. Because patients typically have focal neurologic signs and obtundation and often show signs of increased ICP, a lumbar puncture is generally unnecessary and should usually be avoided because it may induce cerebral herniation.

TREATMENT

Intracerebral Hemorrhage

ACUTE MANAGEMENT

After immediate attention to blood pressure and airway protection (see above), focus can switch to medical and surgical management. Approximately 40% of patients with a hypertensive ICH die, but survivors can have a good to complete recovery. The ICH Score (Table 428-2) is a validated clinical grading scale that is useful for stratification of mortality risk and clinical outcome. However, a specific ICH clinical grading scale should not be used to precisely prognosticate outcome because of the concern of creating a self-fulfilling prophecy of poor outcome if early aggressive care is withheld. Any identified coagulopathy should be corrected as soon as possible. For patients taking vitamin K antagonists (VKAs), rapid correction of coagulopathy can be achieved by infusing prothrombin complex concentrates (PCCs), which can be administered quickly, with vitamin

TABLE 428-2 The ICH Score

CLINICAL OR IMAGING FACTOR	POINT SCORE
Age	
<80 years	0
≥80 years	1
Hematoma Volume	
<30 cc	0
≥30 cc	1
Intraventricular Hemorrhage Present	
No	0
Yes	1
Infratentorial Origin of Hemorrhage	
No	0
Yes	1
Glasgow Coma Scale Score	
13–15	0
5–12	1
3–4	2
Total Score	0–6 Sum of each category above

Source: Reproduced with permission from JC Hemphill 3rd et al: The ICH score: A simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 32:891, 2001.

K administered concurrently. Fresh frozen plasma (FFP) is an alternative, but since it requires larger fluid volumes and longer time to achieve adequate reversal than PCC, it is not recommended if PCC is available. Idarucizumab is a monoclonal antibody to dabigatran, and the administration of two doses reverses the anticoagulation effect of dabigatran quickly. The oral Xa inhibitors apixaban and rivaroxaban can be reversed with andexanet alfa. PCC may partially reverse the effects of oral factor Xa inhibitors and are reasonable to administer if andexanet alfa is not available. When ICH is associated with thrombocytopenia (platelet count <50,000/ μ L), transfusion of fresh platelets is indicated. A clinical trial of platelet transfusions in patients with ICH and without thrombocytopenia who were taking antiplatelet drugs showed no benefit and possible harm.

Hematomas may expand for several hours following the initial hemorrhage, even in patients without coagulopathy. The precise mechanism is unclear. A phase 3 trial of treatment with recombinant factor VIIa reduced hematoma expansion; however, clinical outcomes were not improved, so use of this drug is not recommended. Blood pressure lowering has been considered due to the theoretical risk of acutely elevated blood pressure on hematoma expansion, although clinical trials did not find a difference in hematoma expansion between the SBP targets of 140–180 mmHg. In deep hemorrhages that involve the basal ganglia, more intensive blood pressure lowering reduced hematoma expansion but had no effect on functional outcome.

Evacuation of supratentorial hematomas does not appear to improve outcome for most patients. The International Surgical Trial in Intracerebral Haemorrhage (STICH) randomized patients with supratentorial ICH to either early surgical evacuation or initial medical management. No benefit was found in the early surgery arm, although analysis was complicated by the fact that 26% of patients in the initial medical management group ultimately had surgery for neurologic deterioration. The follow-up study, STICH-II, found that surgery within 24 h of lobar supratentorial hemorrhage did not improve overall outcome but might have a role in select severely affected patients. Therefore, existing data do not support routine surgical evacuation of supratentorial hemorrhages in stable patients. However, many centers still consider surgery for patients deemed salvageable and who are experiencing progressive neurologic deterioration due to herniation. Surgical techniques continue to evolve. A minimally invasive endoscopic hematoma evacuation followed by thrombolysis with the aim of decreasing clot

size has not been shown to improve outcome in clinical trials. The administration of tranexamic acid was not found to alter outcome in a large randomized trial.

For cerebellar hemorrhages, a neurosurgeon should be consulted immediately to assist with the evaluation; most cerebellar hematomas >3 cm in diameter will require surgical evacuation. If the patient is alert without focal brainstem signs and if the hematoma is <1 cm in diameter, surgical removal is usually unnecessary. Patients with hematomas between 1 and 3 cm require careful observation for signs of impaired consciousness, progressive hydrocephalus, and precipitous respiratory failure. Hydrocephalus due to cerebellar hematoma requires surgical evacuation and should not be treated solely with ventricular drainage.

Tissue surrounding hematomas is displaced and compressed but not necessarily infarcted. Hence, in survivors, major improvement commonly occurs as the hematoma is reabsorbed and the adjacent tissue regains its function. Careful management of the patient during the acute phase of the hemorrhage can lead to considerable recovery.

Surprisingly, ICP is often normal even with large ICHs. However, if the hematoma causes marked midline shift of structures with consequent obtundation, coma, or hydrocephalus, osmotic agents can be instituted in preparation for placement of a ventriculostomy or parenchymal ICP monitor (Chap. 307). Once ICP is recorded, CSF drainage (if available), osmotic therapy, and blood pressure management can be tailored to maintain cerebral perfusion pressure (MAP minus ICP) at least 50–70 mmHg. For example, if ICP is found to be high, CSF can be drained from the ventricular space and osmotic therapy continued; persistent or progressive elevation in ICP may prompt surgical evacuation of the clot. Alternately, if ICP is normal or only mildly elevated, interventions such as osmotic therapy may be tapered. Because hyperventilation may actually produce ischemia by cerebral vasoconstriction, induced hyperventilation should be limited to acute resuscitation of the patient with presumptive high ICP and eliminated once other treatments (osmotic therapy or surgical treatments) have been instituted. Glucocorticoids are not helpful for the edema from intracerebral hematoma.

PREVENTION

Hypertension is the leading cause of primary ICH. Prevention is aimed at reducing chronic hypertension, eliminating excessive alcohol use, and discontinuing use of illicit drugs such as cocaine and amphetamines. Current guidelines recommend that patients with CAA should generally avoid oral anticoagulant medications, but antiplatelet agents may be administered if there is an indication based on atherothrombotic vascular disease.

VASCULAR ANOMALIES

Vascular anomalies can be divided into congenital vascular malformations and acquired vascular lesions.

■ CONGENITAL VASCULAR MALFORMATIONS

True AVMs, venous anomalies, and capillary telangiectasias are lesions that usually remain clinically silent through life. AVMs are probably congenital, but cases of acquired lesions have been reported.

True AVMs are congenital shunts between the arterial and venous systems that may present with headache, seizures, and intracranial hemorrhage. AVMs consist of a tangle of abnormal vessels across the cortical surface or deep within the brain substance. AVMs vary in size from a small blemish a few millimeters in diameter to a large mass of tortuous channels composing an arteriovenous shunt of sufficient magnitude to raise cardiac output and precipitate heart failure. Blood vessels forming the tangle interposed between arteries and veins are usually abnormally thin and histologically resemble both arteries and veins. AVMs occur in all parts of the cerebral hemispheres, brainstem,

and spinal cord, but the largest ones are most frequently located in the posterior half of the hemispheres, commonly forming a wedge-shaped lesion extending from the cortex to the ventricle.

Bleeding, headache, and seizures are most common between the ages of 10 and 30, occasionally as late as the fifties. AVMs are more frequent in men, and rare familial cases have been described. Familial AVM may be a part of the autosomal dominant syndrome of hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber) syndrome due to mutations in either endoglin or activin receptor-like kinase 1, both involved in transforming growth factor (TGF) signaling and angiogenesis.

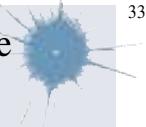
Headache (without bleeding) may be hemicranial and throbbing, like migraine, or diffuse. Focal seizures, with or without generalization, occur in ~30% of cases. One-half of AVMs become evident as ICHs. In most, the hemorrhage is mainly intraparenchymal with extension into the subarachnoid space in some cases. Unlike primary SAHs (Chap. 429), blood from a ruptured AVM is usually not deposited in the basal cisterns, and symptomatic cerebral vasospasm is rare. The risk of AVM rupture is strongly influenced by a history of prior rupture. Although unruptured AVMs have a hemorrhage rate of ~2–4% per year, previously ruptured AVMs may have a rate as high as 17% a year, at least for the first year. Hemorrhages may be massive, leading to death, or may be as small as 1 cm in diameter, leading to minor focal symptoms or no deficit. The AVM may be large enough to steal blood away from adjacent normal brain tissue or to increase venous pressure significantly to produce venous ischemia locally and in remote areas of the brain. This is seen most often with large AVMs in the territory of the middle cerebral artery.

Large AVMs of the anterior circulation may be associated with a systolic and diastolic bruit (sometimes self-audible) over the eye, forehead, or neck and a bounding carotid pulse. Headache at the onset of AVM rupture is generally not as explosive as with aneurysmal rupture. MRI is better than CT for diagnosis, although noncontrast CT scanning sometimes detects calcification of the AVM and contrast may demonstrate the abnormal blood vessels. Once identified, conventional x-ray angiography is the gold standard for evaluating the precise anatomy of the AVM.

Surgical treatment of AVMs presenting with hemorrhage, often done in conjunction with preoperative embolization to reduce operative bleeding, is usually indicated for accessible lesions. Stereotactic radiosurgery, an alternative to conventional surgery, can produce a slow sclerosis of the AVM over 2–3 years.

Several angiographic features can be used to help predict future bleeding risk. Paradoxically, smaller lesions seem to have a higher hemorrhage rate. The presence of deep venous drainage, venous outflow stenosis, and intranidal aneurysms may increase rupture risk. Because of the relatively low annual rate of hemorrhage and the risk of complications due to surgical or endovascular treatment, the indications for surgery in asymptomatic AVMs are uncertain. The ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) trial randomized patients to medical management versus intervention (surgery, endovascular embolization, combination embolization and surgery, or gamma-knife). The trial was stopped prematurely for harm, with the medical arm achieving the combined endpoint of death or symptomatic stroke in 10% of patients compared to 31% in the intervention group at a mean follow-up time of 33 months. This highly significant finding argues against routine intervention for patients presenting without hemorrhage, although debate ensues regarding the generalizability of these results.

Venous anomalies are the result of development of anomalous cerebral, cerebellar, or brainstem venous drainage. These structures, unlike AVMs, are functional venous channels. They are of little clinical significance and should be ignored if found incidentally on brain imaging studies. Surgical resection of these anomalies may result in venous infarction and hemorrhage. Venous anomalies may be associated with cavernous malformations (see below), which do carry some bleeding risk.



Capillary telangiectasias are true capillary malformations that often form extensive vascular networks through an otherwise normal brain structure. The pons and deep cerebral white matter are typical locations, and these capillary malformations can be seen in patients with hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber) syndrome. If bleeding does occur, it rarely produces mass effect or significant symptoms. No treatment options exist.

■ ACQUIRED VASCULAR LESIONS

Cavernous angiomas (cavernous malformations) are tufts of capillary sinusoids that form within the deep hemispheric white matter and brainstem with no normal intervening neural structures. The pathogenesis is unclear. Familial cavernous angiomas have been mapped to several different genes: *KRIT1*, *CCM2*, and *PDCD10*. Both *KRIT1* and *CCM2* have roles in blood vessel formation, whereas *PDCD10* is an apoptotic gene. Cavernous angiomas are typically <1 cm in diameter and are often associated with a venous anomaly. Bleeding is usually of small volume, causing slight mass effect only. The bleeding risk for single cavernous malformations is 0.7–1.5% per year and may be higher for patients with prior clinical hemorrhage or multiple malformations. Seizures may occur if the malformation is located near the cerebral cortex. Surgical resection eliminates bleeding risk and may reduce seizure risk, but it is usually reserved for those malformations that form near the brain surface. Radiation treatment has not been shown to be of benefit. Recent retrospective data show that intracranial hemorrhage from cavernous malformations is likely not increased with administration of antiplatelet and anticoagulant medications prescribed for other medical conditions.

Dural arteriovenous fistulas are acquired connections usually from a dural artery to a dural sinus. Patients may complain of a pulse-synchronous cephalic bruit ("pulsatile tinnitus") and headache. Depending on the magnitude of the shunt, venous pressures may rise high enough to cause cortical ischemia or venous hypertension and hemorrhage, particularly SAH. Surgical and endovascular techniques are usually curative. These fistulas may form because of trauma, but most are idiopathic. There is an association between fistulas and dural sinus thrombosis. Fistulas have been observed to appear months to years following venous sinus thrombosis, suggesting that angiogenesis factors elaborated from the thrombotic process may cause these anomalous connections to form. Alternatively, dural arteriovenous fistulas can produce venous sinus occlusion over time, perhaps from the high pressure and high flow through a venous structure.

■ FURTHER READING

- A CS et al: Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 368:2355, 2013.
- C H et al: European stroke organization guideline on reversal of oral anticoagulants in acute intracerebral hemorrhage. *Euro Stroke J* 4:294, 2019.
- F J et al: Guideline for reversal of antithrombotics in intracranial hemorrhage. A statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care* 24:6, 2016.
- H JC et al: Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 46:2032, 2015.
- M JP et al: Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): A multicentre, non-blinded, randomised trial. *Lancet* 383:614, 2014.
- S T et al: European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke* 9:840, 2014.

Subarachnoid hemorrhage (SAH) renders the brain critically ill from both primary and secondary brain insults. Excluding head trauma, the most common cause of SAH is rupture of a saccular aneurysm. Other causes include bleeding from a vascular malformation (arteriovenous malformation or dural arteriovenous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Some idiopathic SAHs are localized to the perimesencephalic cisterns and are benign; they probably have a venous or capillary source, and angiography is unrevealing.

■ SACCULAR "BERRY" ANEURYSM

Autopsy and angiography studies have found that ~2% of adults harbor intracranial aneurysms, for a prevalence of 4 million persons in the United States; the aneurysm will rupture, producing SAH, in 25,000–30,000 cases per year. The overall mortality rate for aneurysmal SAH is ~35%, with around one-third of these patients dying immediately and prior to hospital admission. Of those who survive, more than half are left with clinically significant neurologic deficits as a result of the initial hemorrhage, cerebral vasospasm with infarction, or hydrocephalus. If the patient survives but the aneurysm is not obliterated, the rate of rebleeding is ~20% in the first 2 weeks, 30% in the first month, and ~3% per year afterward. Given these alarming figures, the major therapeutic emphasis is on preventing the predictable early complications of the SAH.

Unruptured, asymptomatic aneurysms are much less dangerous than a recently ruptured aneurysm. The annual risk of rupture for aneurysms <10 mm in size is ~0.1%, and for aneurysms ≥10 mm in size is ~0.5–1%; the surgical morbidity rate far exceeds these percentages. Aneurysm location may also factor into risk, with basilar bifurcation aneurysms appearing to have a somewhat higher rupture risk. Because of the longer length of exposure to risk of rupture, younger patients with aneurysms >10 mm in size may benefit from prophylactic treatment. As with the treatment of asymptomatic carotid stenosis, this risk-benefit ratio strongly depends on the complication rate of treatment.

Giant aneurysms, those >2.5 cm in diameter, occur at the same sites (see below) as small aneurysms, and account for 5% of cases. The three most common locations are the terminal internal carotid artery, middle cerebral artery (MCA) bifurcation, and top of the basilar artery. Their risk of rupture is ~6% in the first year after identification and may remain high indefinitely. They often cause symptoms by compressing the adjacent brain or cranial nerves.

Mycotic aneurysms are usually located distal to the first bifurcation of major arteries of the circle of Willis. Most result from infected emboli due to bacterial endocarditis causing septic degeneration of arteries and subsequent dilation and rupture. Whether these lesions should be sought and repaired prior to rupture or left to heal spontaneously with antibiotic treatment remains controversial.

Pathophysiology Saccular aneurysms occur at the bifurcations of the large- to medium-sized intracranial arteries; rupture is into the subarachnoid space in the basal cisterns and sometimes into the parenchyma of the adjacent brain. Approximately 85% of aneurysms occur in the anterior circulation, mostly on the circle of Willis. About 20% of patients have multiple aneurysms, many at mirror sites bilaterally. As an aneurysm develops, it typically forms a neck with a dome. The length of the neck and the size of the dome vary greatly and are important factors in planning neurosurgical obliteration or endovascular embolization. The arterial internal elastic lamina disappears at the base of the neck. The media thins, and connective tissue replaces smooth-muscle cells. At the site of rupture (most often the dome), the wall thins, and the tear that allows bleeding is often ≤ 0.5 mm long.

Aneurysm size and site are important in predicting risk of rupture. Those >7 mm in diameter and those at the top of the basilar artery and at the origin of the posterior communicating artery are at greater risk of rupture.

Clinical Manifestations Most unruptured intracranial aneurysms are completely asymptomatic. Symptoms are usually due to rupture and resultant SAH, although some unruptured aneurysms present with mass effect on cranial nerves or brain parenchyma. At the moment of aneurysmal rupture with major SAH, the intracranial pressure (ICP) suddenly rises. This may account for the sudden transient loss of consciousness that occurs in nearly half of patients. Sudden loss of consciousness may be preceded by a brief moment of excruciating headache, but most patients first complain of headache upon regaining consciousness. In 10% of cases, aneurysmal bleeding is severe enough to cause loss of consciousness for several days. In ~45% of cases, severe headache associated with exertion is the presenting complaint. The patient often calls the headache “the worst headache of my life”; however, the most important characteristic is sudden onset. Occasionally, these ruptures may present as headache of only moderate intensity or as a change in the patient’s usual headache pattern. The headache is usually generalized, often with neck stiffness, and vomiting is common.

Although sudden headache in the absence of focal neurologic symptoms is the hallmark of aneurysmal rupture, focal neurologic deficits may occur. Anterior communicating artery or MCA bifurcation aneurysms may rupture into the adjacent brain or subdural space and form a hematoma large enough to produce mass effect. The deficits that result can include hemiparesis, aphasia, and mental slowness (abulia).

Occasionally, prodromal symptoms suggest the location of a progressively enlarging unruptured aneurysm. A third cranial nerve palsy, particularly when associated with pupillary dilation, loss of ipsilateral (but retained contralateral) light reflex, and focal pain above or behind the eye, may occur with an expanding aneurysm at the junction of the posterior communicating artery and the internal carotid artery. A sixth nerve palsy may indicate an aneurysm in the cavernous sinus, and visual field defects can occur with an expanding supraclinoid carotid or anterior cerebral artery (ACA) aneurysm. Occipital and posterior cervical pain may signal a posterior inferior cerebellar artery or anterior inferior cerebellar artery aneurysm (*Chap. 426*). Pain in or behind the eye and in the low temple can occur with an expanding MCA aneurysm. Thunderclap headache is a variant of migraine that simulates an SAH. Before concluding that a patient with sudden, severe headache has thunderclap migraine, a definitive workup for aneurysm or other intracranial pathology is required.

Aneurysms can undergo small ruptures and leaks of blood into the subarachnoid space, so-called *sentinel bleeds*. Sudden unexplained headache at any location should raise suspicion of SAH and be investigated because a major hemorrhage may be imminent.

The initial clinical manifestations of SAH can be graded using the Hunt-Hess or World Federation of Neurosurgical Societies classification schemes (*Table 429-1*). For ruptured aneurysms, prognosis for good outcomes falls as the grade increases. For example, it is unusual for a Hunt-Hess grade 1 patient to die if the aneurysm is treated, but the mortality rate for grade 4 and 5 patients may be as high as 60%.

Delayed Neurologic Deficits There are four major causes of delayed neurologic deficits: rerupture, hydrocephalus, delayed cerebral ischemia (DCI), and hyponatremia.

1. **Rerupture.** The incidence of rerupture of an untreated aneurysm in the first month following SAH is ~30%, with the peak in the first 7 days. Rerupture is associated with a 50% mortality rate and poor outcome. Early treatment eliminates this risk.

2. **Hydrocephalus.** Acute hydrocephalus can cause stupor and coma and can be mitigated by placement of an external ventricular drain. More often, subacute hydrocephalus may develop over a few days or weeks and causes progressive drowsiness or slowed mentation with incontinence. Hydrocephalus is differentiated from cerebral

TABLE 429-1 Grading Scales for Subarachnoid Hemorrhage

GRADE	HUNT-HESS SCALE	WORLD FEDERATION OF NEUROSURGICAL SOCIETIES (WFNS) SCALE
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS ^a score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS score 13–14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS score 13–14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS score 7–12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS score 3–6, with or without motor deficits

^aGlasgow Coma Scale; see Table 443-1.

vasospasm with a CT scan, CT angiogram, transcranial Doppler (TCD) ultrasound, or conventional x-ray angiography. Hydrocephalus may clear spontaneously or require temporary ventricular drainage. Chronic hydrocephalus may develop weeks to months after SAH and manifest as gait difficulty, incontinence, or impaired mentation. Subtle signs may be a lack of initiative in conversation or a failure to recover independence.

3. **Delayed cerebral ischemia.** Vasospasm is the narrowing of the arteries at the base of the brain following SAH. This may cause symptomatic ischemia and infarction in ~30% of patients and is the major cause of delayed morbidity and death. Signs of DCI appear 4–14 days after the hemorrhage, most often at 7 days. The severity and distribution of vasospasm determine whether infarction will occur.

- Vasospasm is believed to result from direct effects of clotted blood and its breakdown products on the arteries within the subarachnoid space. In general, the more blood that surrounds the arteries, the greater is the chance of symptomatic vasospasm. Spasm of major arteries produces symptoms referable to the appropriate vascular territory (*Chap. 426*). All of these focal symptoms may present abruptly, fluctuate, or develop over a few days. In most cases, focal spasm is preceded by a decline in mental status.

- Vasospasm of the large arteries can be detected reliably with conventional x-ray angiography, but this procedure is invasive and carries the risk of stroke and other complications. TCD ultrasound is based on the principle that the velocity of blood flow within an artery will rise as the lumen diameter is narrowed. By directing the probe along the MCA and proximal ACA, carotid terminus, and vertebral and basilar arteries on a daily or every-other-day basis, vasospasm can be reliably detected and treatments initiated to prevent cerebral ischemia (see below). CT angiography is another method that can detect vasospasm. The addition of CT perfusion imaging may help identify reversible ischemic deficits.

- Severe cerebral edema in patients with infarction from vasospasm may increase the ICP enough to reduce cerebral perfusion pressure. Treatment may include cerebrospinal fluid (CSF) drainage, mannitol or hypertonic saline, and, for intractable cases, hemicraniectomy; moderate hypothermia may have a role as well.

4. **Hyponatremia.** Hyponatremia may be profound and can develop quickly in the first 2 weeks following SAH. There is both natriuresis and volume depletion with SAH, so that patients become both hyponatremic and hypovolemic. Both atrial natriuretic peptide and brain natriuretic peptide have a role in producing this “cerebral salt-wasting syndrome.” Typically, it clears over the course of 1–2 weeks and, in the setting of SAH, should not be treated with free-water restriction as this may increase the risk of stroke (see below).

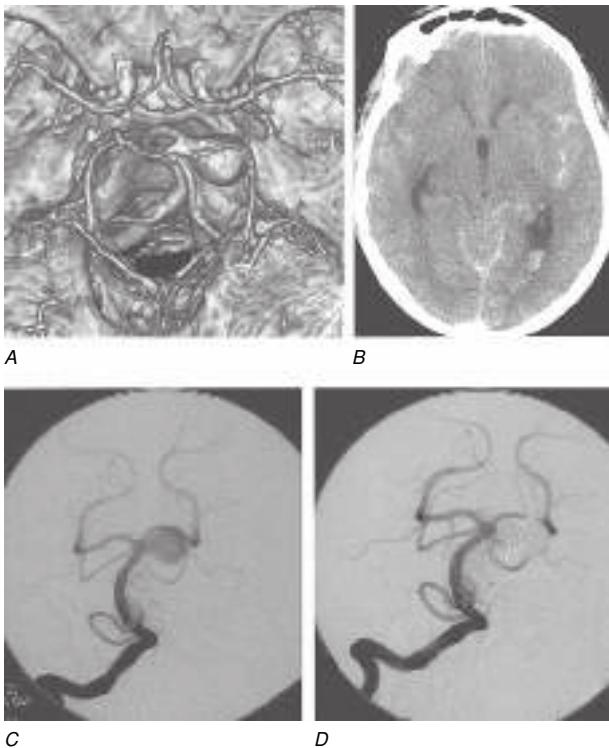


FIGURE 429-1 Subarachnoid hemorrhage. *A*, Computed tomography (CT) angiography revealing an aneurysm of the left superior cerebellar artery. *B*, Noncontrast CT scan at the level of the third ventricle revealing subarachnoid blood (bright) in the left sylvian fissure and within the left lateral ventricle. *C*, Conventional anteroposterior x-ray angiogram of the right vertebral and basilar artery showing the large aneurysm. *D*, Conventional angiogram following coil embolization of the aneurysm, whereby the aneurysm body is filled with platinum coils delivered through a microcatheter navigated from the femoral artery into the aneurysm neck.

Laboratory Evaluation and Imaging (Fig. 429-1) The hallmark of aneurysmal rupture is blood in the CSF. More than 95% of cases have enough blood to be visualized on a high-quality noncontrast CT scan obtained within 72 h. If the scan fails to establish the diagnosis of SAH and no mass lesion or obstructive hydrocephalus is found, a lumbar puncture should be performed to establish the presence of subarachnoid blood. Lysis of the red blood cells and subsequent conversion of hemoglobin to bilirubin stains the spinal fluid yellow within 6–12 h. This xanthochromic spinal fluid peaks in intensity at 48 h and lasts for 1–4 weeks, depending on the amount of subarachnoid blood.

The extent and location of subarachnoid blood on a noncontrast CT scan help locate the underlying aneurysm, identify the cause of any neurologic deficit, and predict the occurrence of vasospasm. A high incidence of symptomatic vasospasm in the MCA and ACA has been found when early CT scans show subarachnoid clots $>5 \times 3$ mm in the basal cisterns or layers of blood >1 mm thick in the cerebral fissures. CT scans less reliably predict vasospasm in the vertebral, basilar, or posterior cerebral arteries.

Lumbar puncture prior to an imaging procedure is indicated only if a CT scan is not available at the time of the suspected SAH. Once the diagnosis of hemorrhage from a ruptured saccular aneurysm is suspected, four-vessel conventional x-ray angiography (both carotids and both vertebrals) is generally performed to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist (Fig. 429-1C). At some centers, the ruptured aneurysm can be treated using endovascular techniques at the time of the initial angiogram as a way to expedite treatment and minimize the number of invasive procedures. CT angiography is an alternative method for locating the aneurysm and may be sufficient to plan definitive therapy.

Close monitoring (daily or twice daily) of electrolytes is important because hyponatremia can occur precipitously during the first 2 weeks following SAH (see above).

The electrocardiogram (ECG) frequently shows ST-segment and T-wave changes similar to those associated with cardiac ischemia. A prolonged QRS complex, increased QT interval, and prominent “peaked” or deeply inverted symmetric T waves are usually secondary to the intracranial hemorrhage. There is evidence that structural myocardial lesions produced by circulating catecholamines and excessive discharge of sympathetic neurons may occur after SAH, causing these ECG changes and a reversible cardiomyopathy sufficient to cause shock or congestive heart failure. Echocardiography reveals a pattern of regional wall motion abnormalities that follow the distribution of sympathetic nerves rather than the major coronary arteries, with relative sparing of the ventricular wall apex. The sympathetic nerves themselves appear to be injured by direct toxicity from the excessive catecholamine release. An asymptomatic troponin elevation is common. Serious ventricular dysrhythmias occurring in-hospital are unusual.

TREATMENT

Subarachnoid Hemorrhage

Early aneurysm repair prevents rerupture and allows the safe application of techniques to improve blood flow (e.g., induced hypertension) should vasospasm and DCI develop. At many centers, definitive repair is carried out within 24 h of the bleed in all patients who are stable enough to tolerate the procedure. An aneurysm can be “clipped” by a neurosurgeon or “coiled” by an endovascular surgeon. Surgical repair involves placing a metal clip across the aneurysm neck, thereby immediately eliminating the risk of rebleeding. This approach requires craniotomy and brain retraction, which is associated with neurologic morbidity. Endovascular techniques involve placing platinum coils, or other embolic material, within the aneurysm via a catheter that is passed from the femoral artery. The aneurysm is packed tightly to enhance thrombosis and over time is walled off from the circulation (Fig. 429-1D). There have been two prospective randomized trials of surgery versus endovascular treatment for ruptured aneurysms: the first was the International Subarachnoid Aneurysm Trial (ISAT), which was terminated early when 24% of patients treated with endovascular therapy were dead or dependent at 1 year compared to 31% treated with surgery, a significant 23% relative reduction. After 5 years, risk of death was lower in the coiling group, although the proportion of survivors who were independent was the same in both groups. Risk of rebleeding was low but more common in the coiling group. These results favoring coiling at 1 year were confirmed in a second trial, although the differences in functional outcome were no longer significant at 3 years. Because some aneurysms have a morphology that is not amenable to endovascular treatment, surgery remains an important treatment option. Newer endovascular techniques using balloon-assisted coiling or placement of flow-diverting stents are increasing the types of aneurysms amenable to endovascular intervention. Centers that combine both endovascular and neurosurgical expertise likely offer the best outcomes for patients, and there are reliable data showing that specialized aneurysm treatment centers can improve mortality rates.

The medical management of SAH focuses on protecting the airway, managing blood pressure before and after aneurysm treatment, preventing rebleeding prior to treatment, managing vasospasm and DCI, treating hydrocephalus, treating hyponatremia, limiting secondary brain insults, and preventing pulmonary embolus (PE).

Intracranial hypertension following aneurysmal rupture occurs secondary to subarachnoid blood, parenchymal hematoma, acute hydrocephalus, or loss of vascular autoregulation. Patients who are stuporous should undergo emergent ventriculostomy to measure ICP and to treat high ICP in order to prevent cerebral ischemia.

Medical therapies designed to combat raised ICP (e.g., osmotic therapy and sedation) can also be used as needed. High ICP refractory to treatment is a poor prognostic sign.

Prior to definitive treatment of the ruptured aneurysm, care is required to maintain adequate cerebral perfusion pressure while avoiding excessive elevation of arterial pressure. If the patient is alert, it is reasonable to lower the systolic blood pressure to below 160 mmHg using nicardipine, labetalol, or esmolol. If the patient has a depressed level of consciousness, ICP should be measured and the cerebral perfusion pressure targeted to 60–70 mmHg. If headache or neck pain is severe, mild sedation and analgesia are prescribed. Extreme sedation is avoided if possible because it can obscure the ability to clinically detect changes in neurologic status. Adequate hydration is necessary to avoid a decrease in blood volume predisposing to brain ischemia.

Seizures are uncommon at the onset of aneurysmal rupture. The quivering, jerking, and extensor posturing that often accompany loss of consciousness with SAH are probably related to the sharp rise in ICP rather than seizures. However, anticonvulsants are sometimes given as prophylactic therapy because a seizure could theoretically promote rebleeding.

Glucocorticoids may help reduce the head and neck ache caused by the irritative effect of the subarachnoid blood. There is no good evidence that they reduce cerebral edema, are neuroprotective, or reduce vascular injury, and their routine use therefore is not recommended.

Antifibrinolytic agents are not routinely prescribed but may be considered in patients in whom aneurysm treatment cannot proceed immediately. They are associated with a reduced incidence of aneurysmal reperfusion but may also increase the risk of DCI and deep-vein thrombosis (DVT). Several recent studies suggest that a shorter duration of use (until the aneurysm is secured or for the first 3 days) may decrease reperfusion and be safer than found in earlier studies of longer duration treatment.

DCI remains the leading cause of morbidity and mortality following aneurysmal SAH. Treatment with the calcium channel antagonist nimodipine (60 mg PO every 4 h) improves outcome, perhaps by preventing ischemic injury rather than reducing the risk of vasospasm. Nimodipine can cause significant hypotension in some patients, which may worsen cerebral ischemia in patients with vasospasm. Symptomatic cerebral vasospasm can also be treated by increasing the cerebral perfusion pressure by raising mean arterial pressure through plasma volume expansion and the judicious use of IV vasopressor agents, usually phenylephrine or norepinephrine. Raised perfusion pressure has been associated with clinical improvement in many patients, but high arterial pressure may promote rebleeding in unprotected aneurysms. Treatment with induced hypertension and intravenous fluids generally requires monitoring of arterial and central venous pressures; it is best to infuse pressors through a central venous line as well. Euvolemia should be targeted as significant hypervolemia may lead to cardiopulmonary complications. Hypovolemia should be strictly avoided.

If DCI due to vasospasm persists despite optimal medical therapy, intraarterial vasodilators and percutaneous transluminal angioplasty are considered (Fig. 429-2). Vasodilatation by direct angioplasty appears to be permanent, allowing hypertensive therapy to be tapered sooner. The pharmacologic vasodilators (verapamil and nicardipine) do not last more than about 24 h, and therefore, multiple treatments may be required until the subarachnoid blood is reabsorbed. Although intraarterial papaverine is an effective vasodilator, there is evidence that papaverine may be neurotoxic, so its use should generally be avoided.

DCI may occur in the absence of significant large-vessel vasospasm. Potential mechanisms include microthrombosis, activation of the inflammatory cascade, microvascular dysregulation and constriction, and cortical spreading depolarization. Targeted treatments for these mechanisms are under investigation.

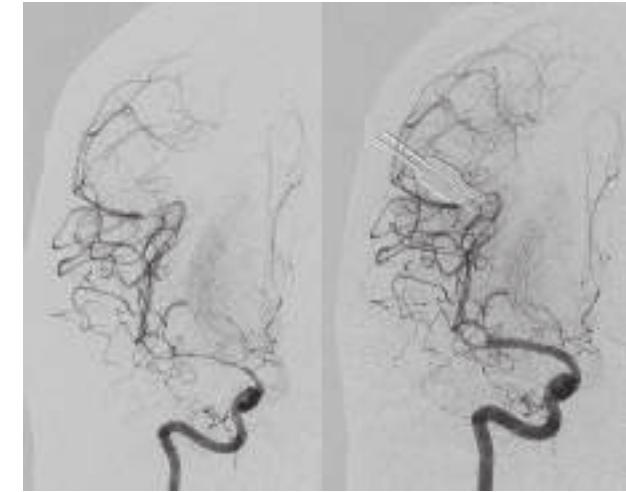


FIGURE 429-2 Vasospasm of the right middle cerebral artery. **A.** Catheter angiography demonstrates significant narrowing of the right middle cerebral artery (MCA). **B.** Because of symptomatic delayed cerebral ischemia, soft-balloon angioplasty was used to dilate the proximal portion of the main MCA stem.

Acute hydrocephalus can cause stupor or coma. It may clear spontaneously or require temporary ventricular drainage. When chronic hydrocephalus develops, ventricular shunting is the treatment of choice.

Free-water restriction is contraindicated in patients with SAH at risk for DCI because hypovolemia and hypotension may occur and precipitate cerebral ischemia. Many patients continue to experience a decline in serum sodium despite receiving parenteral fluids containing normal saline. Frequently, supplemental oral salt coupled with normal saline will mitigate hyponatremia, but often patients also require intravenous hypertonic saline. Care must be taken not to correct serum sodium too quickly in patients with marked hyponatremia of several days' duration, as the osmotic demyelination syndrome (Chap. 307) may occur.

All patients should have pneumatic compression stockings applied to prevent PE. Unfractionated heparin administered subcutaneously for DVT prophylaxis can be initiated within 1–2 days following endovascular treatment or craniotomy with surgical clipping and is a useful adjunct to pneumatic compression stockings. Treatment of PE depends on whether the aneurysm has been treated and whether or not the patient has had a craniotomy. Systemic anticoagulation with heparin is contraindicated in patients with ruptured and untreated aneurysms. It is a relative contraindication following craniotomy for several days, and it may delay thrombosis of a coiled aneurysm. If DVT or PE occurs within the first days following craniotomy, use of an inferior vena cava filter may be considered to prevent additional PEs, whereas systemic anticoagulation with heparin is preferred following successful endovascular treatment.

FURTHER READING

- D MN et al: Critical care management of patients following aneurysmal subarachnoid hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care* 15:211, 2011.
- M AJ et al: The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet* 385:691, 2015.
- T RG et al: Diagnosis and treatment of unruptured intracranial aneurysms and aneurysmal subarachnoid hemorrhage. *Mayo Clin Proc* 96:1970, 2021.

Peter J. Goadsby



The general approach to headache as a cardinal symptom is covered elsewhere (Chap. 16); here, disorders in which headache and associated features occur in the absence of any exogenous cause are discussed. The most common are migraine, tension-type headache (TTH), and the trigeminal autonomic cephalgias (TACs), notably cluster headache; the complete list is summarized in Table 430-1.

MIGRAINE

Migraine, the second most common cause of headache, and the most common headache-related, and indeed neurologic, cause of disability in the world, afflicts ~15% of women and 6% of men over a 1-year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. A useful description of migraine is a recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures (Table 430-2). A migraine attack has three phases: premonitory (prodrome), headache phase, and postdrome; each has distinct and sometimes disabling symptoms, which may overlap. About 20–25% of migraine patients have a fourth, aura, phase. Migraine can often be recognized by its activators, referred to as *triggers*.

Migraineurs are particularly sensitive to environmental and sensory stimuli; migraine-prone patients do not habituate easily to sensory stimuli. This sensitivity is amplified in women during the menstrual cycle. Headache can be initiated or amplified by various triggers, including glare, bright lights, sounds, or other types of afferent stimulation; hunger; let-down from stress; physical exertion; stormy weather or barometric pressure changes; hormonal fluctuations during menses; lack of or excess sleep; and alcohol or other chemical stimulation, such as with nitrates. Knowledge of a patient's susceptibility to specific triggers can be useful in management strategies involving lifestyle adjustments, although it is becoming recognized that some apparent triggers may in fact be part of the initial phase of the attack; i.e., the premonitory phase or prodrome.

Pathogenesis The sensory sensitivity that is characteristic of migraine is probably due to dysfunction of monoaminergic sensory control systems located in the brainstem and hypothalamus (Fig. 430-1).

Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP), at vascular terminals of the trigeminal nerve and within the trigeminal nucleus. CGRP receptor antagonists, *gепants*, have now been shown to be effective in the acute and preventive treatment of migraine, and four monoclonal antibodies to CGRP, or its receptor, have been shown to be effective in migraine prevention. Centrally, the second-order trigeminal neurons cross the midline and project to ventrobasal and posterior nuclei of the thalamus for further processing. Additionally, there are projections to the periaqueductal gray and hypothalamus, from which reciprocal descending systems have established antinociceptive effects. Other brainstem regions likely to be involved in descending modulation of trigeminal pain include the nucleus locus caeruleus in the pons and the rostroventromedial medulla.

Pharmacologic and other data point to the involvement of the neurotransmitter 5-hydroxytryptamine (5-HT; also known as *serotonin*) in migraine. In the late 1950s, methysergide was found to antagonize certain peripheral actions of 5-HT and was introduced, based on its anti-inflammation properties, as a migraine preventive. The *triptans* were designed to stimulate selectively subpopulations of 5-HT receptors; at least 14 different 5-HT receptors exist in humans. The triptans are potent agonists of 5-HT_{1B} and 5-HT_{1D} receptors, and some are

active at the 5-HT_{1F} receptor; the latter's exclusive agonists are called *ditans*. Triptans arrest nerve signaling in the nociceptive pathways of the trigeminovascular system, at least in the trigeminal nucleus caudalis and trigeminal sensory thalamus, in addition to promoting cranial vasoconstriction, whereas *ditans*, now shown conclusively to be effective in acute migraine, act only at neural and not vascular targets. A range of other neural targets are currently under investigation for the acute and preventive management of migraine.

Data also support a role for dopamine in the pathophysiology of migraine. Most migraine symptoms can be induced by dopaminergic stimulation. Moreover, there is dopamine receptor hypersensitivity in migraineurs, as demonstrated by the induction of yawning, nausea, vomiting, hypotension, and other symptoms of a migraine attack by dopaminergic agonists at doses that do not affect nonmigraineurs. Dopamine receptor antagonists are effective therapeutic agents in migraine, especially when given parenterally or concurrently with other antimigraine agents. Moreover, hypothalamic activation, anterior to that seen in cluster headache, has now been shown in the premonitory (prodromal) phase of migraine using functional imaging, and this may hold a key to understanding some part of the role of dopamine in the disorder.

Migraine genes identified by studying families with familial hemiplegic migraine (FHM) reveal involvement of ion channels, suggesting that alterations in membrane excitability can predispose to migraine. Mutations involving the Ca_{2.1} (P/Q)-type voltage-gated calcium channel CACNA1A gene are now known to cause FHM 1; this mutation is responsible for about 50% of FHM cases. Mutations in the Na⁺-K⁺ATPase ATP1A2 gene, designated FHM 2, are responsible for about 20% of FHMs. Mutations in the neuronal voltage-gated sodium channel SCN1A cause FHM 3. Functional neuroimaging has suggested that brainstem regions in migraine (Fig. 430-2) and the posterior hypothalamic gray matter region close to the human circadian pacemaker cells of the suprachiasmatic nucleus in cluster headache (Fig. 430-3) are good candidates for specific involvement in these primary headaches.

Diagnosis and Clinical Features Classic diagnostic criteria for migraine headache are listed in Table 430-3 and should be considered together with the extended features in Table 430-2. A high index of suspicion is required to diagnose migraine: the migraine aura, consisting of visual disturbances with flashing lights or zigzag lines moving across the visual field or of other neurologic symptoms, is reported in only 20–25% of patients. It should be distinguished from the pan-field television static-like disturbance now recognized as the *visual snow syndrome*. The first phase of a migraine attack for most patients is the premonitory (prodromal) phase consisting of some or all of the following: yawning, tiredness, cognitive dysfunction, mood change, neck discomfort, polyuria, and food cravings; this can last from a few hours to days. Typically, the headache phase follows with its associated features, such as nausea, photophobia, and phonophobia as well as allodynia. When questioned, these typical migraine symptoms also emerge in the premonitory phase, and typical premonitory symptoms also continue into the headache phase. As the headache lessens, many patients enter a postdrome, most commonly feeling tired/weary, having problems concentrating, and experiencing mild neck discomfort that can last for hours and sometimes up to a day. A headache diary can often be helpful in making the diagnosis; this is also helpful in assessing disability and the frequency of acute attacks. Patients with episodes of migraine on 8 or more days per month and with at least 15 total days of headache per month are considered to have chronic migraine (see "Chronic Daily Headache" in Chap. 16). Migraine must be differentiated from TTH (discussed below), which is reported to be the most common primary headache syndrome. Migraine has several forms that have been defined (Table 430-1): migraine with and without aura and chronic migraine are the most important. *Migraine at its most basic level is headache with associated features, and TTH is headache that is featureless. Most patients with disabling headache probably have migraine.*

Patients with acephalic migraine (typical aura without headache, 1.2.1.2 in Table 430-1) experience recurrent neurologic symptoms, often with nausea or vomiting, but with little or no headache. Vertigo

TABLE 430-1 Primary Headache Disorders, Modified from International Classification of Headache Disorders-III-Beta (Headache Classification Committee of the International Headache Society, 2018)

1. Migraine	1.1 Migraine without aura 1.2 Migraine with aura <ul style="list-style-type: none"> 1.2.1 Migraine with typical aura <ul style="list-style-type: none"> 1.2.1.1 Typical aura with headache 1.2.1.2 Typical aura without headache 1.2.2 Migraine with brainstem aura 1.2.3 Hemiplegic migraine <ul style="list-style-type: none"> 1.2.3.1 Familial hemiplegic migraine (FHM) 1.2.3.1.1 Familial hemiplegic migraine type 1 1.2.3.1.2 Familial hemiplegic migraine type 2 1.2.3.1.3 Familial hemiplegic migraine type 3 1.2.3.1.4 Familial hemiplegic migraine, other loci 1.2.4 Retinal migraine 1.3 Chronic migraine 1.4 Complications of migraine <ul style="list-style-type: none"> 1.4.1 Status migrainosus 1.4.2 Persistent aura without infarction 1.4.3 Migrainous infarction 1.4.4 Migraine aura-triggered seizure 1.5 Probable migraine <ul style="list-style-type: none"> 1.5.1 Probable migraine without aura 1.5.2 Probable migraine with aura 1.6 Episodic syndromes that may be associated with migraine <ul style="list-style-type: none"> 1.6.1 Recurrent gastrointestinal disturbance <ul style="list-style-type: none"> 1.6.1.1 Cyclical vomiting syndrome 1.6.1.2 Abdominal migraine 1.6.2 Benign paroxysmal vertigo 1.6.3 Benign paroxysmal torticollis
2. Tension-type headache	2.1 Infrequent episodic tension-type headache 2.2 Frequent episodic tension-type headache 2.3 Chronic tension-type headache 2.4 Probable tension-type headache
3. Trigeminal autonomic cephalgias	3.1 Cluster headache <ul style="list-style-type: none"> 3.1.1 Episodic cluster headache 3.1.2 Chronic cluster headache 3.2 Paroxysmal hemicrania <ul style="list-style-type: none"> 3.2.1 Episodic paroxysmal hemicrania 3.2.2 Chronic paroxysmal hemicrania 3.3 Short-lasting unilateral neuralgiform headache attacks <ul style="list-style-type: none"> 3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) <ul style="list-style-type: none"> 3.3.1.1 Episodic SUNCT 3.3.1.2 Chronic SUNCT 3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) <ul style="list-style-type: none"> 3.3.2.1 Episodic SUNA 3.3.2.2 Chronic SUNA 3.4 Hemicrania continua 3.5 Probable trigeminal autonomic cephalgia
4. Other primary headache disorders	4.1 Primary cough headache 4.2 Primary exercise headache 4.3 Primary headache associated with sexual activity 4.4 Primary thunderclap headache 4.5 Cold-stimulus headache <ul style="list-style-type: none"> 4.5.1 Headache attributed to external application of a cold stimulus 4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus 4.6 External-pressure headache <ul style="list-style-type: none"> 4.6.1 External-compression headache 4.6.2 External-traction headache 4.7 Primary stabbing headache 4.8 Nummular headache 4.9 Hypnic headache 4.10 New daily persistent headache (NDPH)

TABLE 430-2 Migraine Symptoms by Attack Phase

Premonitory (prodromal)
- Neck discomfort
- Higher center
• Cognitive impairment (brain "fog")
• Mood change
• Fatigue
- Homeostatic
• Yawning/sleepiness
• Polyuria/polydipsia
• Food cravings
Aura
- Neurologic disturbance, such as scintillating scotoma
Headache Phase
- Pain
- Nausea/vomiting
- Sensory sensitivity
• Photophobia
• Phonophobia
• Osmophobia
• Allodynia
• Vertigo
Postdrome
- Tiredness
- Weariness
- Concentration impairment

Source: Adapted from PJ Goadsby et al: Pathophysiology of migraine: A disorder of sensory processing. *Physiol Rev* 97:553, 2017.

can be prominent; it has been estimated that one-third of patients referred for vertigo or dizziness have a primary diagnosis of migraine. Migraine aura can have prominent brainstem symptoms, and the terms *basilar artery* and *basilar-type migraine* have now been replaced by *migraine with brainstem aura* (Table 430-1).

TREATMENT

Migraine Headache

Once a diagnosis of migraine has been established, it is important to assess the extent of a patient's disease and disability. The Migraine Disability Assessment Score (MIDAS) is a well-validated, easy-to-use tool (Fig. 430-4).

Patient education is an important aspect of migraine management. Information for patients is available at websites such as the American Migraine Foundation (www.americanmigrainefoundation.org) and the Migraine Trust (www.migrainetrust.org). It is helpful for patients to understand that migraine is an inherited tendency to headache; that migraine can be modified and controlled by lifestyle adjustments and medications, but it cannot be eradicated; and that, except on some occasions in women on oral estrogens or contraceptives, migraine is not associated with serious or life-threatening illnesses.

NONPHARMACOLOGIC MANAGEMENT

Migraine can often be managed to some degree by a variety of nonpharmacologic approaches. When patients can identify reliable triggers, their avoidance can be useful. A regulated lifestyle is helpful, including a healthy diet, regular exercise, regular sleep patterns, avoidance of excess caffeine and alcohol, and avoidance

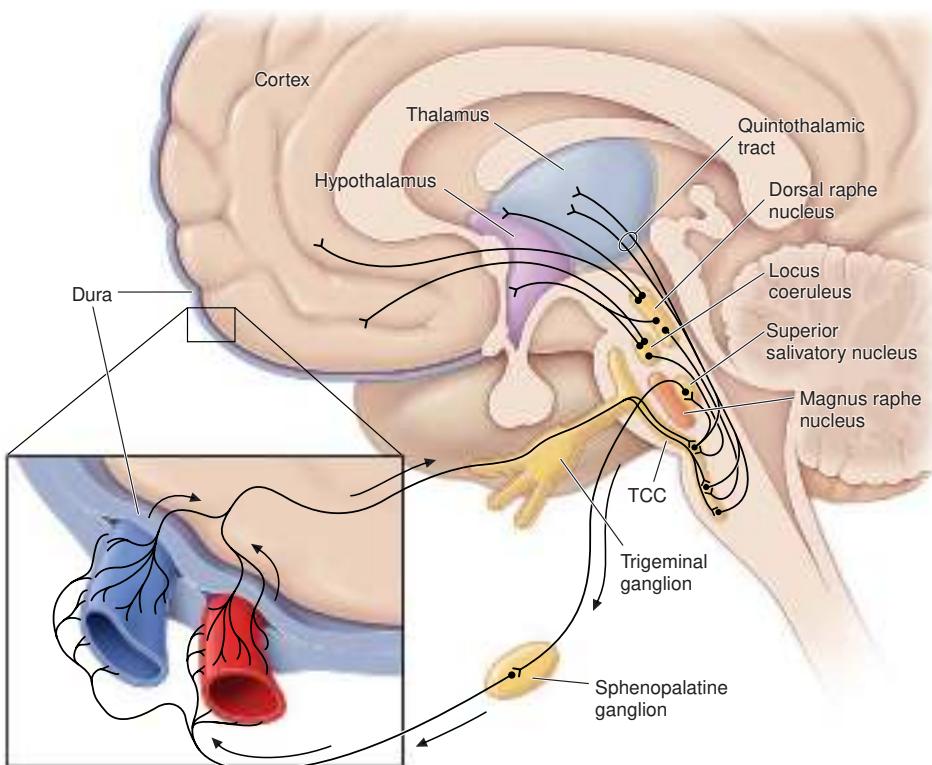


FIGURE 430-1 Brainstem pathways that modulate sensory input. The key pathway for pain in migraine is the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex (TCC). These neurons in turn project in the quintothalamic tract and, after decussating in the brainstem, synapse on neurons in the thalamus. Important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus coeruleus, and nucleus raphe magnus.

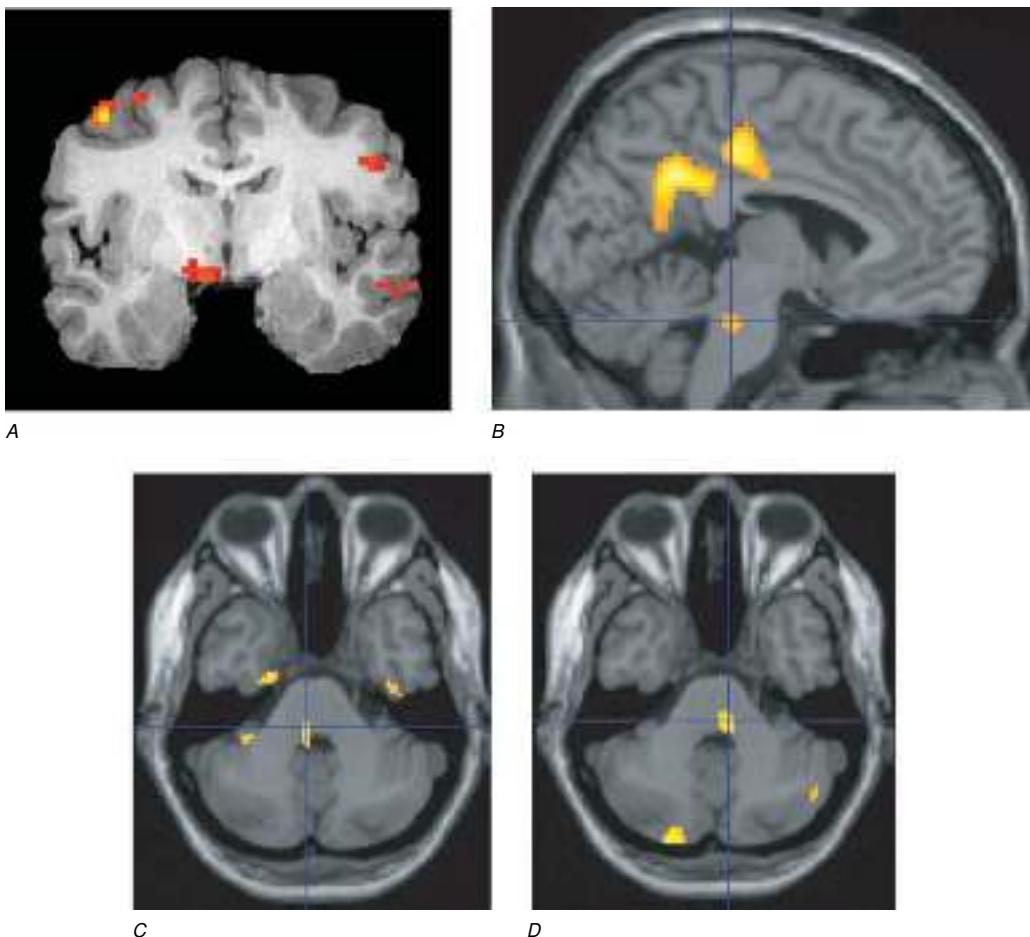


FIGURE 430-2 Positron emission tomography (PET) activation in migraine. Hypothalamic, dorsal midbrain, and dorsolateral pontine activation are seen in triggered attacks in the premonitory phase before pain, whereas in migraine attacks, dorsolateral pontine activation persists, as it does in chronic migraine (not shown). The dorsolateral pontine area, which includes the noradrenergic locus coeruleus, is fundamental to the expression of migraine. Moreover, lateralization of changes in this region of the brainstem correlates with lateralization of the head pain in hemispheric migraine; the scans shown in panels C and D are of patients with acute migraine headache on the right and left side, respectively. (Panel A from FH Maniyar et al: Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain* 137:232, 2014; panel B reproduced with permission from SK Afridi et al: A positron emission tomographic study in spontaneous migraine. *Arch Neurol* 62:1270, 2005.; Panels C and D from SK Afridi et al: A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. *Brain* 128:932, 2005.)

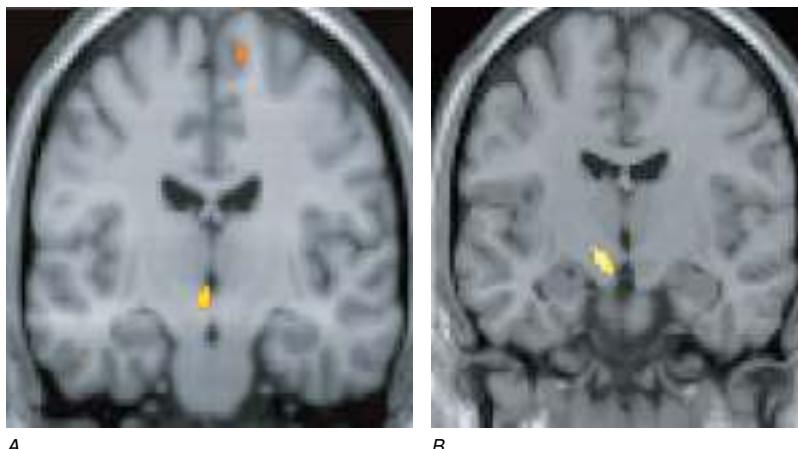


FIGURE 430-3 A. Posterior hypothalamic gray matter region activation demonstrated by positron emission tomography in a patient with acute cluster headache. B. High-resolution T1-weighted magnetic resonance image obtained using voxel-based morphometry demonstrates increased gray matter activity, lateralized to the side of pain in a patient with cluster headache. (Panel A from A May et al: Hypothalamic activation in cluster headache attacks. *Lancet* 352:275, 1998. Panel B from A May et al: Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat Med* 5:836, 1999.)

TABLE 430-3 Simplified Diagnostic Criteria for Migraine

REPEATED ATTACKS OF HEADACHE LASTING 4–72 H IN PATIENTS WITH A NORMAL PHYSICAL EXAMINATION, NO OTHER REASONABLE CAUSE FOR THE HEADACHE, AND:	
AT LEAST 2 OF THE FOLLOWING FEATURES:	PLUS AT LEAST 1 OF THE FOLLOWING FEATURES:
Unilateral pain	Nausea/vomiting
Throbbing pain	Photophobia and phonophobia
Aggravation by movement	
Moderate or severe intensity	

Source: Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, *Cephalgia* 38:1, 2018).

of acute changes in stress levels, being particularly wary of the let-down effect.

The measures that benefit a given individual should be used routinely because they provide a simple, cost-effective approach to migraine management. Patients with migraine do not encounter more stress than headache-free individuals; overresponsiveness to changes in stress appears to be the issue. Because the stresses of everyday living cannot be eliminated, lessening one's response to stress by various techniques is helpful for many patients. These may include yoga, transcendental meditation, hypnosis, and conditioning techniques such as biofeedback. For most patients seen in clinical practice, this approach is, at best, an adjunct to pharmacotherapy. Nonpharmacologic measures are unlikely to prevent all migraine attacks, and pharmacologic approaches are often needed.

ACUTE ATTACK THERAPIES FOR MIGRAINE

The mainstay of pharmacologic therapy is the judicious use of one or more of the many medicines that are effective in migraine (Table 430-4). The selection of the optimal regimen for a given

patient depends on a number of factors, the most important of which is the severity of the attack. Mild migraine attacks can usually be managed by oral agents; the average efficacy rate is 50–70%. Severe migraine attacks may require parenteral therapy. Most drugs effective in the treatment of migraine are members of one of five major pharmacologic classes: nonsteroidal anti-inflammatory drugs; 5-HT_{1B/1D} receptor agonists—triptans; CGRP receptor antagonists— gepants; 5-HT_{1F} receptor agonists—ditans; and dopamine receptor antagonists.

In general, an adequate dose of whichever agent is chosen should be used as soon as possible after the onset of an attack. If additional medication is required within 60 min because symptoms return or have not abated, the initial dose should be increased for subsequent attacks or a different class of drug tried as first-line treatment. Repeat dosing of the same medicine at 2 hours while safe, has been established to be ineffective for triptans. An exception to this rule may be gepants, for which there are data to show that retreatment with the same dose is helpful. Migraine therapy must be individualized; a standard approach for all patients is not possible. A therapeutic regimen may need to be constantly refined until one is identified that provides the patient with rapid, complete, and consistent relief with minimal side effects (Table 430-5).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Both the severity and duration of a migraine attack can be reduced significantly by NSAIDs (Table 430-4). Indeed, many undiagnosed migraineurs self-treat with nonprescription NSAIDs. A general consensus is that NSAIDs are most effective when taken early in the migraine attack. However, the effectiveness of these agents in migraine is usually less than optimal in moderate or severe migraine attacks. The combination of acetaminophen (paracetamol), aspirin, and caffeine has been approved for use by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate migraine. The combination of aspirin and metoclopramide has been shown to

*MIDAS Questionnaire	
INSTRUCTIONS: Please answer the following questions about ALL headaches you have had over the last 3 months. Write zero if you did not do the activity in the last 3 months.	
1. On how many days in the last 3 months did you miss work or school because of your headaches?	_____ days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches (<i>do not include days you counted in question 1 where you missed work or school</i>)?	_____ days
3. On how many days in the last 3 months did you not do household work because of your headaches?	_____ days
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches (<i>do not include days you counted in question 3 where you did not do household work</i>)?	_____ days
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?	_____ days
A. On how many days in the last 3 months did you have a headache? (<i>If a headache lasted more than one day, count each day</i>)	_____ days
B. On a scale of 0–10, on average how painful were these headaches? (<i>Where 0 = no pain at all, and 10 = pain as bad as it can be</i>)	_____
<small>*Migraine Disability Assessment Score (Questions 1–5 are used to calculate the MIDAS score.)</small>	
<small>Grade I—Minimal or Infrequent Disability: 0–5</small>	
<small>Grade II—Mild or Infrequent Disability: 6–10</small>	
<small>Grade III—Moderate Disability: 11–20</small>	
<small>Grade IV—Severe Disability: > 20</small>	
<small>© Innovative Medical Research 1997</small>	

FIGURE 430-4 The Migraine Disability Assessment Score (MIDAS) Questionnaire.

TABLE 430-4 Treatment of Acute Migraine

DRUG	TRADE NAME	DOSAGE
Simple Analgesics		
Acetaminophen, aspirin, caffeine	Excedrin Migraine	Two tablets or caplets q6h (max 8 per day)
NSAIDs		
Naproxen	Aleve, Anaprox, generic	220–550 mg po bid
Ibuprofen	Advil, Motrin, Nuprin, generic	400 mg po q3–4h
Tolfenamic acid	Clotam Rapid	200 mg po; may repeat ×1 after 1–2 h
Diclofenac K	Cambia	50 mg po with water
5-HT_{1B/1D} Receptor Agonists—Triptans		
Oral		
Ergotamine 1 mg, caffeine 100 mg	Cafergot	One or two tablets at onset, then one tablet q1/2h (max 6 per day, 10 per week)
Naratriptan	Amerge	2.5-mg tablet at onset
Rizatriptan	Maxalt	5–10-mg tablet at onset
Sumatriptan	Maxalt-MLT	
Frovatriptan	Imitrex	50–100-mg tablet at onset
Almotriptan	Frova	2.5-mg tablet at onset
Betriptan	Axert	12.5-mg tablet at onset
Zolmitriptan	Relpax	40 or 80 mg at onset
Nasal	Zomig	
Dihydroergotamine	Zomig Rapimelt	2.5-mg tablet at onset
Sumatriptan	Migranal Nasal Spray	Prior to nasal spray, the pump must be primed 4 times; 1 spray (0.5 mg) is administered, followed in 15 min by a second spray
Zolmitriptan	Trudhesa Nasal Spray	One spray into each nostril
Parenteral	Imitrex Nasal Spray	5–20 mg intranasal spray as 4 sprays of 5 mg or a single 20 mg spray
Dihydroergotamine	Zomig	5 mg intranasal spray as one spray
Sumatriptan	DHE-45	1 mg IV, IM, or SC at onset and q1h (max 3 mg/d, 6 mg per week)
	Imitrex Injection	6 mg SC at onset (may repeat once after 1 h for max of 2 doses in 24 h)
Alsumma		
Sumavel DosePro		
CGRP Receptor Antagonists—Gepants		
Oral		
Rimegepant	Nurtec	75 mg ODT po
Ubrogepant	Ubrelvy	50 or 100 mg po; a second dose may be taken 2 hours after the first, if needed.
5-HT _{1F} Receptor Agonist—Ditans		
Oral		
Lasmiditan	Reyovw	50, 100, or 200 mg po
Dopamine Receptor Antagonists		
Oral		
Metoclopramide	Reglan, ^a generic ^a	5–10 mg/d
Prochlorperazine	Compazine, ^a generic ^a	1–25 mg/d
Parenteral		
Chlorpromazine	Generic ^a	0.1 mg/kg IV at 2 mg/min; max 35 mg/d
Metoclopramide	Reglan, ^a generic	10 mg IV
Prochlorperazine	Compazine, ^a generic ^a	10 mg IV
Other		
Oral		
Acetaminophen, 325 mg, plus dichloralphenazone, 100 mg, plus isometheptene, 65 mg	Midrin, generic	Two capsules at onset followed by 1 capsule q1h (max 5 capsules)
Parenteral		
Opioids	Generic ^a	Multiple preparations and dosages; see Table 13-1
Other		
Neuromodulation		
Single-pulse transcranial magnetic stimulation (sTMS)	sTMSmini	Two pulses at onset followed by two further pulses
Noninvasive vagus nerve stimulation (nVNS)	gammaCore	Two doses each of 120 s
Remote electrical neuromodulation	Nerivio	30- to 45-min stimulation to the upper arm
Transcutaneous supraorbital nerve stimulation	Cefaly	60-min stimulation

^aNot all drugs are specifically indicated by the FDA for migraine. Local regulations and guidelines should be consulted.

Note: Antiemetics (e.g., domperidone 10 mg or ondansetron 4 or 8 mg) or prokinetics (e.g., metoclopramide 10 mg) are sometimes useful adjuncts.

Abbreviations: 5-HT, 5-hydroxytryptamine; NSAIDs, nonsteroidal anti-inflammatory drugs; ODT, orally disintegrating tablets.

TABLE 430-5 Clinical Stratification of Acute Specific Migraine Treatments

CLINICAL SITUATION	TREATMENT OPTIONS
Failed NSAIDs/analgesics	First tier Sumatriptan 50 mg or 100 mg PO Almotriptan 12.5 mg PO Rizatriptan 10 mg PO Eltipteran 40 mg PO Zolmitriptan 2.5 mg PO Rimegepant 75 mg Ubrogepant 50 or 100 mg Lasmiditan 50, 100, or 200 mg Slower effect/better tolerability Naratriptan 2.5 mg PO Frovatriptan 2.5 mg PO Infrequent headache Ergotamine/caffeine 1–2/100 mg PO Dihydroergotamine nasal spray 2 mg
Early nausea or difficulties taking tablets	Zolmitriptan 5 mg nasal spray Sumatriptan 20 mg nasal spray Rizatriptan 10 mg MLT wafer
Headache recurrence	Ergotamine 2 mg (most effective PR/usually with caffeine) Naratriptan 2.5 mg PO Almotriptan 12.5 mg PO Eltipteran 40 mg Rimegepant 75 mg Ubrogepant 50 or 100 mg
Tolerating acute treatments poorly	Naratriptan 2.5 mg Almotriptan 12.5 mg Rimegepant 75 mg Ubrogepant 50, 100 mg Single-pulse transcranial magnetic stimulation Noninvasive vagus nerve stimulation
Early vomiting	Zolmitriptan 5 mg nasal spray Sumatriptan 25 mg PR Sumatriptan 6 mg SC
Menses-related headache	Prevention Ergotamine po at night Estrogen patches Rimegepant 75 mg po taken during the menses Treatment Triptans Dihydroergotamine nasal spray
Very rapidly developing symptoms	Zolmitriptan 5 mg nasal spray Sumatriptan 6 mg SC Dihydroergotamine 1 mg IM

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

be comparable to a single dose of oral sumatriptan. Important side effects of NSAIDs include dyspepsia and gastrointestinal irritation.

5-HT_{1B/1D} RECEPTOR AGONISTS—TRIPTANS

Oral Stimulation of 5-HT_{1B/1D} receptors can stop an acute migraine attack. Ergotamine and dihydroergotamine are nonselective receptor agonists, whereas the triptans are selective 5-HT_{1B/1D} receptor agonists. A variety of triptans—sumatriptan, almotriptan, eltipteran, frovatriptan, naratriptan, rizatriptan, and zolmitriptan—are available for the treatment of migraine.

Each drug in the triptan class has similar pharmacologic properties, varying slightly in terms of clinical efficacy. Rizatriptan and eletriptan are, on a population basis, the most efficacious of the triptans. Sumatriptan and zolmitriptan have similar rates of efficacy as well as time to onset, with an advantage of having multiple formulations, whereas almotriptan has a similar rate of efficacy to sumatriptan and is better tolerated, and frovatriptan and naratriptan are somewhat slower in onset and are also well tolerated. Clinical efficacy appears to be related more to the t_{max} (time to peak plasma level) than to the potency, half-life, or bioavailability. This observation is consistent with a large body of data indicating that faster-acting analgesics are more effective than slower-acting ones.

Unfortunately, monotherapy with a selective oral 5-HT_{1B/1D} receptor agonist does not result in rapid, consistent, and complete relief of migraine in all patients. Triptans are generally not effective in migraine with aura unless given after the aura is completed and the headache initiated. Side effects are common, although often mild and transient. Moreover, 5-HT_{1B/1D} receptor agonists are contraindicated in individuals with a history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. Recurrence of headache, within the usual time course of an attack, is another important limitation of triptan use and occurs at least occasionally in most patients. Evidence from randomized controlled trials shows that coadministration of a longer-acting NSAID, naproxen 500 mg, with sumatriptan will augment the initial effect of sumatriptan and, importantly, reduce rates of headache recurrence.

Ergotamine preparations offer a nonselective means of stimulating 5-HT₁ receptors. A nonnauseating dose of ergotamine should be sought because a dose that provokes nausea is too high and may intensify head pain. Oral (excluding sublingual) formulations of ergotamine also contain 100 mg caffeine (theoretically to enhance ergotamine absorption and possibly to add additional analgesic activity). The average oral ergotamine dose for a migraine attack is 2 mg. Because the clinical studies demonstrating the efficacy of ergotamine in migraine predated the clinical trial methodologies used with the triptans, it is difficult to assess the comparative efficacy of ergotamine versus the triptans. In general, with use of ergotamine there appears to be a much higher incidence of nausea than with triptans but less headache recurrence.

Nasal Nasal formulations of dihydroergotamine, zolmitriptan, or sumatriptan can be useful in patients requiring a nonoral route of administration. The nasal sprays result in substantial blood levels within 30–60 min. Although in theory nasal sprays might provide faster and more effective relief of a migraine attack than oral formulations, their reported efficacy is only ~50–60%. Studies with a new inhalational formulation of dihydroergotamine indicate that its absorption problems can be overcome to produce rapid onset of action with good tolerability.

Parenteral Administration of drugs by injection, such as dihydroergotamine and sumatriptan, is approved by the FDA for the rapid relief of a migraine attack. Peak plasma levels of dihydroergotamine are achieved 3 min after IV dosing, 30 min after intramuscular (IM) dosing, and 45 min after subcutaneous (SC) dosing. If an attack has not already peaked, SC or IM administration of 1 mg of dihydroergotamine is adequate for about 80–90% of patients. Sumatriptan, 4–6 mg SC, is effective in ~50–80% of patients and can now be administered by a needle-free device.

CALCITONIN GENE-RELATED PEPTIDE (CGRP) RECEPTOR ANTAGONISTS—GEPANTS

Oral gepants are small-molecule CGRP receptor antagonists that are effective in the acute treatment of migraine. Two are currently approved by the FDA: rimegepant and ubrogepant. Both were more likely to render patients pain-free at 2 hours and most bothersome symptom-free when compared with placebo in large phase 3 clinical trials. The most bothersome symptom is derived by asking

patients to identify which symptom—of nausea, photophobia and phonophobia—was most bothersome during the treated attack; success required that this symptom was eliminated at 2 hours. Gepants are extremely well tolerated with only a few percent of patients reporting troublesome side effects, such as mild nausea.

5-HT_{1F} RECEPTOR AGONISTS—DITANS

Lasmiditan, a highly selective, orally available, 5-HT_{1F} receptor agonist, has been approved by the FDA for the acute treatment of migraine based on large phase 3 studies where it was superior to placebo. Ditans have no vascular effects because the 5-HT_{1F} receptor is located in the central and peripheral nervous system but not vasculature; the class thus unequivocally fills a gap in therapy for patients with cardiovascular and cerebrovascular disease. The major side effect is dizziness, occurring in about 15% of patients in clinical trials, and somnolence in 6%. Patients are advised not to drive for 8 hours after treatment.

DOPAMINE RECEPTOR ANTAGONISTS

Oral Oral dopamine receptor antagonists can be considered as adjunctive therapy in migraine. Drug absorption is impaired during migraine because of reduced gastrointestinal motility. Delayed absorption occurs even in the absence of nausea and is related to the severity of the attack and not its duration. Therefore, when oral NSAIDs and/or triptan agents fail, the addition of a dopamine receptor antagonist, such as metoclopramide 10 mg or domperidone 10 mg (not available in the United States), should be considered to enhance gastric absorption. In addition, dopamine receptor antagonists decrease nausea/vomiting and restore normal gastric motility.

Parenteral Dopamine receptor antagonists (e.g., chlorpromazine, prochlorperazine, metoclopramide) by injection can also provide significant acute relief of migraine; they can be used in combination with parenteral 5-HT_{1B/1D} receptor agonists. A common IV protocol used for the treatment of severe migraine is the administration over 2 min of a mixture of 5 mg of prochlorperazine and 0.5 mg of dihydroergotamine.

OTHER OPTIONS FOR ACUTE MIGRAINE

Oral The combination of acetaminophen, dichloralphenazone, and isometheptene, one to two capsules, has been classified by the FDA as “possibly” effective in the treatment of migraine. Because the clinical studies demonstrating the efficacy of this combination analgesic in migraine predated the clinical trial methodologies used with the triptans, it is difficult to compare the efficacy of this sympathomimetic compound with other agents.

Parenteral Opioids are modestly effective in the acute treatment of migraine. For example, IV meperidine (50–100 mg) is given frequently in the emergency department (ED). This regimen “works” in the sense that the pain of migraine is eliminated. Importantly, it is clear from a recent randomized controlled trial that prochlorperazine is superior to hydromorphone in the ED setting. However, opioids are clearly suboptimal for patients with recurrent headache. Opioids do not treat the underlying headache mechanism; rather, they act to alter the pain sensation, and there is evidence their use may decrease the likelihood of a response to triptans in the future. Moreover, in patients taking oral opioids, such as oxycodone or hydrocodone, habituation or addiction can greatly confuse the treatment of migraine. Opioid craving and/or withdrawal can aggravate and accentuate migraine. Therefore, it is recommended that opioid use in migraine be limited to patients with severe, but infrequent, headaches that are unresponsive to other pharmacologic approaches or who have contraindications to other therapies.

Neuromodulation Single-pulse transcranial magnetic stimulation (sTMS) is FDA approved for the acute treatment of migraine. Two pulses can be applied at the onset of an attack, and this can be repeated. The use of sTMS is safe where there is no cranial metal implant, and offers an option to patients seeking nonpharmacological approaches to treatment. Similarly, a noninvasive vagus nerve

stimulator (nVNS) is FDA approved for the treatment of migraine attacks in adults. One to two 120-s doses may be applied for attack treatment. Remote electrical neuromodulation using a smartphone app that stimulates the upper arm for 30–45 min is also effective for treatment of acute migraine, as is transcutaneous supraorbital nerve stimulation for 60 min; both are FDA approved.

MEDICATION-OVERUSE HEADACHE

Acute attack medications, particularly opioid or barbiturate-containing compound analgesics, have a propensity to aggravate headache frequency and induce a state of refractory daily or near-daily headache called *medication-overuse headache*. This condition is likely not a separate headache entity but a reaction of the patient's underlying migraine biology to a particular medicine. Migraine patients who have two or more headache days a week should be cautioned about frequent analgesic use (see “Chronic Daily Headache” in Chap. 16).

PREVENTIVE TREATMENTS FOR MIGRAINE

Patients with an increasing frequency of migraine attacks or with attacks that are either unresponsive or poorly responsive to abortive treatments are good candidates for preventive agents. In general, a preventive medication should be considered in patients with four or more attacks a month. Significant side effects are associated with the use of many of these agents; furthermore, determination of dose can be difficult because the recommended doses have been derived for conditions other than migraine. The mechanism of action of these drugs is unclear; it seems likely that the brain sensitivity that underlies migraine is modified. Patients are usually started on a low dose of a chosen treatment; the dose is then gradually increased, up to a reasonable maximum, to achieve clinical benefit.

Treatments that have the capacity to stabilize migraine are listed in Table 430-6. Most treatments must be taken daily, and there is usually a lag of 2–12 weeks before an effect is seen. The drugs that have been approved by the FDA for the preventive treatment of migraine include propranolol, timolol, rimegeptan, sodium valproate, topiramate, eptinezumab, erenumab, fremanezumab, and galcanezumab. In addition, a number of other drugs appear to display preventive efficacy. This group includes amitriptyline, candesartan, nortriptyline, flunarizine, phenelzine, and cyproheptadine. Placebo-controlled trials of onabotulinum toxin type A in episodic migraine were negative, whereas, overall, placebo-controlled trials in chronic migraine were positive. The FDA has approved sTMS for the preventive treatment of migraine. It offers a well-tolerated, effective option for patients. Phenelzine is a monoamine oxidase inhibitor (MAOI); therefore, tyramine-containing foods, decongestants, and meperidine are contraindicated, and it is reserved for only very recalcitrant cases. Methysergide is now of historical interest only because it is no longer manufactured. Melatonin has been reported to be useful, with controlled trial evidence, but is not approved in the United States. Monoclonal antibodies to the CGRP receptor (erenumab) or to the peptide (eptinezumab, fremanezumab, and galcanezumab) have all proven effective and well tolerated in migraine and are now available as novel, migraine-specific preventative agents.

The probability of success with any one of the antimigraine drugs is ~50%. Many patients are managed adequately with well-tolerated doses of candesartan, propranolol, amitriptyline, topiramate, or valproate. If these agents fail or produce unacceptable side effects, neuromodulation approaches, such as sTMS, or related agents from the above classes, can be used (Table 430-6). Once effective stabilization is achieved, the drug is continued for ~6 months and then slowly tapered, assuming the patient agrees, to assess the continued need. Many patients are able to discontinue medication and experience fewer and milder attacks for long periods, suggesting that these drugs may alter the natural history of migraine. The advent of CGRP monoclonal antibodies and CGRP receptor antagonists has significantly changed the landscape of preventive treatment; with the combination of efficacy that is often within the first month and excellent tolerability, expectations of outcomes are changing.

TABLE 430-6 Preventive Treatments in Migraine^a

DRUG	DOSE	SELECTED SIDE EFFECTS
Beta blocker Propranolol Metoprolol	40–120 mg bid 25–100 mg bid	Reduced energy Tiredness Postural symptoms Contraindicated in asthma
Antidepressants Amitriptyline Doseulepin Nortriptyline	10–75 mg at night 25–75 mg at night 25–75 mg at night	Drowsiness <i>Note:</i> Some patients may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required.
Venlafaxine	75–150 mg/d	
Anticonvulsants Topiramate	25–200 mg/d	Paresthesias Cognitive symptoms Weight loss Glaucoma Caution with nephrolithiasis
Valproate	400–600 mg bid	Drowsiness Weight gain Tremor Hair loss Fetal abnormalities Hematologic or liver abnormalities
Serotonergic drugs Pizotifen ^b	0.5–2 mg qd	Weight gain
CGRP antagonists Eptinezumab Erenumab Fremanezumab Galcanezumab Rimege pant	100 or 300 mg IV every 12 weeks 70 or 140 mg SC monthly 225 mg monthly or 675 mg q3 months, SC 240 mg loading then 120 mg monthly, SC 75 mg every other day	Nasopharyngitis Nasopharyngitis, constipation Injection site reactions Nasopharyngitis Nausea abdominal pain/dyspepsia
Other classes Flunarizine ^b	5–15 mg qd	Drowsiness Weight gain Depression Parkinsonism
Candesartan Memantine Melatonin	4–24 mg daily 5–20 mg daily 3–12 mg nightly	Dizziness Dizziness, tiredness Drowsiness
Neuromodulation Single-pulse transcranial magnetic stimulation (sTMS)	4–24 pulses per day	Lightheadedness Tingling Tinnitus
Chronic migraine Onabotulinum toxin type A	155 U	Loss of brow furrow
No convincing evidence from controlled trials		
Verapamil		
Controlled trials demonstrate no effect		
Nimodipine Clonidine Selective serotonin reuptake inhibitors: fluoxetine		

^aCommonly used preventives are listed with typical doses and common side effects. Not all listed medicines are approved by the U.S. Food and Drug Administration; local regulations and guidelines should be consulted.

^bNot available in the United States.

TENSION TYPE HEADACHE

Clinical Features The term *tension-type headache* is commonly used to describe a chronic head-pain syndrome characterized by bilateral tight, bandlike discomfort. The pain typically builds slowly, fluctuates in severity, and may persist more or less continuously for many days. The headache may be episodic or chronic (present >15 days per month).

A useful clinical approach is to diagnose TTH in patients whose headaches are completely without accompanying features such as nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, and aggravation with movement. Such an approach neatly separates migraine, which has one or more of these features and is the main differential diagnosis, from TTH. The International Headache Society's main definition of TTH allows an admixture of nausea, photophobia, or phonophobia in various combinations, although the appendix definition does not; this illustrates the difficulty in distinguishing these two clinical entities. In clinical practice, using the appendix definition to dichotomize patients on the basis of the presence of associated features (migraine) and the absence of associated features (TTH) is highly recommended. Indeed, patients whose headaches fit the TTH phenotype and who have migraine at other times, along with a family history of migraine, migrainous illnesses of childhood, or typical migraine triggers to their migraine attacks, may be biologically different from those who have TTH headache with none of the features. TTH may be infrequent (episodic) or occur on 15 days or more a month (chronic).

Pathophysiology The pathophysiology of TTH is incompletely understood. It seems likely that TTH is due to a primary disorder of central nervous system pain modulation alone, unlike migraine, which involves a more generalized disturbance of sensory modulation. Data suggest a genetic contribution to TTH, but this may not be a valid finding; given the current diagnostic criteria, the studies undoubtedly included many migraine patients. The name *tension-type headache* implies that pain is a product of *nervous tension*, but there is no clear evidence for tension as an etiology. Muscle contraction has been considered to be a feature that distinguishes TTH from migraine, but there appear to be no differences in contraction between the two headache types.

TREATMENT

Tension-Type Headache

The pain of TTH can generally be managed with simple analgesics such as acetaminophen, aspirin, or NSAIDs. Behavioral approaches including relaxation can also be effective. Clinical studies have demonstrated that triptans in pure TTH are not helpful, although triptans are effective in TTH when the patient also has migraine. For chronic TTH, amitriptyline is the only proven treatment (Table 430-6); other tricyclics, selective serotonin reuptake inhibitors, and the benzodiazepines have not been shown to be effective. There is no evidence for the efficacy of acupuncture. Placebo-controlled trials of onabotulinum toxin type A in chronic TTH were negative.

TRIGEMINAL AUTONOMIC CEPHALGALGIAS TACs , INCLUDING CLUSTER HEADACHE

The TACs describe a grouping of primary headaches including cluster headache, paroxysmal hemicrania (PH), SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)/SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms), and hemicrania continua (Table 430-1). TACs are characterized by relatively short-lasting attacks of head pain associated with lateralized cranial autonomic symptoms, such as lacrimation, conjunctival injection, aural fullness, or nasal congestion (Table 430-7). Pain is usually severe and may occur more than once a day. Because of the associated nasal congestion or rhinorrhea, patients are often misdiagnosed with “sinus headache” and treated with decongestants, which are ineffective.

TABLE 430-7 Clinical Features of the Trigeminal Autonomic Cephalgias

	CLUSTER HEADACHE	PAROXYSMAL HEMICRANIA	SUNCT/SUNA
Gender	M > F	F = M	F ~ M
Pain			
Type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp
Severity	Excruciating	Excruciating	Severe to excruciating
Site	Orbit, temple	Orbit, temple	Periorbital
Attack frequency	1/alternate day–8/d	1–20/d (>5/d for more than half the time)	3–200/d
Duration of attack	15–180 min	2–30 min	5–240 s
Autonomic features	Yes	Yes	Yes (prominent conjunctival injection and lacrimation) ^a
Migrainous features ^b	Yes	Yes	Yes
Alcohol trigger	Yes	No	No
Cutaneous triggers	No	No	Yes
Indomethacin effect	—	Yes ^c	—
Abortive treatment	Sumatriptan injection or nasal spray Zolmitriptan nasal spray Oxygen nVNS ^c	No effective treatment	Lidocaine (IV)
Preventive treatment	Verapamil Galcanezumab Topiramate Melatonin Lithium	Indomethacin ^d	Lamotrigine Topiramate Gabapentin

^aIf conjunctival injection and tearing are not present, consider SUNA. ^bNausea, photophobia, or phonophobia; photophobia and phonophobia are typically unilateral on the side of the pain. ^cNoninvasive vagus nerve stimulation is FDA approved in episodic cluster headache. ^dIndicates complete response to indomethacin.

Abbreviations: SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

TACs must be differentiated from short-lasting headaches that do not have prominent cranial autonomic syndromes, notably trigeminal neuralgia (TN), primary stabbing headache, and hypnic headache. The cycling pattern and length, frequency, and timing of attacks are useful in classifying patients. Patients with TACs should be considered, if clinically indicated, to undergo pituitary imaging and pituitary function tests because there is an excess of TAC presentations in patients with pituitary tumor-related headache, particularly prolactin and growth hormone secreting tumors.

Cluster Headache Cluster headache is a relatively rare form of primary headache, although nonetheless a common condition, with a population frequency of ~0.1%. The pain is deep, usually retroorbital, often excruciating in intensity, nonfluctuating, and explosive in quality. A core feature of cluster headache is periodicity. At least one of the daily attacks of pain recurs at about the same hour each day for the duration of a cluster bout. The typical cluster headache patient has daily bouts of one to two attacks of relatively short-duration unilateral pain for 8–10 weeks a year; this is usually followed by a pain-free interval that averages a little less than 1 year. Cluster headache is characterized as chronic when there is <3 months of sustained remission without treatment. Patients are generally perfectly well between episodes. Onset of attacks is nocturnal in about 50% of patients, and men are affected three times more often than women. Patients with cluster headache tend to move about during attacks, pacing, rocking, or rubbing their head for relief; some may even become aggressive during attacks. This is in sharp contrast to patients with migraine, who prefer to remain motionless during attacks.

Cluster headache is associated with ipsilateral symptoms of cranial parasympathetic activation: conjunctival injection or lacrimation, aural fullness, rhinorrhea or nasal congestion, or cranial sympathetic dysfunction such as ptosis. The sympathetic deficit is peripheral and likely to be due to parasympathetic activation with injury to ascending sympathetic fibers surrounding a dilated carotid artery as it passes

into the cranial cavity. When present, photophobia and phonophobia are far more likely to be unilateral and on the same side of the pain, rather than bilateral, as is seen in migraine. This phenomenon of unilateral photophobia/phonophobia is characteristic of TACs. Cluster headache is likely to be a disorder involving central pacemaker neurons and neurons in the posterior hypothalamic region (Fig. 430-3).

TREATMENT

Cluster Headache

The most satisfactory treatment is the administration of drugs to prevent cluster attacks until the bout is over. However, treatment of acute attacks is required for all cluster headache patients at some time.

ACUTE ATTACK TREATMENT

Cluster headache attacks peak rapidly, and thus a treatment with rapid onset is required. Many patients with acute cluster headache respond very well to oxygen inhalation. This should be given as 100% oxygen at 10–12 L/min for 15–20 min. It appears that high flow and high oxygen content are important. Sumatriptan 6 mg SC is rapid in onset and will usually shorten an attack to 10–15 min; there is no evidence of tachyphylaxis. Sumatriptan (20 mg) and zolmitriptan (5 mg) nasal sprays are both effective in acute cluster headache, offering a useful option for patients who may not wish to self-inject daily. Noninvasive vagus nerve stimulation (nVNS) is FDA approved for the acute treatment of attacks in episodic cluster headache using three 2-min stimulation cycles applied consecutively at the onset of headache on the side of pain; this may be repeated after 9 min. Oral sumatriptan is not effective for prevention or for acute treatment of cluster headache.

PREVENTIVE TREATMENTS (TABLE 430-8)

The choice of a preventive treatment in cluster headache depends in part on the length of the bout. Patients with long bouts or those

TABLE 430-8 Preventive Management of Cluster Headache

SHORT-TERM PREVENTION	LONG-TERM PREVENTION
EPISODIC CLUSTER HEADACHE	EPISODIC CLUSTER HEADACHE AND PROLONGED CHRONIC CLUSTER HEADACHE
Prednisone 1 mg/kg up to 60 mg qd, tapering over 21 days	Verapamil 160–960 mg/d nVNS ^b 6–24 stimulations/d
Verapamil 160–960 mg/d	Melatonin ^a 9–12 mg/d
Galcanezumab 300 mg SC	Topiramate ^a 100–400 mg/d
Greater occipital nerve injection	Lithium 400–800 mg/d Gabapentin ^a 1200–3600 mg/d

^aUnproven but of potential benefit. ^bNoninvasive vagus nerve stimulation.

with chronic cluster headache require medicines that are safe when taken for long periods. For patients with relatively short bouts, limited courses of oral glucocorticoids can be very useful. A 10-day course of prednisone, beginning at 60 mg daily for 7 days and followed by a rapid taper, may interrupt the pain bout for many patients. Greater occipital nerve injection with lidocaine and corticosteroids has been shown to be effective in randomized controlled trials, with a benefit that lasts up to 6–8 weeks. The CGRP monoclonal antibody galcanezumab has been approved by the FDA for treatment of episodic cluster headache; it reduces attack frequency, is well tolerated, and is often an effective option.

Most experts favor verapamil as the first-line preventive treatment for patients with chronic cluster headache or with prolonged bouts. While verapamil compares favorably with lithium in practice, some patients require verapamil doses far in excess of those administered for cardiac disorders. The initial dose range is 40–80 mg twice daily; effective doses may be as high as 960 mg/d. Side effects such as constipation, leg swelling, or gingival hyperplasia can be problematic. Of paramount concern, however, is the cardiovascular safety of verapamil, particularly at high doses. Verapamil can cause heart block by slowing conduction in the atrioventricular node, a condition that can be monitored by following the PR interval on a standard electrocardiogram (ECG). Approximately 20% of patients treated with verapamil develop ECG abnormalities, which can be observed with doses as low as 240 mg/d; these abnormalities can worsen over time in patients on stable doses. A baseline ECG is recommended for all patients. The ECG is repeated 10 days after a dose change in patients whose dose is being increased above 240 mg daily. Dose increases are usually made in 80-mg increments. For patients on long-term verapamil, ECG monitoring every 6 months is advised.

NEUROMODULATION THERAPY

When medical therapies fail in chronic cluster headache, neuro-modulation strategies can be used. Sphenopalatine ganglion (SPG) stimulation with an implanted battery-free stimulator has been shown in randomized controlled trials to be effective in aborting attacks and reducing their frequency over time. nVNS compares favorably with standard-of-care in open-label experience. Similarly, occipital nerve stimulation has been used open label and appears to be beneficial. Deep-brain stimulation of the region of the posterior hypothalamic gray matter is successful in about 50% of patients treated, although its risk-versus-benefit ratio makes it inappropriate before all other less invasive options have been explored.

■ PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania (PH) is characterized by frequent unilateral, severe, short-lasting episodes of headache. Like cluster headache, the pain tends to be retroorbital but may be experienced all over the head and is associated with autonomic phenomena such as lacrimation and nasal congestion. Patients with remissions are said to have episodic PH, whereas those with the nonremitting form are said to have chronic PH. The essential features of PH are: unilateral very severe pain; short-lasting attacks (2–45 min); very frequent attacks (usually >5 a

day); marked autonomic features ipsilateral to the pain; rapid course (<72 h); and excellent response to indomethacin. In contrast to cluster headache, which predominantly affects males, the male-to-female ratio in PH is close to 1:1.

Indomethacin (25–75 mg tid), which can completely suppress attacks of PH, is the treatment of choice. Although therapy may be complicated by indomethacin-induced gastrointestinal side effects, currently there are no consistently effective alternatives. Topiramate is helpful in some cases. Verapamil, an effective treatment for cluster headache, does not appear to be useful for PH. nVNS can be very effective in these patients. In occasional patients, PH can coexist with TN (PH-tic syndrome); similar to cluster-tic syndrome, each component may require separate treatment.

Secondary PH has been reported with lesions in the region of the sella turcica, including arteriovenous malformation, cavernous sinus meningioma, pituitary pathology, and epidermoid tumors. Secondary PH is more likely if the patient requires high doses (>200 mg/d) of indomethacin. In patients with apparent bilateral PH, raised cerebrospinal fluid (CSF) pressure should be suspected. It is important to note that indomethacin reduces CSF pressure. When a diagnosis of PH is considered, MRI is indicated to exclude a pituitary lesion.

■ SUNCT/ SUNA

SUNCT is a rare primary headache syndrome characterized by severe, unilateral orbital or temporal pain that is stabbing or throbbing in quality. Diagnosis requires at least 20 attacks, lasting for 5–240 s; ipsilateral conjunctival injection and lacrimation should be present. In some patients, conjunctival injection or lacrimation is missing, and the diagnosis of SUNA can be made.

DIAGNOSIS The pain of SUNCT/SUNA is unilateral and may be located anywhere in the head. Three basic patterns can be seen: single stabs, which are usually short-lived; groups of stabs; or a longer attack comprising many stabs between which the pain does not completely resolve, thus giving a “saw-tooth” phenomenon with attacks lasting many minutes. Each pattern may be seen in the context of an underlying continuous head pain. Characteristics that lead to a suspected diagnosis of SUNCT are the cutaneous (or other) triggers of attacks, a lack of refractory period to triggering between attacks, and the lack of a response to indomethacin. Apart from trigeminal sensory disturbance, the neurologic examination is normal in primary SUNCT/SUNA.

The diagnosis of SUNCT/SUNA is often confused with TN particularly in first-division TN (Chap. 441). Minimal or no cranial autonomic symptoms and a clear refractory period to triggering indicate a diagnosis of TN.

SECONDARY (SYMPTOMATIC) SUNCT SUNCT can be seen with posterior fossa or pituitary lesions. All patients with SUNCT/SUNA should be evaluated with pituitary function tests and a brain MRI with pituitary views.

TREATMENT

SUNCT/ SUNA

ABORTIVE THERAPY

Therapy of acute attacks is not a useful concept in SUNCT/SUNA because the attacks are of such short duration. However, IV lidocaine, which arrests the symptoms, can be used in hospitalized patients.

PREVENTIVE THERAPY

Long-term prevention to minimize disability and hospitalization is the goal of treatment. The most effective treatment for prevention is lamotrigine, 200–400 mg/d. Topiramate and gabapentin may also be effective. Carbamazepine, 400–500 mg/d, has been reported by patients to offer modest benefit.

Surgical approaches such as microvascular decompression or destructive trigeminal procedures are seldom useful and often produce long-term complications. Greater occipital nerve injection has

produced limited benefit in some patients. Occipital nerve stimulation is probably helpful in a subgroup of these patients. For intractable cases, short-term prevention with IV lidocaine can be effective.

■ HEMICRANIA CONTINUA

The essential features of hemicrania continua are moderate and continuous unilateral pain associated with fluctuations of severe pain; complete resolution of pain with indomethacin; and exacerbations that may be associated with autonomic features, including conjunctival injection, lacrimation, and photophobia on the affected side. The age of onset ranges from 10 to 70 years; women are affected twice as often as men. The cause is unknown.

TREATMENT

Hemicrania Continua

Treatment consists of indomethacin; other NSAIDs appear to be of little or no benefit. The IM injection of 100 mg of indomethacin has been proposed as a diagnostic tool, and administration with a placebo injection in a blinded fashion can be very useful diagnostically. Alternatively, a trial of oral indomethacin, starting with 25 mg tid, then 50 mg tid, and then 75 mg tid, can be given. Up to 2 weeks at the maximal dose may be necessary to assess whether a dose has a useful effect. Topiramate can be helpful in some patients. nVNS can be very useful in these patients. Occipital nerve stimulation probably has a role in patients with hemicrania continua who are unable to tolerate indomethacin.

■ OTHER PRIMARY HEADACHE DISORDERS

Primary Cough Headache Primary cough headache is a generalized headache that begins suddenly, lasts for seconds or several minutes, sometimes up to a few hours, and is precipitated by coughing; it is preventable by avoiding coughing or other precipitating events, which can include sneezing, straining, laughing, or stooping. In all patients with this syndrome, serious etiologies must be excluded before a diagnosis of "benign" primary cough headache can be established. A Chiari malformation or any lesion causing obstruction of CSF pathways or displacing cerebral structures can be the cause of the head pain. Other conditions that can present with cough or exertional headache as the initial symptom include cerebral aneurysm, carotid stenosis, and vertebrobasilar disease. Benign cough headache can resemble benign exertional headache (below), but patients with the former condition are typically older.

TREATMENT

Primary Cough Headache

Indomethacin 25–50 mg two to three times daily is the treatment of choice. Some patients with cough headache obtain complete cessation of their attacks with lumbar puncture; this is a simple option when compared to prolonged use of indomethacin, and it is effective in about one-third of patients. The mechanism of this response is unclear.

Primary Exercise Headache Primary exercise headache has features resembling both cough headache and migraine. It may be precipitated by any form of exercise; it often has the pulsatile quality of migraine. The pain lasts <48 h, is bilateral, and is often throbbing at onset; migrainous features may develop in patients susceptible to migraine. The duration tends to be shorter in adolescents than in older adults. Primary exercise headache can be prevented by avoiding excessive exertion, particularly in hot weather or at high altitude.

The mechanism of primary exercise headache is unclear. Acute venous distension likely explains one syndrome—the acute onset of headache with straining and breath holding, as in weightlifter's

headache. Because exercise can trigger headache in a number of serious underlying conditions (Chap. 16), these must be considered in patients with exercise headache. Pain from angina may be referred to the head, probably by central connections of vagal afferents, and may present as exercise headache (cardiac cephalgia). The link to exercise is the main clinical clue that headache is of cardiac origin. Pheochromocytoma may occasionally cause exercise headache. Intracranial lesions and stenosis of the carotid arteries are other possible etiologies.

TREATMENT

Primary Exercise Headache

Exercise regimens should begin modestly and progress gradually to higher levels of intensity. Indomethacin at daily doses from 25–150 mg is generally effective in benign exertional headache. Indomethacin (50 mg), a gepant, ergotamine (1 mg orally), and dihydroergotamine (2 mg by nasal spray) are useful preventive measures.

Primary Headache Associated with Sexual Activity Three types of sex headache are reported: a dull bilateral ache in the head and neck that intensifies as sexual excitement increases; a sudden, severe, explosive headache occurring at orgasm; and a postural headache developing after coitus. The last arises from vigorous sexual activity and is a form of low CSF pressure headache and thus not a primary headache disorder (Chap. 16). Headaches developing at the time of orgasm are not always benign; 5–12% of cases of subarachnoid hemorrhage are precipitated by sexual intercourse. Sex headache is reported by men more often than women and may occur at any time during the years of sexual activity. It may appear on several occasions in succession and then not trouble the patient again, even without an obvious change in sexual activity. In patients who stop sexual activity when headache is first noticed, the pain may subside within a period of 5 min to 2 h. In about half of patients, sex headache will subside within 6 months. Most patients with sex headache do not have exercise or cough headache; this clinical paradox is generally a marker of primary sex headache. Migraine is probably more common in patients with sex headache.

TREATMENT

Primary Sex Headache

Benign sex headaches recur irregularly and infrequently. Management can often be limited to reassurance and advice about ceasing sexual activity if a mild, warning headache develops. Propranolol can be used to prevent headache that recurs regularly or frequently, but the dosage required varies from 40–200 mg/d. An alternative is the calcium channel-blocking agent diltiazem, 60 mg tid. Indomethacin (25–50 mg), frovatriptan (2.5 mg), or a gepant taken 30–45 min prior to sexual activity can also be helpful.

Primary Thunderclap Headache Sudden onset of severe headache may occur in the absence of any known provocation. The differential diagnosis includes the sentinel bleed of an intracranial aneurysm, cervicocephalic arterial dissection, and cerebral venous thrombosis. Headaches of explosive onset may also be caused by the ingestion of sympathomimetic drugs or of tyramine-containing foods in a patient who is taking MAOIs, or they may be a symptom of pheochromocytoma. Whether thunderclap headache can be the presentation of an unruptured cerebral aneurysm is uncertain. When neuroimaging studies and lumbar puncture exclude subarachnoid hemorrhage, patients with thunderclap headache usually do very well over the long term. In one study of patients whose CT scans and CSF findings were negative, ~15% had recurrent episodes of thunderclap headache, and nearly half subsequently developed migraine or TTH.

The first presentation of any sudden-onset severe headache should be diligently investigated with neuroimaging (CT or, when possible,

MRI with MR angiography) and CSF examination. Reversible segmental cerebral vasoconstriction may be seen in primary thunderclap headache without an intracranial aneurysm, and it is thought that this may be an underdiagnosed condition. In the presence of posterior leukoencephalopathy, the differential diagnosis includes cerebral angiitis, drug toxicity (cyclosporine, intrathecal methotrexate/cytarabine, pseudoephedrine, or cocaine), posttransfusion effects, and postpartum angiopathy. Treatment with nimodipine may be helpful, although the vasoconstriction of primary thunderclap headache resolves spontaneously.

Cold-Stimulus Headache This refers to head pain triggered by application or ingestion/inhalation of something cold. It is brought on quickly and typically resolves within 10–30 min of the stimulus being removed. It is best recognized as “brain-freeze” headache or ice-cream headache when due to ingestion. Although cold may be uncomfortable at some level for many people, it is the reliable, severe, and somewhat prolonged nature of these pains that set them apart. The transient receptor potential cation subfamily M member 8 (TRPM8) channel, a known cold-temperature sensor, may be a mediator of this syndrome. Naproxen 500 mg taken 30 min prior to exposure can be helpful for this problem.

External Pressure Headache External pressure from compression or traction on the head can produce a pain that may have some generalized component, although the pain is largely focused around the site of the pressure. It typically resolves within an hour of the stimulus being removed. Examples of stimuli include helmets, swimming goggles, or very long ponytails. Treatment is to recognize the problem and remove the stimulus.

Primary Stabbing Headache The essential features of primary stabbing headache are stabbing pain confined to the head or, rarely, the face, lasting from 1 to many seconds and occurring as a single stab or a series of stabs; absence of associated cranial autonomic features; absence of cutaneous triggering of attacks; and a pattern of recurrence at irregular intervals (hours to days). When present in adolescents, primary stabbing headache may be a presenting and very troublesome problem for the patient. The pains have been variously described as “ice-pick pains” or “jabs and jolts.” They are more common in patients with other primary headaches, such as migraine, the TACs, and hemispheric continua. A key clinical feature is an irregular cadence compared to the regular cadence of the throbbing or pounding that characterizes migraine.

TREATMENT

Primary Stabbing Headache

The response of primary stabbing headache to indomethacin (25–50 mg two to three times daily) is usually excellent. As a general rule, the symptoms wax and wane, and after a period of control on indomethacin, it is appropriate to withdraw treatment and observe the outcome.

Nummular Headache Nummular headache is felt as a round or elliptical discomfort that is fixed in place, ranges in size from 1–6 cm, and may be continuous or intermittent. Uncommonly it may be multifocal. It may be episodic but is more often continuous during exacerbations. Accompanying the pain there may be a local sensory disturbance, such as allodynia or hypesthesia. Local dermatologic or bony lesions need to be excluded by examination and investigation. This condition can be difficult to treat when present in isolation; tricyclics, such as amitriptyline, or anticonvulsants, such as topiramate or valproate, are most often tried. This phenotype can be seen in combination with migraine and the TACs, in which cases treatment of the associated condition is often effective for the nummular headache as well.

Hypnic Headache This headache syndrome typically begins a few hours after sleep onset. The headaches last from 15–30 min and

are typically moderately severe and generalized, although they may be unilateral and can be throbbing. Patients may report falling back to sleep only to be awakened by a further attack a few hours later; up to three repetitions of this pattern occur through the night. Daytime naps can also precipitate head pain. Most patients are female, and the onset is usually after age 60 years. Headaches are typically bilateral but may be unilateral. Photophobia, phonophobia, and nausea are usually absent. The major secondary consideration in this headache type is poorly controlled hypertension; 24-h blood pressure monitoring is recommended to detect this treatable condition.

TREATMENT

Hypnic Headache

Patients with hypnic headache generally respond to a bedtime dose of lithium carbonate (200–600 mg). For those intolerant of lithium, verapamil (160 mg) is an alternative strategy. One to two cups of coffee, or caffeine 60 mg orally, at bedtime may be effective in approximately one-third of patients. Case reports also suggest that flunarizine, 5 mg nightly, or indomethacin, 25–75 mg nightly, can be effective.

New Daily Persistent Headache Primary new daily persistent headache (NDPH) occurs in both men and women. It can be of the migrainous type, with features of migraine, or it can be featureless, appearing as new-onset TTH. Those with migrainous features are the most common form and include unilateral headache and throbbing pain; each feature is present in about one-third of patients. Nausea, photophobia, and/or phonophobia occur in about half of patients. Some patients have a previous history of migraine; however, the proportion of NDPH sufferers with preexisting migraine is no greater than the frequency of migraine in the general population. NDPH may be more common in adolescents. Treatment of migrainous-type primary NDPH consists of using the preventive therapies effective in migraine (see above). Featureless NDPH is one of the primary headache forms most refractory to treatment. Standard preventive therapies can be offered but are often ineffective. The secondary NDPHs are discussed elsewhere (*Chap. 16*).

A

The editors acknowledge the contributions of Neil H. Raskin to earlier editions of this chapter.

FURTHER READING

- A M. Migraine. *N Engl J Med* 383:1866, 2020.
- G PJ: Primary headache disorders—five new things. *Neurology Clinical Practice* 9:233, 2019.
- G PJ et al: A controlled trial of erenumab for episodic migraine. *N Engl J Med* 377:2123, 2017.
- G PJ et al: Pathophysiology of migraine: A disorder of sensory processing. *Physiol Rev* 97:553, 2017.
- G PJ et al: Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med* 381:132, 2019.
- H J, M A: Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol* 17:75, 2018.
- L RB et al: Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 68:343, 2007.
- S CJ et al: “Visual snow”—a disorder distinct from persistent migraine aura. *Brain* 137:1419, 2014.
- S SD et al: Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med* 377:2113, 2017.
- T EA et al: From migraine genes to mechanisms. *Pain* 156 Suppl 1: S64, 2015.
- W DY, G PJ: Cluster headache pathogenesis—mechanisms from current and emerging treatments. *Nat Rev Neurol* 17:308, 2021.



ALZHEIMER'S DISEASE

Approximately 50 million people across the world are living with dementia. Alzheimer's disease (AD) is the most common cause of dementia, contributing to an estimated 60–70% of all cases. It is estimated that the median annual total cost of caring for a single patient with advanced AD is >\$50,000, while the emotional toll for family members and caregivers is immeasurable. AD can manifest as early as the third decade of life, but it is the most common cause of dementia in the elderly. Patients most often present with an insidious loss of episodic memory followed by a slowly progressive dementia. In typical amnestic AD, brain atrophy begins in the medial temporal lobes before spreading to the inferior temporal, lateral, medial parietal, and dorsolateral frontal cortices. Microscopically, there are widespread neuritic plaques containing amyloid beta (A β), neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau filaments, and A β accumulation in blood vessel walls in cortex and leptomeninges (amyloid angiopathy, see "Pathology," below). The identification of causative mutations and susceptibility genes for AD has provided a foundation for progress in understanding the biologic basis of the disorder. The major genetic risk factor for AD is the e4 allele of the apolipoprotein E (*ApoE*) gene. Carrying one e4 allele increases the risk for AD by two- to threefold in women whereas carrying two alleles increases the risk ten- to fifteenfold in both sexes. Rapid progress in the development of imaging, cerebrospinal fluid (CSF), and plasma biomarkers of A β and phosphorylated tau has enabled detection of AD pathologic hallmarks in living people, opening the door to early detection and intervention with biologically specific therapies.

CLINICAL MANIFESTATIONS

The cognitive changes of AD tend to follow a characteristic pattern, beginning with memory impairment and progressing to deficits in executive, language, and visuospatial functions. Yet ~20% of patients with AD present with nonmemory complaints such as word-finding, organizational, or navigational difficulty. In other patients, visual processing dysfunction (referred to as posterior cortical atrophy syndrome) or a progressive "logopenic" aphasia characterized by difficulties with naming and repetition are the primary manifestations of AD for years before progressing to involve memory and other cognitive domains. Still, other patients may present with an asymmetric akinetic-rigid-dystonic ("corticobasal") syndrome or a dysexecutive/behavioral, i.e., "frontal" variant of AD. Depression, social withdrawal, and anxiety occur in early disease stages and may represent a prodrome before cognitive symptoms are apparent.

In early stages of typical amnestic AD, the memory loss may go unrecognized or be ascribed to benign forgetfulness of aging. The term *subjective cognitive decline* refers to self-perceived worsening in memory or other cognitive abilities that may not be noticeable to others or apparent on formal neuropsychologic testing. Once the memory loss becomes noticeable to the patient and family and friends and is confirmed on standardized memory tests, the term *mild cognitive impairment* (MCI) is often used. This construct provides useful prognostic information, because ~50% of patients with MCI (roughly 12% per year) will progress to AD over 4 years. Increasingly, the MCI construct is being replaced by the notion of "early symptomatic AD" to signify that AD is considered the underlying disease (based on clinical or biomarker evidence) in a patient who remains functionally compensated. Even earlier in the course, "preclinical AD" refers to a person with CSF or positron emission tomography (PET) biomarker evidence of amyloid pathology (with or without tau pathology) in the absence of symptoms. It is estimated that preclinical biomarker changes may precede clinical symptoms by 20 years or more, creating a window of

opportunity for early-stage treatment and prevention trials. New evidence suggests that partial and sometimes generalized seizures herald AD and can occur even prior to dementia onset, especially in younger patients and patients with autosomal dominant AD-causing mutations.

Eventually, with AD, the cognitive problems begin to interfere with daily activities, such as keeping track of finances, following instructions on the job, driving, shopping, and housekeeping. Some patients are unaware of these difficulties (*anosognosia*), but most remain acutely attuned to their deficits in early disease stages. Changes in environment (travel, relocation, hospitalization) tend to destabilize the patient. Over time, patients become lost on walks or while driving. Social graces, routine behavior, and superficial conversation may be surprisingly intact, even into the later stages of the illness.

In the middle stages of AD, the patient is unable to work, is easily lost and confused, and requires daily supervision. Language becomes impaired—first naming, then comprehension, and finally fluency. Word-finding difficulties and circumlocution can be evident in the early stages, even when formal testing demonstrates intact naming and fluency. *Apraxia* emerges, manifesting as trouble performing learned sequential motor tasks such as using utensils or appliances. Visuospatial deficits begin to interfere with dressing, eating, or even walking, and patients fail to solve simple puzzles or copy geometric figures. Simple calculations and clock reading become difficult in parallel.

In the late stages, some persons remain ambulatory, wandering aimlessly. Loss of judgment and reasoning is inevitable. Delusions are prevalent and usually simple, with common themes of theft, infidelity, or misidentification. Disinhibition and uncharacteristic belligerence may occur and alternate with passivity and withdrawal. Sleep-wake patterns are disrupted, and nighttime wandering becomes disturbing to the household. Some patients develop a shuffling gait with generalized muscle rigidity associated with slowness and awkwardness of movement. Patients often look parkinsonian (Chap. 435) but rarely have a high-amplitude, low-frequency tremor at rest. There is a strong overlap between dementia with Lewy bodies (DLB) (Chap. 434) and AD, and some AD patients develop more classical parkinsonian features.

In the end stages, patients with AD become rigid, mute, incontinent, and bedridden, and need help with eating, dressing, and toileting. Hyperactive tendon reflexes and myoclonic jerks (sudden brief contractions of various muscles or the whole body) may occur spontaneously or in response to physical or auditory stimulation. Often death results from malnutrition, secondary infections, pulmonary emboli, heart disease, or, most commonly, aspiration. The typical duration of symptomatic AD is 8–10 years, but the course ranges from 1–25 years. For unknown reasons, some patients with AD show a steady decline in function while others have prolonged plateaus without major deterioration.

DIAGNOSIS

A detailed discussion of the diagnosis of dementia is presented in Chap. 29. Early in the disease course, other etiologies of dementia should be excluded (see Tables 29-1, 29-3, and 29-4). Neuroimaging studies (CT and MRI) do not show a single specific pattern with AD and may be normal early in the disease. As AD progresses, more distributed but usually posterior-predominant cortical atrophy becomes apparent, along with atrophy of the medial temporal memory structures (see Fig. 29-1). The main purpose of imaging is to exclude other disorders, such as primary and secondary neoplasms, vascular dementia, diffuse white matter disease, and normal-pressure hydrocephalus (NPH). Imaging also helps to distinguish AD from other degenerative disorders, such as frontotemporal dementia (FTD) (Chap. 432) or the prion disorder Creutzfeldt-Jakob disease (CJD) (Chap. 438), which feature imaging patterns that are different from AD. Functional imaging studies, such as fluorodeoxyglucose (FDG) PET, reveal hypometabolism in the posterior temporal-parietal cortex in AD (see Fig. 29-1).

Amyloid PET imaging (e.g., with radiotracers [^{11}C]PIB, [^{18}F]florbetapir, [^{18}F]florbetaben, or [^{18}F]flutemetamol) confirms the presence of neuritic and diffuse A β plaques throughout the neocortex (Fig. 431-1). Although amyloid PET binding is detected in AD, approximately 25% of cognitively unimpaired older individuals also have positive scans,

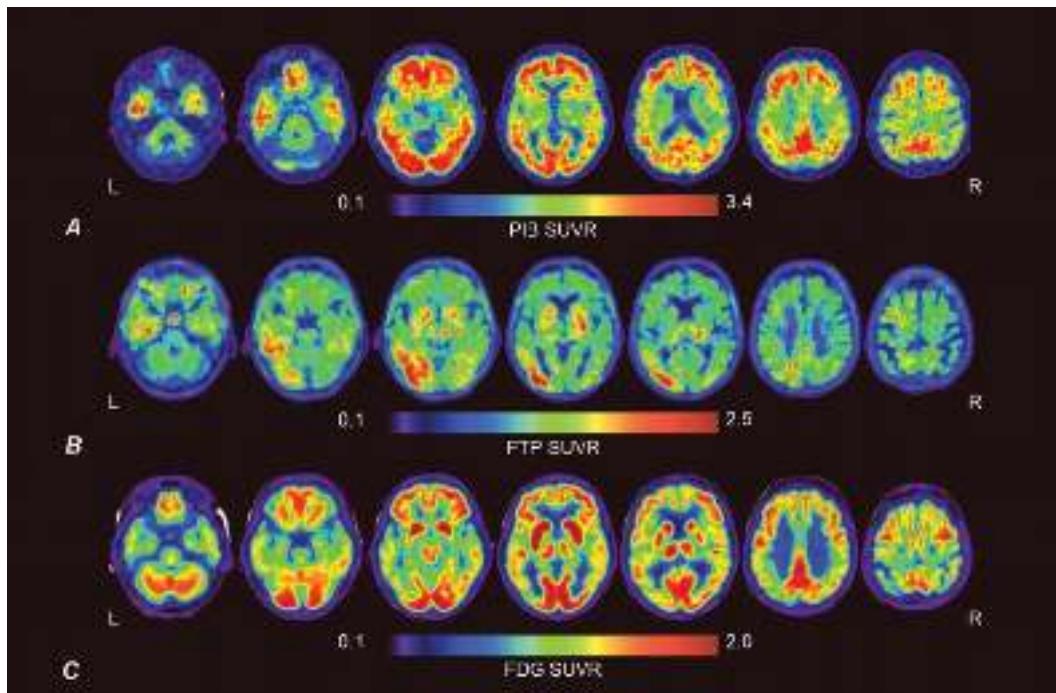


FIGURE 431-1 Molecular imaging of Alzheimer's disease pathophysiology in an 81-year-old with mild Alzheimer's disease. **A.** A β positron emission tomography (PET) with [^{11}C]PiB reveals extensive radiotracer retention in neocortex, consistent with the known distribution of amyloid plaques. **B.** Tau PET with [^{18}F]FTP shows asymmetric uptake predominantly in left temporal cortex, consistent with intermediate-stage NFTs. Tracer uptake in midbrain and basal ganglia represents "off-target" (non-tau related) tracer retention. **C.** FDG-PET reveals reduced tracer uptake in left greater than right temporal and parietal cortex, indicative of decreased synaptic activity. The pattern of hypometabolism corresponds more closely to the pattern of tau than amyloid deposition. **A–C.** Axial brain slices are shown in neurologic orientation. L, left; R, right; SUVR, standardized uptake value ratio, a quantitative measure of PET radiotracer retention.

thought to represent preclinical disease and an increase in the risk of converting to clinical AD. Similarly, dementia due to a non-AD disorder can be the underlying etiology in a patient who tests positively on amyloid PET. Amyloid PET ligands also bind to vascular A β deposits in cerebral amyloid angiopathy (Chap. 428). Therefore, clinical use of amyloid PET should be restricted to specific scenarios in which knowledge of amyloid status is expected to impact diagnosis and change management. For example, a negative amyloid PET scan in a patient with dementia makes an AD diagnosis unlikely.

Tau PET radiotracers (e.g., [^{18}F]flortaucipir, [^{18}F]MK-6240) bind to the paired helical filaments that form NFTs and are primarily available in the research setting. The pattern of binding is largely consistent with Braak neuropathologic staging of NFTs, with early retention in medial temporal regions, followed by spread into temporoparietal and cingulate cortices, dorsolateral prefrontal regions, and, ultimately, primary sensory and motor areas.

Routine spinal fluid examination is generally normal, but CSF reductions in A β_{42} levels and the A β_{42} /A β_{40} ratio correlate with amyloid deposition, increases in phosphorylated tau (at residue 181 or 217) correlate with tangle inclusions, and increases in total tau levels represent a nonspecific finding seen in AD but also in other causes of neurodegeneration. Plasma measurements of A β and phosphorylated tau with ultra-sensitive immunoassays or mass spectrometry show great promise and are likely to increase access and affordability of AD molecular biomarkers.

Electroencephalogram (EEG) is normal or shows nonspecific slowing; prolonged EEG can be used to seek out intermittent nonconvulsive seizures.

Slowly progressive decline in memory and orientation, normal results on laboratory tests, and an MRI or CT scan showing only distributed or posteriorly predominant cortical and hippocampal atrophy are highly suggestive of AD. A clinical diagnosis of AD reached after careful evaluation is confirmed at autopsy 70–90% of the time, with misdiagnosed

cases usually resulting from pathologic limbic-predominant age-related TDP-43 encephalopathy (LATE) neuropathologic changes with or without hippocampal sclerosis, primary age-related tauopathy, DBL, vascular pathology, or frontotemporal lobar degeneration (FTD).

Simple clinical clues are useful in the differential diagnosis. Early prominent gait disturbance with only mild memory loss suggests vascular dementia or, rarely, NPH (see below). Resting tremor with stooped posture, bradykinesia, and masked facies suggest PD (Chap. 435) or DBL (Chap. 434). When dementia occurs after a well-established diagnosis of PD, PD dementia (PDD) is usually the correct diagnosis, but many patients with this diagnosis will show a mixture of AD and DBL at autopsy. The early appearance of parkinsonian features in association with fluctuating alertness, visual hallucinations, or delusional misidentification suggests DBL. Chronic alcoholism should prompt the search for vitamin deficiency. Loss of joint position and vibration sensibility accompanied by Babinski signs suggests vitamin B₁₂ deficiency, especially in a patient with a history of autoimmune disease, small bowel resection or irradiation, or veganism (Chap. 99). Early onset of a focal seizure suggests a metastatic or primary brain neoplasm (Chap. 90). Previous or ongoing depression raises suspicion for depression-related cognitive impairment, although significant cognitive changes with depression are uncommon and AD and DBL can feature a depressive or anxious prodrome. A history of treatment for insomnia, anxiety, psychiatric disturbance, or epilepsy suggests chronic drug intoxication. Rapid progression over a few weeks or months associated with rigidity and myoclonus suggests CJD (Chap. 438). Prominent behavioral changes with intact navigation and focal anterior-predominant atrophy on brain imaging are typical of FTD. A positive family history of dementia suggests either one of the familial forms of AD or one of the other genetic disorders associated with dementia, such as FTD (Chap. 432), Huntington's disease (HD) (Chap. 436), prion disease (Chap. 438), or rare hereditary ataxias (Chap. 439).

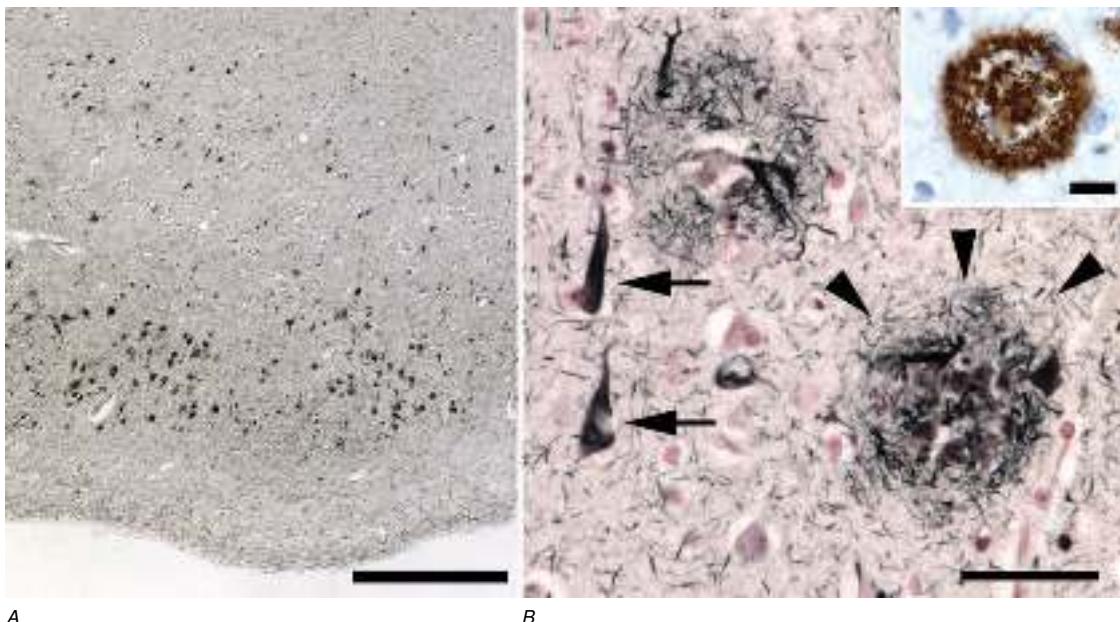


FIGURE 431-2 Neuropathology of Alzheimer's disease. **A.** Early neurofibrillary degeneration, consisting of NFTs and neuropil threads, preferentially affects the medial temporal lobes, especially the stellate pyramidal neurons that compose the layer 2 islands of entorhinal cortex, as shown using Gallyas silver staining. **B.** Higher magnification view reveals the fibrillar nature of tangles (arrows) and the complex structure of neuritic plaques (arrowheads), whose major component is A β (inset shows immunohistochemistry for A β). Scale bars are 500 μ M in **A**, 50 μ M in **B**, and 20 μ M in **B** inset.

■ EPIDEMIOLOGY

The most important risk factors for AD are increasing age and a positive family history. In the United States, approximately 10% of people over age 65 years have AD, including 3% of people age 65–74 years, 17% of people age 75–84 years, and 32% of people age 85 years and older. A positive family history of dementia suggests a genetic contribution to AD, which is usually attributable to the *ApoE ε4* risk allele. Autosomal dominant inheritance occurs in only 1–2% of patients and is typically accompanied by a multigenerational history of early-onset dementia. Female sex is a risk factor independent of the greater longevity of females, and women who carry a single *ApoE ε4* allele are more susceptible than are male ε4 carriers. A history of mild-to-severe traumatic brain injury increases the risk for AD. AD is more common in groups with low educational attainment, but education influences test-taking ability, and it is clear that AD can affect persons of all intellectual levels. One study found that the capacity to express complex written language in early adulthood correlated with a decreased risk for AD. Similarly, illiteracy and low educational attainment are risk factors for dementia. Numerous environmental factors, including aluminum, mercury, and viruses, have been proposed as causes of AD, but rigorous studies have failed to demonstrate a significant role for any of these exposures. Similarly, several studies suggest that the use of nonsteroidal anti-inflammatory agents is associated with a decreased risk of AD, but this risk has not been confirmed in large prospective studies. Vascular disease, and stroke in particular, seems to lower the threshold for the clinical expression of AD. Also, in many patients with AD, amyloid angiopathy can lead to microhemorrhages, large lobar hemorrhages, ischemic infarctions most often in the subcortical white matter, or in rare cases an inflammatory leukoencephalopathy. Diabetes increases the risk of AD threefold. Elevated homocysteine and cholesterol levels; hypertension; obesity; hearing loss; tobacco use; diminished serum levels of folic acid; low dietary intake of fruits, vegetables, and red wine; sleep disorders; low levels of exercise; and air pollution exposure are all being explored as potential risk factors for dementia in general and AD in particular.

■ PATHOLOGY

At autopsy, the earliest and most severe degeneration is usually found in the medial temporal lobe (entorhinal/perirhinal cortex and

hippocampus), inferolateral temporal cortex, and nucleus basalis of Meynert. The characteristic microscopic findings are neuritic plaques and NFTs (Fig. 431-2). These lesions accumulate in small numbers during normal brain aging but dominate the picture in AD. The overall burden of AD neuropathologic changes can be graded based on the topography of A β plaques, the density of neuritic plaques, and the spatial extent of NFTs present. Increasing evidence suggests that soluble amyloid species called *oligomers* may cause cellular dysfunction and represent the early toxic molecule in AD. Eventually, further amyloid polymerization and fibril formation lead to neuritic plaques, which contain a central core of amyloid, proteoglycans, ApoE, α -antichymotrypsin, and other proteins. A β is a protein of 39–42 amino acids that is derived proteolytically from a larger transmembrane protein, *amyloid precursor protein* (APP), when APP is cleaved by β and γ secretases (Fig. 431-3). The normal function of the A β peptides remains uncertain. APP has neurotrophic and neuroprotective properties. The plaque core is surrounded by a halo, which contains dystrophic, tau-immunoreactive neurites and activated microglia. The accumulation of A β in cerebral arterioles is termed *amyloid angiopathy*. NFTs are composed of silver-staining neuronal cytoplasmic fibrils composed of abnormally phosphorylated tau protein; they appear as paired helical filaments by electron microscopy. Tau binds to and stabilizes microtubules, supporting axonal transport of organelles, glycoproteins, neurotransmitters, and other important cargoes throughout the neuron. Once hyperphosphorylated, tau can no longer bind properly to microtubules and redistributes from the axon to throughout the neuronal cytoplasm and distal dendrites, compromising function. Other theories emphasize that abnormal conformations of tau induce misfolding of native (unfolded) tau into pathologic conformations and that this prion-like templating process is responsible for tau spreading (Chap. 424). Finally, patients with AD often show comorbid DLB, TDP-43, or vascular pathology. Most prevailing rodent models of AD involve expression of mutant transgenes that leads to A β_{42} accumulation in the absence of tauopathy. Even in these models, diminishing neuronal tau ameliorates cognitive deficits and nonconvulsive seizures while A β_{42} continues to accumulate, raising hope for tau-lowering therapies in humans. Biochemically, AD is associated with a decrease in the cortical levels of several proteins and neurotransmitters, especially acetylcholine, its

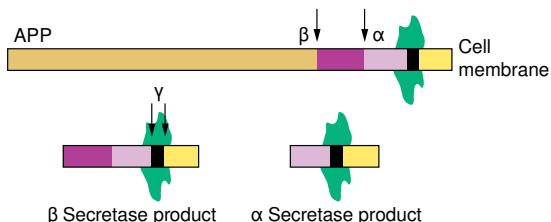
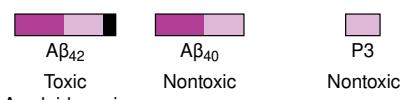
Step 1: Cleavage by either α or β secretaseStep 2: Cleavage by γ secretase

FIGURE 431-3 Amyloid precursor protein (APP) is catabolized by α , β , and γ secretases. A key initial step is the digestion by either β secretase (BACE) or α secretase (ADAM10 or ADAM17 [TACE]), producing smaller nontoxic products. Cleavage of the β secretase product by γ secretase (Step 2) results in either the toxic $\text{A}\beta_{42}$ or the nontoxic $\text{A}\beta_{40}$ peptide; cleavage of the α secretase product by γ secretase produces the nontoxic P3 peptide. Excess production of $\text{A}\beta_{42}$ is a key initiator of cellular damage in Alzheimer's disease (AD). Therapeutics for AD have focused on attempts to reduce accumulation of $\text{A}\beta_{42}$ by antagonizing β or γ secretases, promoting α secretase, or clearing $\text{A}\beta_{42}$ that has already formed by use of specific antibodies.

synthetic enzyme choline acetyltransferase, and nicotinic cholinergic receptors. Reduction of acetylcholine reflects degeneration of cholinergic neurons in the nucleus basalis of Meynert, located just below the thalamus and adjacent to the third ventricle, that project throughout the cortex. There is also noradrenergic and serotonergic depletion due to degeneration of upper brainstem nuclei such as the locus coeruleus (norepinephrine) and dorsal raphe (serotonin), where tau-immunoreactive neuronal cytoplasmic inclusions can be identified in early adult life, even in individuals lacking entorhinal cortex NFTs.

■ GENETIC CONSIDERATIONS

Several genes play an important role in the pathogenesis of AD. One is the *APP* gene on chromosome 21. Adults with trisomy 21 (Down's syndrome) consistently develop the typical neuropathologic hallmarks of AD if they survive beyond age 40 years, and many develop a progressive dementia superimposed on their baseline deficits. The extra dose of the *APP* gene on chromosome 21 is the initiating cause of AD in adult Down's syndrome and results in excess cerebral amyloid production. Supporting this hypothesis, some families with early-age-of-onset familial AD (FAD) have point mutations in *APP*. Although very rare, these families were the first examples of single-gene autosomal dominant transmission of AD.

Investigation of large families with multigenerational FAD led to the discovery of two additional AD-causing genes, the *presenilins*. Presenilin-1 (*PSEN-1*) is on chromosome 14 and encodes presenilin-1 protein (also known as S182). Mutations in this gene cause an early-age-of-onset AD, with onset typically before age 60 and often before age 50, transmitted in an autosomal dominant, highly penetrant fashion. More than 100 different mutations have been found in the *PSEN-1* gene in families from a wide range of ethnic backgrounds. Presenilin-2 (*PSEN-2*) is on chromosome 1 and encodes the presenilin-2 protein (also known as STM2). A mutation in the *PSEN-2* gene was first found in a group of American families with Volga German ethnic background. Mutations in *PSEN-1* are much more common than those in *PSEN-2*. The presenilins are highly homologous and encode similar proteins that at first appeared to have seven transmembrane domains (hence the designation *STM*), but subsequent studies have suggested eight such domains, with a ninth submembrane region. Both presenilins are cytoplasmic neuronal proteins that are widely expressed throughout the nervous system. They are homologous to a cell-trafficking protein, *sel-12*, found in the nematode *Caenorhabditis elegans*. Prior to symptom

onset, patients with mutations in the presenilin genes have elevated CSF levels of $\text{A}\beta_{42}$, and *PSEN-1* mutations produce increased $\text{A}\beta_{42}$ in the media in cell culture. *PSEN-1* is involved in the cleavage of APP at the γ secretase site and mutations in either gene (*PSEN-1* or *APP*) may disturb γ secretase cleavage. Mutations in *PSEN-1* are the most common cause of early-age-of-onset FAD, representing 40–70% of all cases. Mutations in *PSEN-1* tend to produce AD with an earlier age of onset (mean onset 45 years) and a shorter, more rapidly progressive course (mean duration 6–7 years) than mutations in *PSEN-2* (mean onset 53 years; duration 11 years). Although some carriers of *PSEN-2* mutations have had onset of dementia after the age of 70 years, mutations in the presenilins rarely lead to late-age-of-onset AD. Clinical genetic testing for these uncommon mutations is available but likely to be revealing only in early-age-of-onset FAD and should be performed in association with formal genetic counseling.

The *APOE* gene on chromosome 19 is involved in the pathogenesis of AD. The protein product, ApoE, participates in cholesterol transport (Chap. 407), and the gene has three alleles: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The *ApoE* $\epsilon 4$ allele confers increased risk of AD in the general population, including sporadic and late-age-of-onset familial forms. Approximately 24–30% of the nondemented white population has at least one $\epsilon 4$ allele (12–15% allele frequency), and about 2% are $\epsilon 4/\epsilon 4$ homozygotes. Among patients with AD, 40–65% have at least one $\epsilon 4$ allele, a highly significant elevation compared with controls. The increased risk associated with a single $\epsilon 4$ allele is especially prominent in women. The risk of AD in *ApoE* $\epsilon 4$ carriers also varies by racial and ethnic background, with increased risk in East Asians and decreased risk in blacks and Hispanics compared with whites. Additionally, many patients with AD have no $\epsilon 4$ allele, and $\epsilon 4$ carriers may never develop AD. Therefore, $\epsilon 4$ is neither necessary nor sufficient to cause AD. Nevertheless, the *ApoE* $\epsilon 4$ allele represents the most important genetic risk factor for sporadic AD and acts as a dose-dependent disease modifier, with each *ApoE* $\epsilon 4$ allele associated with an approximately 10-year earlier age of onset. The association between *ApoE* $\epsilon 4$ and AD is strongest in patients 60–85 years of age and is weaker in younger patients and in the very old. The precise mechanisms through which *ApoE* $\epsilon 4$ confers AD risk or hastens onset remain unclear, but $\epsilon 4$ leads to less efficient amyloid clearance and production of toxic fragments from cleavage of the molecule. ApoE can be identified in neuritic plaques and may also be involved in NFT formation, because it binds to tau protein. *ApoE* $\epsilon 4$ decreases neurite outgrowth in dorsal root ganglion neuronal cultures, perhaps indicating a deleterious role in the brain's response to injury. Increasing evidence suggests that the $\epsilon 2$ allele may reduce AD risk. Use of *ApoE* testing in AD diagnosis remains controversial because its predictive value remains unclear and many individuals with the $\epsilon 4$ allele will never develop dementia. Cognitively normal $\epsilon 4$ heterozygotes and homozygotes may show decreased posterior cerebral cortical metabolic function by PET imaging, suggesting presymptomatic abnormalities due to AD or an inherited vulnerability of the AD-targeted network. In demented persons who meet clinical criteria for AD, finding an $\epsilon 4$ allele increases the reliability of diagnosis; however, the absence of an $\epsilon 4$ allele cannot be considered evidence against AD. Nevertheless, *ApoE* $\epsilon 4$ remains the single most important biologic marker associated with AD risk, and studies of $\epsilon 4$'s functional role and diagnostic utility are progressing rapidly. *ApoE* genotyping is available in some straight-to-consumer genetic testing platforms. The $\epsilon 4$ allele is associated with increased risk for cerebral amyloid angiopathy (CAA), DLB, and vascular dementia, while its association with FTD is uncertain. Some evidence suggests that $\epsilon 4$ may worsen the expression of non-AD degenerative disorders, head trauma, and other brain injuries. Additional genes are also likely to be involved in AD, especially as minor-risk alleles for sporadic forms of the disease. Genome-wide association studies have identified more than 20 additional common genetic variants that, individually, have small (i.e., odds ratios ~1.1–1.2 or 0.8–0.9) impacts on the risk of AD. Implicated genes converge in biologic pathways related to innate immunity, lipid metabolism, and synaptic function. Examples include the clusterin (*CLU*), phosphatidylinositol-binding clathrin assembly protein (*PICALM*), and complement component (3b/4b) receptor 1 (*CRI*) genes, among others. *CLU*

may play a role in synapse turnover, *PICALM* participates in clathrin-mediated endocytosis, and *CRI* may be involved in amyloid clearance or synapse loss through the complement pathway. *TREM2* is a gene involved with inflammation that increases the likelihood of dementia. Homozygous mutation carriers develop a frontal dementia with bone cysts (Nasu-Hakola disease), whereas heterozygotes are predisposed to the development of AD. *TREM2* risk alleles are rare but have strong effects, with odds ratios estimated at 3–4 for developing clinical AD. Polygenic hazard scores that integrate the presence of multiple risk and protective alleles may be useful in predicting an individual's lifetime risk of developing AD. The vast majority of AD genetic studies have focused on white populations of European descent, and much less is known about the genetics of AD in nonwhite populations.

TREATMENT

Alzheimer's Disease

The management of AD is challenging and gratifying despite the absence of a cure or a robust pharmacologic treatment. The primary focus is on long-term amelioration of associated behavioral and neurologic problems, as well as providing caregiver support, though many potential disease-modifying therapies are currently being tested in human trials.

PATIENT AND CAREGIVER EDUCATION

Building rapport with the patient, family members, and other caregivers is essential. In the early stages of AD, memory aids such as notebooks and posted daily reminders can be helpful. Family members should emphasize activities that are pleasant while curtailing those that increase stress on the patient. Kitchens, bathrooms, stairways, and bedrooms need to be made safe, and eventually patients will need to stop driving. Loss of independence and change of environment may worsen confusion, agitation, and anger. Communication and repeated calm reassurance are necessary. Caregiver "burnout" is common, often resulting in nursing home placement of the patient or new health problems for the caregiver. Respite breaks for the caregiver help to maintain a successful long-term therapeutic milieu. Use of adult day-care centers can be helpful. Local and national support groups, such as the Alzheimer's Association and the Family Caregiver Alliance, are valuable resources. Internet access to these resources has become available to clinicians and families in recent years.

NEUROTRANSMITTER-BASED THERAPIES

Donepezil (target dose, 10 mg daily), rivastigmine (target dose, 6 mg twice daily or 9.5-mg patch daily), galantamine (target dose 24 mg daily, extended-release), and memantine (target dose, 10 mg twice daily) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD. Due to hepatotoxicity, tacrine is no longer used. Dose escalations for each of these medications must be carried out over 4–6 weeks to minimize side effects. The pharmacologic action of donepezil, rivastigmine, and galantamine is inhibition of the cholinesterases, primarily acetylcholinesterase, with a resulting increase in cerebral acetylcholine levels. Memantine appears to act by blocking overexcited *N*-methyl-*D*-aspartate (NMDA) glutamate receptors. Double-blind, placebo-controlled, crossover studies with cholinesterase inhibitors (in mild-to-severe AD dementia) and memantine (in moderate-to-severe AD dementia) have shown them to be associated with modestly improved caregiver ratings of patients' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 3 years. The average patient on an anticholinesterase inhibitor maintains his or her mini-mental state examination (MMSE) score for close to a year, whereas a placebo-treated patient declines 2–3 points over the same time period. Memantine, used in conjunction with cholinesterase inhibitors or by itself, slows cognitive deterioration and decreases caregiver burden for patients with moderate-to-severe AD but is not approved for mild AD. Neither cholinesterase inhibitors nor memantine has proven efficacious in

patients with MCI. Cholinesterase inhibitors are relatively easy to administer, and their major side effects are gastrointestinal symptoms (nausea, diarrhea, cramps), altered sleep with unpleasant or vivid dreams, bradycardia (usually benign), and muscle cramps. Potential side effects associated with memantine include constipation, dizziness, headache, and somnolence. A common approach to AD drug therapy is to initiate a cholinesterase inhibitor for a patient diagnosed with mild AD dementia, and to add memantine when patients enter the moderate stage of disease. Cholinesterase inhibitors may also be effective in treating delusions and hallucinations, while memantine can reduce agitation.

THERAPIES TARGETING AMYLOID- β

AD drug development over the past two decades has focused on the prevention or clearance of $A\beta$ pathology. In June 2021, aducanumab, a monoclonal antibody targeting the N-terminus of the $A\beta$ peptide, was granted accelerated approval by the FDA based on reduction in $A\beta$ plaques (measured by PET) in two phase 3, double-blinded, randomized placebo-controlled trials. However, a clinical benefit over placebo (measured by slower decline on cognitive and functional scales) was observed with high-dose treatment (10 mg/kg) in only one of the two trials, and lower antibody doses did not show a benefit vs. placebo in either trial. Data interpretation was further complicated by differences in dosing between trials and early termination of both trials based on a prespecified futility analysis, which ultimately proved erroneous. Given these circumstances, continued FDA approval will be contingent upon verification of clinical benefit in confirmatory trials.

According to the FDA label, aducanumab should only be considered for treatment of patients with MCI or early dementia due to AD, mirroring the early clinical stage of patients enrolled in the phase 3 clinical trials. Patients with pre-clinical (i.e., asymptomatic, biomarker-positive) AD or patients with moderate-severe AD dementia should not be treated until data on safety or efficacy in these populations is available. Expert recommendations further stipulate that biomarker confirmation of $A\beta$ based on CSF or PET be required prior to initiating treatment, since clinical diagnosis in isolation is not sufficient to ensure the presence of $A\beta$ plaques. Patients with confounding neurological or psychiatric conditions, unstable medical illnesses, evidence of prior brain hemorrhages (including multiple microhemorrhages), or active anticoagulant treatment should be excluded.

Aducanumab is administered as an intravenous infusion every 4 weeks, with gradual dose titration from 1 mg/kg to 10 mg/kg over seven infusions. Amyloid-related imaging abnormalities (ARIA) are the most common adverse effect, occurring in 41% of patients treated with high-dose aducanumab vs. 10% in the placebo groups. ARIA can manifest as vasogenic edema (ARIA-E) or cortical microhemorrhages and superficial siderosis (ARIA-H). Of ARIA cases in the phase 3 trials, 74% were asymptomatic and detected by safety MRIs. The most common symptoms associated with ARIA were headache, altered mental status, dizziness, visual disturbances, and nausea. Symptoms were usually mild and transient, though severe cases with focal neurologic deficits have been described. Most cases occurred within the first eight infusions, though ARIA can occur at any time. Baseline and safety surveillance MRI scans (at minimum following the 7th and 12th infusions) are required for aducanumab treatment, and an MRI is also indicated in treated patients in whom ARIA is suspected clinically. Therefore, patients with contraindications to MRI cannot safely receive this therapy. *ApoE* genotyping may also be considered to inform risk-benefit discussions prior to treatment, because ARIA-E is more common in *ApoE e4* carriers (43%) compared to noncarriers (20%). It is highly recommended that the antibody only be prescribed by clinicians who have adequate training and access to the resources needed to safely deliver this complex therapy.

ADDITIONAL THERAPIES

Mild-to-moderate depression is common in the early stages of AD and may respond to antidepressants or cholinesterase inhibitors.

Selective serotonin reuptake inhibitors (SSRIs) are commonly used due to their low anticholinergic side effects (for example, escitalopram, target dose 5–10 mg daily). Seizures can be treated with levetiracetam unless the patient had a different regimen that was effective prior to the onset of AD. Agitation, insomnia, hallucinations, and belligerence are especially troublesome characteristics of some AD patients, and these behaviors can lead to nursing home placement. The newer generation of atypical antipsychotics, such as risperidone, quetiapine, and olanzapine, are being used in low doses to treat these neuropsychiatric symptoms. The few controlled studies comparing drugs against behavioral intervention in the treatment of agitation suggest mild efficacy with significant side effects related to sleep, gait, and cardiovascular complications, including an increased risk of death. All antipsychotics carry a black box FDA warning for use in elderly patients with dementia and thus should be prescribed only with caution; however, careful, daily, nonpharmacologic behavior management is often not available, rendering medications necessary for some patients. Medications with strong anticholinergic effects should be vigilantly avoided, including prescription and over-the-counter sleep aids (e.g., diphenhydramine) or incontinence therapies (e.g., oxybutynin).

Several commonly used medications and supplements, including estrogen hormone replacement therapy, statins, vitamin E, and ginkgo biloba, appeared to be associated with a decreased risk of AD in epidemiologic or observational studies, but did not show efficacy in prospective, randomized, double-blinded, placebo-controlled trials. Many vitamins and dietary supplements are marketed directly to consumers as “memory enhancing” or protective against AD without clinical evidence. Patients and families may come across anecdotal reports of “miraculous” responses to aggressive treatments such as anti-interferon intrathecal infusions, intravenous immunoglobulin, antibiotics (purportedly to treat Lyme disease or another questionable infection), metal chelation, and stem cell therapies, but there is no scientific evidence to support use of any of these approaches to treating AD, and significant concern for harm.

EXPERIMENTAL THERAPIES

The design of AD clinical trials has been transformed by the availability of PET and CSF biomarkers of A β and tau. Many trials now require biomarker evidence of AD for trial inclusion. Biomarkers help assess target engagement (e.g., changes in CSF or PET A β in an antiamyloid trial) or modification of downstream disease pathophysiology (e.g., changes in CSF or PET tau in an antiamyloid trial), with the pivotal trials leading to approval of aducanumab being emblematic of this novel approach. Increasingly, many trials have shifted toward enrolling patients in the asymptomatic (preclinical) or very early symptomatic stages of AD, using positive biomarkers as the primary inclusion criterion. Primary (biomarker-negative) and secondary (biomarker-positive but no symptoms) prevention trials are underway in autosomal dominant mutation carriers, *ApoE* $\epsilon 4$ homozygotes, and even in the normally aging population.

Beyond aducanumab, several additional anti-A β monoclonal antibodies (e.g., lecanemab, gantenerumab, and donanemab) have shown evidence of robust amyloid plaque lowering on PET and are currently being evaluated in clinical trials across the continuum from preclinical disease to mild dementia due to AD. As with aducanumab, ARIA-E and ARIA-H represent a safety concern for this class of drugs. Active vaccination against A β is another approach that aims to promote immune-mediated clearance of amyloid pathology. The first A β_{42} vaccine trial in humans was aborted after a minority of patients developed meningoencephalitis, but subsequent trials with less immunogenic formulations have shown more favorable safety profiles.

Oral drugs that inhibit β and γ secretase reduce the cleavage of APP to A β_{42} and showed promise in ameliorating pathology and behavioral changes in AD transgenic mice. Unfortunately, placebo-controlled trials failed to show clinical efficacy, and trials of β secretase inhibitors in particular, consistently found significant

worsening of cognition in treated patients vs. placebo, though fortunately this effect proved transient after discontinuing the drug. It is unclear whether toxicity of β and γ secretase inhibitors was directly related to changes in A β metabolism or to “off-target” drug effects.

Monoclonal antibodies directed against phosphorylated tau are in earlier stages of development. These antibodies aim to prevent the transsynaptic spread of tau and have proven effective in tau-transgenic mice. Safety profiles in human studies have proven favorable thus far. Additional therapeutic approaches targeting tau include: active immunization; inhibition of tau phosphorylation, acetylation, and aggregation; microtubule stabilization; and lowering of tau expression via antisense oligonucleotides or small interfering RNA. Other druggable pathways represented in the AD drug development pipeline include neuroinflammation, metabolism/bioenergetics, synaptic plasticity, neuroprotection, and neurotransmitter-based treatment of neuropsychiatric symptoms.

A general approach to the symptomatic management of dementia is presented in Chap. 25.

OTHER CAUSES OF DEMENTIA

FTD (Chap. 432), vascular dementia (Chap. 433), DLB (Chap. 434), and prion diseases (Chap. 438) are covered in dedicated chapters.

Prion diseases such as CJD are rare neurodegenerative conditions (prevalence ~1 per million) that produce dementia. CJD is a rapidly progressive disorder associated with dementia, focal cortical signs, rigidity, and myoclonus, causing death <1 year after first symptoms appear. The rapidity of progression seen with CJD is uncommon in AD so that the distinction between the two disorders is usually straightforward, although AD can on occasion present as a rapidly progressive dementia. In general, corticobasal degeneration (CBD) (Chap. 432) and DLB (Chap. 426), more rapid degenerative dementias with prominent movement abnormalities, are more likely to be mistaken for CJD. The differential diagnosis for CJD includes other rapidly progressive dementing conditions such as viral or bacterial encephalitides, Hashimoto's encephalopathy, central nervous system (CNS) vasculitis, lymphoma, or paraneoplastic/autoimmune syndromes (Chap. 94). The markedly abnormal periodic complexes on EEG and cortical ribboning and basal ganglia hyperintensities on diffusion-weighted imaging or fluid-attenuated inversion recovery MRI are diagnostic features of CJD, although rarely, prolonged focal or generalized seizures can produce a similar imaging appearance.

Huntington's disease (HD) (Chap. 436) is an autosomal dominant degenerative brain disorder. Clinical hallmarks of HD include chorea, behavioral disturbance, and executive impairment. Symptoms typically begin in the fourth or fifth decade of life, but there is a wide range, from childhood to >70 years. Memory is frequently not impaired until late in the disease, but attention, judgment, self-awareness, and executive functions are often deficient at an early stage. Depression, apathy, social withdrawal, irritability, and intermittent disinhibition are common. Delusions and obsessive-compulsive behavior may occur. Disease duration is variable but typically lasts ~15 years.

Normal-pressure hydrocephalus is a relatively uncommon but treatable syndrome. The clinical, physiologic, and neuroimaging characteristics of NPH must be carefully distinguished from those of other dementias associated with gait impairment. Historically, many patients treated for NPH have suffered from other dementias, particularly AD, vascular dementia, DLB, and progressive supranuclear palsy (PSP) (Chap. 432). For NPH, the clinical triad includes an abnormal gait (ataxic or apractic), dementia (usually mild to moderate, with an emphasis on executive impairment), and urinary urgency or incontinence. Neuroimaging reveals enlarged lateral ventricles (hydrocephalus) with little or no cortical atrophy, although the Sylvian fissures may appear propped open (so-called boxcarring), which can be mistaken for perisylvian atrophy. Crowding of dorsal frontal-parietal gyri helps distinguish NPH from other movement disorders, such as PSP and CBD, in which dorsal atrophy with sulcal widening is common. NPH is a communicating hydrocephalus with a patent aqueduct of Sylvius

3376 (see Fig. 29-3), in contrast to aqueductal stenosis, in which the aqueduct is small. Lumbar puncture opening pressure falls in the high-normal range, and the CSF protein, glucose, and cell counts are normal. NPH may be caused by obstruction to normal CSF flow over the cerebral convexities and delayed resorption into the venous system. The indolent nature of the process results in enlarged lateral ventricles with relatively little increase in CSF pressure. Presumed edema, stretching, and distortion of subfrontal white matter tracts may lead to clinical symptoms, but the precise underlying pathophysiology remains unclear. Some patients provide a history of conditions that produce meningeal scarring (blocking CSF resorption) such as previous meningitis, subarachnoid hemorrhage, or head trauma. Others with long-standing but asymptomatic congenital hydrocephalus may have adult-onset deterioration in gait or memory that is confused with NPH. In contrast to AD, the patient with NPH complains of an early and prominent gait disturbance without cortical atrophy on CT or MRI.

Numerous attempts have been undertaken to improve NPH diagnosis with various special studies and to predict the success of ventricular shunting. These tests include radionuclide cisternography (showing a delay in CSF absorption over the convexity) and various efforts to monitor and alter CSF flow dynamics, including a constant-pressure infusion test. None has proven to be specific or consistently useful. A transient improvement in gait or cognition may follow lumbar puncture (or serial punctures) with removal of 30–50 mL of CSF, but this finding has also not proved to be consistently predictive of postshunt improvement. Perhaps the most reliable strategy is a period of close inpatient evaluation before, during, and after lumbar CSF drainage. Occasionally, when a patient with AD presents with gait impairment (at times due to comorbid subfrontal vascular injury) and absent or only mild cortical atrophy on CT or MRI, distinguishing NPH from AD can be challenging. Hippocampal atrophy on MRI favors AD, whereas a characteristic “magnetic” gait with external hip rotation, low foot clearance, and short strides, along with prominent truncal sway or instability, favors NPH. The diagnosis of NPH should be avoided when hydrocephalus is not detected on imaging studies, even if the symptoms otherwise fit. Of those patients identified by careful diagnosis as having NPH, 30–50% will improve with ventricular shunting. Gait may improve more than cognition, but many reported failures to improve cognitively may have resulted from comorbid AD. Importantly, the presence of positive CSF AD biomarkers or amyloid PET is associated with lower likelihood of response to shunting. Short-lasting improvement is common. Patients should be carefully selected for shunting, because subdural hematoma, infection, and shunt failure are known complications and can be a cause for early nursing home placement in an elderly patient with previously mild dementia.

Intracranial hypotension, sometimes called sagging brain syndrome, is a disorder caused by low CSF pressure, leading to downward pressure on the subcortical structures and disruption of cerebral function. It presents in a variable manner with headache, often exacerbated by coughing or a Valsalva maneuver or by moving from lying to standing. Other common symptoms include dizziness, vomiting, disruption of sleep-wake cycles, and sometimes a progressive behavioral variant FTD-like syndrome (Chap. 432). Although sometimes idiopathic, this syndrome can be caused by CSF leaks secondary to lumbar puncture, head trauma, or spinal cord arachnoid cysts. Treatment consists of finding and patching the CSF leak.

Dementia can accompany *chronic alcoholism* (Chap. 453) and may result from associated malnutrition, especially of B vitamins, particularly thiamine. Other poorly defined aspects of chronic alcoholism may, however, also produce cerebral damage. A rare idiopathic syndrome of dementia and seizures with degeneration of the corpus callosum has been reported primarily in male Italian red wine drinkers (Marchiafava-Bignami disease).

Thiamine (vitamin B₁) deficiency causes Wernicke's encephalopathy (Chap. 307). The clinical presentation is usually a malnourished patient (frequently but not necessarily alcoholic) with confusion, ataxia, and diplopia resulting from inflammation and necrosis of periventricular midline structures, including dorsomedial thalamus, mammillary bodies, midline cerebellum, periaqueductal gray matter,

and trochlear and abducens nuclei. Damage to the dorsomedial thalamus correlates most closely with the memory loss. Prompt administration of parenteral thiamine (100 mg intravenously for 3 days followed by daily oral dosage) may reverse the disease if given within the first days of symptom onset. Prolonged untreated thiamine deficiency can result in an irreversible and profound amnestic syndrome (Korsakoff's syndrome) or even death.

In *Korsakoff's syndrome*, the patient is unable to recall new information despite normal immediate memory, attention span, and level of consciousness. Memory for new events is seriously impaired, whereas knowledge acquired prior to the illness remains relatively intact. Patients are easily confused, disoriented, and cannot store information for more than a few minutes. Superficially, they may be conversant, engaging, and able to perform simple tasks and follow immediate commands. Confabulation is common, although not always present. There is no specific treatment because the previous thiamine deficiency has produced irreversible damage to the medial thalamic nuclei and mammillary bodies. Mammillary body atrophy may be visible on MRI in the chronic phase (see Fig. 307-6).

Vitamin B₁₂ deficiency, as can occur in pernicious anemia, causes a megaloblastic anemia and may also damage the nervous system (Chaps. 99 and 442). Neurologically, it most commonly produces a spinal cord syndrome (myelopathy) affecting the posterior columns (loss of vibration and position sense) and corticospinal tracts (hyperactive tendon reflexes with Babinski signs); it also damages peripheral nerves (neuropathy), resulting in sensory loss with depressed tendon reflexes. Damage to myelinated axons may also cause dementia. The mechanism of neurologic damage is unclear but may be related to a deficiency of S-adenosyl methionine (required for methylation of myelin phospholipids) due to reduced methionine synthase activity or accumulation of methylmalonate, homocysteine, and propionate, providing abnormal substrates for fatty acid synthesis in myelin. Use of histamine blockers or metformin, vegan diets, autoimmunity against gastric parietal cells, and various causes of malabsorption are the typical causes for vitamin B₁₂ deficiency. The neurologic sequelae of vitamin B₁₂ deficiency may occur in the absence of hematologic manifestations, making it critical to avoid using the complete blood count (CBC) and blood smear as a substitute for measuring B₁₂ blood levels. Treatment with parenteral vitamin B₁₂ (1000 µg intramuscularly daily for a week, weekly for a month, and monthly for life for pernicious anemia) stops progression of the disease if instituted promptly, but complete reversal of advanced nervous system damage will not occur.

Deficiency of nicotinic acid (*pellagra*) is associated with skin rash over sun-exposed areas, glossitis, and angular stomatitis (Chap. 333). Severe dietary deficiency of nicotinic acid along with other B vitamins such as pyridoxine may result in spastic paraparesis, peripheral neuropathy, fatigue, irritability, and dementia. This syndrome has been seen in prisoners of war and in concentration camps but should be considered in any malnourished individual. Low serum folate levels appear to be a rough index of malnutrition, but isolated folate deficiency has not been proved as a specific cause of dementia.

CNS infections usually cause delirium and other acute neurologic syndromes. However, some chronic CNS infections, particularly those associated with chronic meningitis (Chap. 139), may produce a dementing illness. The possibility of chronic infectious meningitis should be suspected in patients presenting with a dementia or behavioral syndrome, who also have headache, meningismus, cranial neuropathy, and/or radiculopathy. Between 20–30% of patients in the advanced stages of HIV infection become demented (Chap. 202). Cardinal features include psychomotor retardation, apathy, and impaired memory. This syndrome may result from secondary opportunistic infections but can also be caused by direct infection of CNS neurons with HIV. Neurosyphilis (Chap. 182) was a common cause of dementia in the preantibiotic era; it is now uncommon but can still be encountered in patients with multiple sex partners, particularly among patients with HIV. Characteristic CSF changes consist of pleocytosis, increased protein, and a positive Venereal Disease Research Laboratory (VDRL) test.

Primary and metastatic *neoplasms of the CNS* (Chap. 90) usually produce focal neurologic findings and seizures rather than dementia, but if tumor growth begins in the frontal or temporal lobes, the initial manifestations may be memory loss or behavioral changes. An autoimmune, sometimes paraneoplastic, syndrome of dementia associated with occult carcinoma (often small-cell lung cancer) is termed *limbic encephalitis*. In this syndrome, confusion, agitation, seizures, poor memory, emotional changes, and frank dementia may occur. Paraneoplastic *encephalitis associated with N-methyl- -aspartate (NMDA) receptor antibodies* presents as a progressive psychiatric disorder with memory loss and seizures; affected patients are often young women with ovarian teratoma. Autoimmune etiologies also include antibodies targeting *leucine-rich glioma-inactivated 1 (LGII)*; faciobrachial dystonic seizures); *contactin-associated protein-like 2 (Caspr2; insomnia, ataxia, myotonia)*; and α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-receptor (limbic encephalitis with relapses), among others (Chap. 94).

A *nonconvulsive seizure disorder* (Chap. 425) may underlie a syndrome of confusion, clouding of consciousness, and garbled speech. Often, psychiatric disease is suspected, but an EEG demonstrates the epileptic nature of the illness. If recurrent or persistent, the condition may be termed *complex partial status epilepticus*. The cognitive disturbance often responds to anticonvulsant therapy. The etiology may be previous small strokes or head trauma; some cases are idiopathic. Nonconvulsive temporal lobe seizures can also emerge early in the course of AD.

It is important to recognize *systemic diseases* that indirectly affect the brain and produce chronic confusion or dementia. Such conditions include hypothyroidism; vasculitis; and hepatic, renal, or pulmonary disease. Hepatic encephalopathy may begin with irritability and confusion and slowly progress to agitation, lethargy, and coma.

Isolated vasculitis of the CNS (CNS granulomatous angiitis) (Chaps. 363 and 427) occasionally causes a chronic encephalopathy associated with confusion, disorientation, and clouding of consciousness. Headache is common, and strokes and cranial neuropathies may occur. Brain imaging studies may be normal or nonspecifically abnormal. CSF analysis reveals a mild pleocytosis or protein elevation. Cerebral angiography can show multifocal stenoses involving medium-caliber vessels, but some patients have only small-vessel disease that is not revealed on angiography. The angiographic appearance is not specific and may be mimicked by atherosclerosis, infection, or other causes of vascular disease. Brain or meningeal biopsy demonstrates endothelial cell proliferation and mononuclear infiltrates within blood vessel walls. The prognosis is often poor, although the disorder may remit spontaneously. Some patients respond to glucocorticoids or chemotherapy.

Chronic metal exposure represents a rare cause of dementia. The key to diagnosis is to elicit a history of exposure at work or home. Chronic lead poisoning from inadequately fire-glazed pottery has been reported. Fatigue, depression, and confusion may be associated with episodic abdominal pain and peripheral neuropathy. Gray lead lines appear in the gums, usually accompanied by an anemia with basophilic stippling of red blood cells. The clinical presentation can resemble that of acute intermittent porphyria (Chap. 416), including elevated levels of urine porphyrins as a result of the inhibition of δ -aminolevulinic acid dehydrase. The treatment is chelation therapy with agents such as ethylenediamine tetraacetic acid (EDTA). Chronic mercury poisoning produces dementia, peripheral neuropathy, ataxia, and tremulousness that may progress to a cerebellar intention tremor or choreoathetosis. The confusion and memory loss of chronic arsenic intoxication is also associated with nausea, weight loss, peripheral neuropathy, pigmentation and scaling of the skin, and transverse white lines of the fingernails (Mees' lines). Treatment is chelation therapy with dimercaprol (British anti-Lewisite, BAL). Aluminum poisoning is rare but was documented with the dialysis dementia syndrome, in which water used during renal dialysis was contaminated with excessive amounts of aluminum. This poisoning resulted in a progressive encephalopathy associated with confusion, nonfluent aphasia, memory loss, agitation, and, later, lethargy and stupor. Speech arrest and myoclonic jerks were common and

associated with severe and generalized EEG changes. The condition has been eliminated by the use of deionized water for dialysis.

Recurrent head trauma in professional athletes may lead to a dementia previously referred to as "punch-drunk" syndrome or *dementia pugilistica* but now known as chronic traumatic encephalopathy (CTE) to signify its relevance to contact sport athletes other than boxers (Chap. 443). The symptoms can be progressive, beginning late in an athlete's career or, more often, after retirement. Early in the course, a personality change occurs, associated with social instability, explosive rage, and sometimes paranoia and delusions. Later, memory loss progresses to full-blown dementia, often associated with parkinsonian signs and ataxia or intention tremor. At autopsy, the cerebral cortex shows tau-immunoreactive NFTs that are more prominent than amyloid plaques (which are usually diffuse or absent rather than neuritic). NFTs and tau-positive reactive astrocytes are often clustered in the depths of cortical sulci and in a perivascular distribution. TDP-43 inclusions (Chap. 432) have also been reported, highlighting the overlap with the FTD spectrum. Loss of neurons in the substantia nigra is a variable feature, and some with TDP-43 inclusions also develop motor neuron disease (MND) (Chap. 437).

Chronic subdural hematoma (Chap. 443) is also occasionally associated with dementia, often in the context of underlying cortical atrophy from conditions such as AD or HD.

Transient global amnesia (TGA) is characterized by the sudden onset of a severe episodic memory deficit, usually occurring in persons aged >50 years. Often the amnesia occurs in the setting of an emotional stimulus or physical exertion. During the attack, the individual is alert and communicative, general cognition seems intact, and there are no other neurologic signs or symptoms. The patient may seem confused and repeatedly ask about his or her location in place and time. The ability to form new memories returns after a period of hours, and the individual returns to normal with no recall for the period of the attack. Frequently no cause is determined, but cerebrovascular disease, epilepsy (7% in one study), migraine, or cardiac arrhythmias have all been implicated. Approximately one-quarter of patients experience recurrent attacks. Rare instances of permanent memory loss have been reported in patients with TGA-like spells, usually representing ischemic infarction of the hippocampus or dorsomedial thalamic nucleus bilaterally. Seizure activity due to AD should always be suspected in this syndrome.

The *ALS/parkinsonian/dementia complex of Guam* is a rare degenerative disease that has occurred in the Chamorro natives on the island of Guam. Individuals may have any combination of parkinsonian features, dementia, and MND. The most characteristic pathologic features are the presence of NFTs in degenerating neurons of the cortex and substantia nigra and loss of motor neurons in the spinal cord, although recent reanalysis has shown that some patients with this illness also show coexisting TDP-43 pathology. Epidemiologic evidence supports a possible environmental cause, such as exposure to a neurotoxin or an infectious agent with a long latency period. One interesting but unproven candidate neurotoxin is the seed of the false palm tree, which Guamanians traditionally used to make flour. The amyotrophic lateral sclerosis (ALS) syndrome is no longer present in Guam, but a dementing illness with rigidity continues to be seen.

Rarely, adult-onset leukodystrophies, lysosomal-storage diseases, and other genetic disorders can present as a dementia in middle to late life. Metachromatic leukodystrophy (MLD) causes a progressive psychiatric or dementia syndrome associated with an extensive, confluent frontal white matter abnormality. MLD is diagnosed by measuring reduced arylsulfatase A enzyme activity in peripheral white blood cells. Adult-onset presentations of adrenoleukodystrophy have been reported in female carriers, and these patients often feature spinal cord and posterior white matter involvement. Adrenoleukodystrophy is diagnosed by demonstrating increased levels of plasma very-long-chain fatty acids. CADASIL is another genetic syndrome associated with white matter disease, often frontally and temporally predominant. Diagnosis is made with skin biopsy, which shows osmophilic granules in arterioles, or increasingly through genetic testing for mutations in Notch 3. The neuronal ceroid lipofuscinoses are a genetically

3378 heterogeneous group of disorders associated with myoclonus, seizures, vision loss, and progressive dementia. Diagnosis is made by finding eosinophilic curvilinear inclusions within white blood cells or neuronal tissue.

Psychogenic amnesia for personally important memories can be seen. Whether this results from deliberate avoidance of unpleasant memories, outright malingering, or unconscious repression remains unknown and probably depends on the patient. Event-specific amnesia is more likely to occur after violent crimes such as homicide of a close relative or friend or sexual abuse. It may develop in association with severe drug or alcohol intoxication and sometimes with schizophrenia. More prolonged psychogenic amnesia occurs in fugue states that also commonly follow severe emotional stress. The patient with a fugue state suffers from a sudden loss of personal identity and may be found wandering far from home. *In contrast to neurologic amnesia, fugue states are associated with amnesia for personal identity and events closely associated with the personal past.* At the same time, memory for other recent events and the ability to learn and use new information are preserved. The episodes usually last hours or days and occasionally weeks or months while the patient takes on a new identity. On recovery, there is a residual amnesia gap for the period of the fugue. Very rarely does selective loss of autobiographic information reflect a focal injury to the brain areas involved with these functions.

Psychiatric diseases may mimic dementia. Severely depressed or anxious individuals may appear demented, a phenomenon sometimes called *pseudodementia*. Memory and language are usually intact when carefully tested, and a significant memory disturbance usually suggests an underlying dementia, even if the patient is depressed. Patients in this condition may feel confused and unable to accomplish routine tasks. Vegetative symptoms, such as insomnia, lack of energy, poor appetite, and concern with bowel function, are common. Onset is often more abrupt, and the psychosocial milieu may suggest prominent reasons for depression. Such patients respond to treatment of the underlying psychiatric illness. Schizophrenia is usually not difficult to distinguish from dementia, but occasionally the distinction can be problematic. Schizophrenia generally has a much earlier age of onset (second and third decades of life) than most dementing illnesses and is associated with intact memory. The delusions and hallucinations of schizophrenia are usually more complex, bizarre, and threatening than those of dementia. Some chronic schizophrenics develop an unexplained progressive dementia late in life that is not related to AD. Conversely, FTD, HD, vascular dementia, DBL, AD, or leukoencephalopathy can begin with schizophrenia-like features, leading to the misdiagnosis of a psychiatric condition. Later age of onset, significant deficits on cognitive testing, or the presence of abnormal neuroimaging suggest a degenerative condition. Memory loss may also be part of a *conversion disorder*. In this situation, patients commonly complain bitterly of memory loss, but careful cognitive testing either does not confirm the deficits or demonstrates inconsistent or unusual patterns of cognitive problems. The patient's behavior and "wrong" answers to questions often indicate that he or she understands the question and knows the correct answer.

Clouding of cognition by *chronic drug or medication use*, often prescribed by physicians, is an important cause of dementia. Sedatives, tranquilizers, and analgesics used to treat insomnia, pain, anxiety, or agitation may cause confusion, memory loss, and lethargy, especially in the elderly. Discontinuation of the offending medication often improves mentation.

FURTHER READING

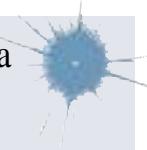
- A SJ et al: Interpretation of risk loci from genome-wide association studies of Alzheimer's disease. *Lancet Neurol* 19:326, 2020.
B ME et al: A quarter century of APOE and Alzheimer's disease: Progress to date and the path forward. *Neuron* 101:820, 2019.
B H, D T K: Where, when, and in what form does sporadic Alzheimer's disease begin? *Curr Opin Neurol* 25:708, 2012.
J CR et al: NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 14:535, 2018.

- L -S OH et al: Diagnostic accuracy of amyloid versus ¹⁸F-Fluorodeoxyglucose positron emission tomography in autopsy-confirmed dementia. *Ann Neurol* 89:389, 2021.
L JM, H DM: Alzheimer disease: An update on pathobiology and treatment strategies. *Cell* 179:312, 2019.
R GD et al: Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. *JAMA* 321:1286, 2019.
R GD: Late-onset Alzheimer Disease. *Continuum* 25:14, 2019.
S DJ, H J: The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* 8:595, 2016.

432

Frontotemporal Dementia

William W. Seeley, Bruce L. Miller



Frontotemporal dementia (FTD) refers to a group of clinical syndromes united by their links to underlying frontotemporal lobar degeneration (FTLD) pathology. FTD, like the other major neurodegenerative diseases, is considered a disease of abnormal protein aggregation, with either tau or transactive response DNA-binding protein of 43 kDa (TDP-43) implicated in most cases. FTD most often begins in the fifth to seventh decades of life and is nearly as prevalent as Alzheimer's disease (AD) in this age group. Early studies suggested that FTD may be more common in men than women; however, more recent reports cast doubt on this finding. Although a family history of dementia is common, autosomal dominant inheritance is seen in only 10–20% of all FTD cases.

CLINICAL MANIFESTATIONS

Familial and sporadic forms of FTLD present with remarkable clinical heterogeneity. Three core clinical syndromes have been described (Fig. 432-1). In the behavioral variant (bvFTD), the most common FTD syndrome, social and emotional dysfunction manifests as apathy, disinhibition, compulsivity, loss of empathy, and overeating, often but not always accompanied by deficits in executive control. Two forms of primary progressive aphasia (PPA), the semantic and nonfluent/agrammatic variants, are commonly due to FTLD and are included under the FTD umbrella. In the semantic variant, patients slowly lose the ability to decode word, object, person-specific, and emotion meaning, whereas patients with the nonfluent/agrammatic variant develop profound inability to produce words, often with prominent motor speech impairment. Any of these three clinical syndromes, but most often bvFTD, may be accompanied by motor neuron disease (MND) (Chap. 437), in which case the term FTD-MND is applied. In addition, the corticobasal syndrome (CBS) and progressive supranuclear palsy–Richardson syndrome (PSP-RS) can be considered part of the FTLD clinical spectrum. Furthermore, patients may evolve from any of the major syndromes described above to have prominent features of another syndrome.

Findings at the bedside are dictated by the anatomic localization of the disorder. Degeneration with atrophy occurs in the medial and orbital frontal and anterior insula in bvFTD; the anterior temporal region in semantic variant PPA; and the lateral frontal and precentral gyrus of the dominant hemisphere in nonfluent/agrammatic PPA. Typically, parietal functions such as visuospatial processing and arithmetic calculations are unaffected even late in the FTD syndromes. Many patients with nonfluent aphasia or bvFTD later develop aspects of PSP-RS as disease spreads into subcortical or brainstem structures, or CBS-like features appear as disease moves into periorchidic cortices.

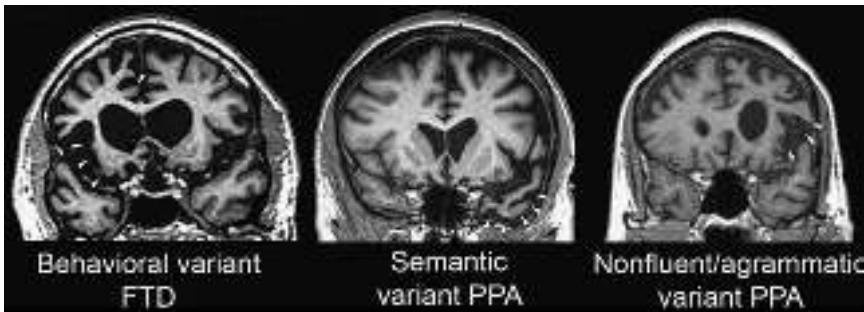


FIGURE 432-1 Three major frontotemporal dementia (FTD) clinical syndromes. Coronal MRI sections from representative patients with behavioral variant FTD (left) and the semantic (center) and nonfluent/agrammatic (right) variants of primary progressive aphasia (PPA). Areas of early and severe atrophy in each syndrome are highlighted (white arrowheads). The behavioral variant features anterior cingulate and frontoinsular atrophy, spreading to orbital and dorsolateral prefrontal cortex. Semantic variant PPA shows prominent temporopolar atrophy, more often on the left. Nonfluent/agrammatic variant PPA is associated with dominant frontal opercular and dorsal insula degeneration.

■ GENETIC CONSIDERATIONS

 Autosomal dominant forms of FTD can result from mutations in *C9orf72* (chromosome 9), *GRN* (chromosome 17), and *MAPT* (chromosome 17) genes. A hexanucleotide (GGGGCC) expansion in a noncoding exon of *C9ORF72* is the most common genetic cause of familial or sporadic FTD (usually presenting as bvFTD with or without MND) and amyotrophic lateral sclerosis (ALS). The expansion is associated with *C9orf72* haploinsufficiency, nuclear mRNA foci containing transcribed portions of the expansion and other mRNAs, neuronal cytoplasmic inclusions containing dipeptide repeat proteins translated from the repeat mRNA, and TDP-43 neuronal cytoplasmic and glial inclusions. The pathogenic significance of these various features is a topic of vigorous investigation. *MAPT* mutations lead to a change in the alternate splicing of tau or cause loss of function in the tau molecule, thereby altering microtubule binding. With *GRN*, mutations in the coding sequence of the gene encoding progranulin protein result in mRNA degradation due to nonsense-mediated decay, leading to a ~50% reduction in circulating progranulin protein levels. Intriguingly, homozygous *GRN* mutations cause neuronal ceroid lipofuscinosis, focusing investigators on the lysosome as a site of molecular dysfunction in *GRN*-related FTD. Progranulin is a growth factor that binds to tumor necrosis factor (TNF) and sortilin receptors and participates in tissue repair and tumor growth. How progranulin mutations lead to FTD remains unknown, but the most likely mechanisms include lysosomal dysfunction and neuroinflammation. Often, *MAPT* and *GRN* mutations are associated with parkinsonian features, whereas ALS is rare. Infrequently, mutations in the valosin-containing protein (*VCP*, chromosome 9), TANK binding kinase 1 (TBK-1), T cell-restricted intracellular antigen-1 (TIA1), and charged multivesicular body protein 2b (*CHMP2b*, chromosome 3) genes also lead to autosomal dominant familial FTD. Mutations in the *TARDBP* (encoding TDP-43) and *FUS* (encoding fused in sarcoma [FUS]) genes (see below) cause familial ALS, sometimes in association with an FTD syndrome, although a few patients presenting with FTD alone have been reported.

■ NEUROPATHOLOGY

The pathologic hallmark of FTLD is a focal atrophy of frontal, insular, and/or temporal cortex, which can be visualized with neuroimaging studies (Fig. 432-1) and is often profound at autopsy. Neuroimaging studies suggest that atrophy often begins focally in one hemisphere before spreading to anatomically interconnected cortical and subcortical regions. Loss of cortical serotonergic innervation is seen in many patients. In contrast to AD, the cholinergic system is relatively spared in FTD, which accounts for the poor efficacy of acetylcholinesterase inhibitors in this group.

Although early studies suggested that 15–30% of patients with FTD showed underlying AD at autopsy, progressive refinement in clinical diagnosis has improved prediction accuracy, and most patients diagnosed with FTD at a dementia clinic will show underlying FTLD

pathology. Microscopic findings seen across all patients with FTLD include gliosis, microvacuolation, and neuronal loss, but the disease is subtyped according to the protein composition of neuronal and glial inclusions, which contain either tau or TDP-43 in ~90% of patients, with the remaining ~10% showing inclusions containing the FET family of proteins (FUS, Ewing sarcoma protein, TAF-15) (Fig. 432-2).

■ PATHOGENESIS

In FTLD-tau, the toxicity and spreading capacity of misfolded tau are critical for the pathogenesis of inherited and sporadic tauopathies, although loss of tau microtubule stabilizing function may

also play a role. In recent years, the characteristic structures of the misfolded tau in each FTLD tauopathy have been resolved using cryo-electron microscopy, opening up new approaches to diagnosis and treatment. TDP-43 and FUS, in contrast, are RNA/DNA binding proteins whose roles in neuronal function are still being actively investigated. TDP-43 is a master regulator of gene expression, and loss of TDP-43 function results in mis-splicing events leading to mRNA degradation (via nonsense-mediated decay) or aberrant transcripts that give rise to stable but dysfunctional peptides. One key role of TDP-43 and FUS proteins may be the chaperoning of mRNAs to the distal neuron for activity-dependent translation within dendritic spines. Because these proteins also form intracellular aggregates and produce similar anatomic progression, protein toxicity and spreading may also factor heavily in the pathogenesis of FTLD-TDP and FTLD-FET.

Increasingly, misfolded proteins in neurodegenerative disease are recognized as having “prion-like” properties in that they can template the misfolding of their natively folded (or unfolded) protein counterparts, a process that creates exponential amplification of protein misfolding within a cell and may promote transcellular and even transsynaptic protein propagation between cells. This hypothesis could provide a unifying explanation for the stereotypical patterns of disease spread observed in each syndrome (Chap. 424).

Although the term *Pick's disease* was once used to describe a progressive degenerative disorder characterized by selective involvement of the anterior frontal and temporal neocortex and pathologically by intraneuronal cytoplasmic inclusions (*Pick bodies*), it is now used only in reference to a specific FTLD-tau histopathologic subtype. Classical Pick bodies are argyrophilic, staining positively with the Bielschowsky silver method (but not with the Gallyas method) and also with immunostaining for hyperphosphorylated tau. Recognition of the three FTLD major molecular classes has allowed delineation of distinct FTLD subtypes within each class. These subtypes, based on the morphology and distribution of the neuronal and glial inclusions (Fig. 432-3), account for the vast majority of patients, and some subtypes show strong clinical or genetic associations (Fig. 432-2). Despite this progress, clinical features do not allow reliable prediction of the underlying FTLD subtype, or even the major molecular class, for all clinical syndromes. Molecular PET imaging with ligands chosen to bind misfolded tau protein shows promise, but at the moment these ligands only show robust and specific binding to AD-related misfolded tau. Because FTLD-tau and FTLD-TDP account for 90% of FTLD patients, the ability to detect pathologic tau (or TDP-43) protein deposition in vivo would greatly improve prediction accuracy, especially when amyloid PET imaging is negative.

■ TREATMENT

Caregivers for patients with FTD carry a heavy burden, especially when the illness disrupts core emotional and personality functions of the loved one. Treatment is symptomatic, and there are currently no therapies known to slow progression or improve symptoms. Many of the

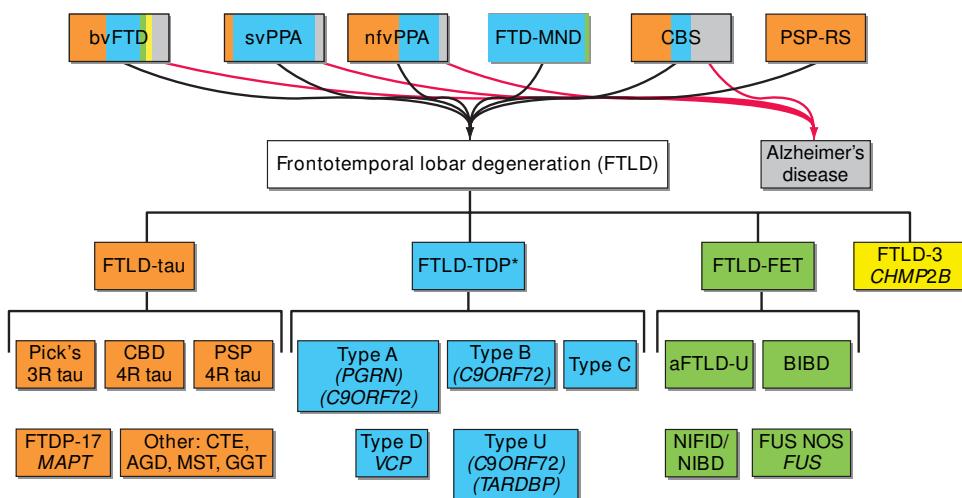


FIGURE 432-2 Frontotemporal dementia syndromes are united by underlying frontotemporal lobar degeneration pathology, which can be divided according to the presence of tau, TDP-43, or FUS-containing inclusions in neurons and glia. Correlations between clinical syndromes and major molecular classes are shown with colored shading. Despite improvements in clinical syndromic diagnosis, a small percentage of patients with some frontotemporal dementia syndromes will show Alzheimer's disease neuropathology at autopsy (gray shading). aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitin-positive inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CTE, chronic traumatic encephalopathy; FET, FUS, Ewing sarcoma protein, TAF-15 family of proteins; FTD-MND, frontotemporal dementia with motor neuron disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; FUS, fused in sarcoma; GGT, globular glial tauopathy; MST, multisystem tauopathy; nfvPPA, nonfluent/aggrammatic variant primary progressive aphasia; NIFID, neuronal intermediate filament inclusion disease; PSP, progressive supranuclear palsy; PSP-RS, progressive supranuclear palsy–Richardson syndrome; svPPA, semantic variant primary progressive aphasia; Type U, unclassifiable type.

behaviors that may accompany FTD, such as depression, hyperorality, compulsions, and irritability, can be ameliorated with antidepressants, especially SSRIs. Because FTD is often accompanied by parkinsonism, antipsychotics, which can exacerbate this problem, must be used with caution. [A general approach to the symptomatic management of dementia is presented in Chap. 29](#).

■ PROGRESSIVE SUPRANUCLEAR PALSY SYNDROME

PSP-RS is a degenerative disorder that involves the brainstem, basal ganglia, diencephalon, and selected areas of cortex. Clinically, PSP-RS begins with falls and executive or subtle personality changes (such as mental rigidity, impulsivity, or apathy). Shortly thereafter, a progressive oculomotor syndrome ensues that begins with square wave jerks, followed by slowed saccades (vertical worse than horizontal) before resulting in progressive supranuclear ophthalmoparesis. Dysarthria, dysphagia, and symmetric axial rigidity can be prominent features that emerge at any point in the illness. A stiff, unstable posture with hyperextension of the neck and a slow, jerky, toppling gait are characteristic. Frequent unexplained and sometimes spectacular falls are common secondary to a combination of axial rigidity, inability to look down, and impaired judgment. Even once patients have severely limited voluntary eye movements, they retain oculocephalic reflexes (demonstrated using a vertical doll's head maneuver); thus, the oculomotor disorder is supranuclear. The dementia overlaps with bvFTD, featuring apathy, frontal-executive dysfunction, poor judgment, slowed thought processes, impaired verbal fluency, and difficulty with sequential actions and with shifting from one task to another. These features are common at presentation and often precede the motor syndrome. Some patients with a pathologic diagnosis of PSP begin with a nonfluent aphasia or motor speech disorder and progress to classical PSP-RS. Response to -dopa is limited or absent; no other treatments exist. Death occurs within 5–10 years of onset. Like Pick's disease, increasingly the term *PSP* is used to refer to a specific histopathologic entity within the FTLD-tau class. In PSP, accumulation of hyperphosphorylated 4-repeat tau is seen within neurons and glia. Tau neuronal inclusions often appear tangle-like and may be large, spherical ("globose") and coarse in subcortical and brainstem structures. The most prominent

involvement is in the subthalamic nucleus, globus pallidus, substantia nigra, periaqueductal gray, tectum, oculomotor nuclei, pontine nuclei, and dentate nucleus of cerebellum. Neocortical tangle-like inclusions, like those in AD, often take on a more flame-shaped morphology, but on electron microscopy PSP tangles can be shown to consist of straight tubules rather than the paired helical filaments found in AD. Furthermore, PSP is associated with prominent tau-positive glial inclusions, such as tufted astrocytes (Fig. 432-3), coiled oligodendroglial inclusions ("coiled bodies"), or, least often, thorny astrocytes. Most patients with PSP-RS show PSP at autopsy, although small numbers will show another tauopathy (corticobasal degeneration [CBD] or Pick's disease; Fig. 432-2).

In addition to its overlap with FTD and CBS (see below), PSP is often confused with idiopathic *Parkinson's disease* (PD). Although elderly patients with PD may have restricted upgaze, they do not develop downgaze paresis or other abnormalities of voluntary eye movements typical of PSP. Dementia ultimately occurs in most patients with PD, often due to the emergence of a full-blown DBL-like syndrome or comorbid AD-type dementia. Furthermore, the behavioral syndromes seen with DBL differ from PSP (see below). Dementia in PD becomes more likely with increasing age, increasing severity of extrapyramidal signs, long disease duration, and the presence of depression. Patients with PD who develop dementia also show cortical atrophy on brain imaging. Neuropathologically, there may be AD-related changes in the cortex or Lewy body disease (LBD)-related α -synuclein inclusions in both the limbic system and cerebral cortex. [DLB and PD are discussed in Chaps. 434 and 435, respectively](#).

■ CORTICOBASAL SYNDROME

CBS is a slowly progressive dementia-movement disorder associated with severe degeneration in the perirolandic cortex and basal ganglia (substantia nigra and striatopallidum). Patients typically present with asymmetric rigidity, dystonia, myoclonus, and apraxia that render a progressively incapacitated limb, at times associated with *alien limb* phenomena in which the limb exhibits unintended motor actions such as grasping, groping, drifting, or undoing. Eventually CBS becomes bilateral and leads to dysarthria, slow gait, action tremor, and a frontal-predominant dementia. Whereas CBS refers to the clinical

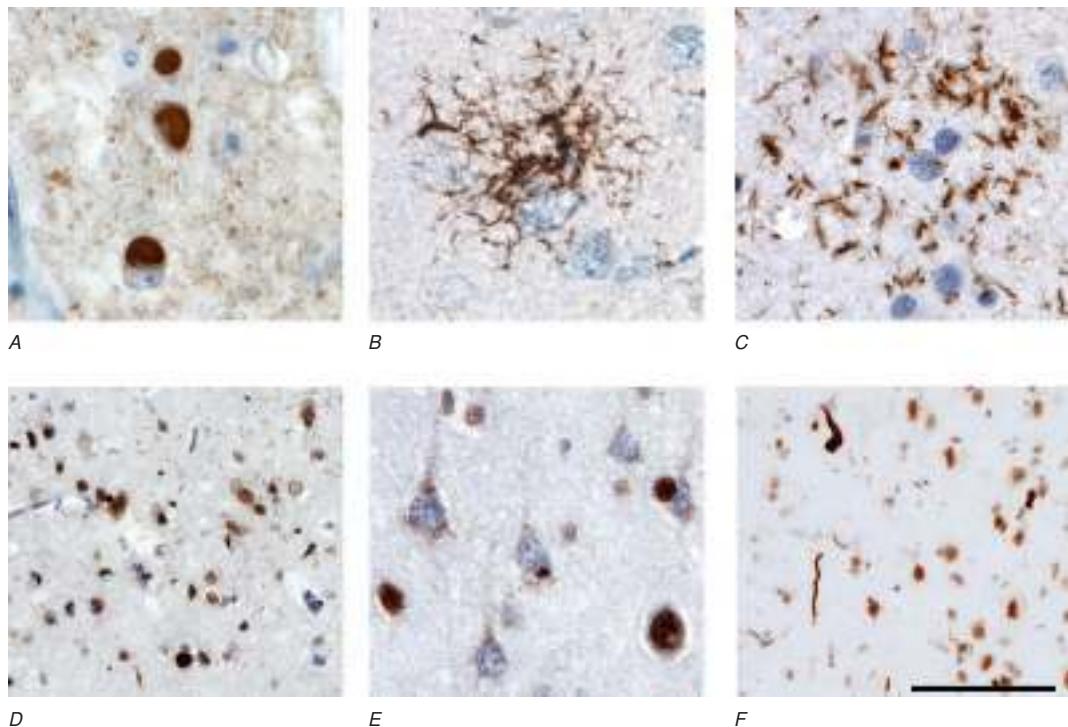


FIGURE 432-3 Neuropathology in frontotemporal lobar degeneration (FTLD). FTLD-tau (*A–C*) and FTLD-TDP (*D–F*) account for >90% of patients with FTLD, and immunohistochemistry reveals characteristic lesions in each of the major histopathologic subtypes within each class: *A*, Pick bodies in Pick's disease; *B*, a tufted astrocyte in progressive supranuclear palsy; *C*, an astrocytic plaque in corticobasal degeneration; *D*, small compact or crescentic neuronal cytoplasmic inclusions and short, thin neuropil threads in FTLD-TDP, type A; *E*, diffuse/granular neuronal cytoplasmic inclusions (with a relative paucity of neuropil threads) in FTLD-TDP, type B; and *F*, long, tortuous dystrophic neurites in FTLD-TDP, type C. TDP can be seen within the nucleus in neurons lacking inclusions but mislocalizes to the cytoplasm and forms inclusions in FTLD-TDP. Immunostains are 3-repeat tau (*A*), phospho-tau (*B* and *C*), and TDP-43 (*D–F*). Sections are counterstained with hematoxylin. Scale bar applies to all panels and represents 50 µm in *A*, *B*, *C*, and *E* and 100 µm in *D* and *F*.

syndrome, CBD refers to a specific histopathological FTLD-tau entity (Fig. 432-2). Although CBS was once thought to be pathognomonic for CBD, increasingly it has been recognized that CBS can be due to CBD, PSP, FTLD-TDP, and AD, the latter accounting for up to 30% of CBS in some series. In CBD, the microscopic features include ballooned, achromatic, tau-positive neurons; astrocytic plaques (Fig. 432-3); and other dystrophic glial tau pathomorphologies that overlap with those seen in PSP. Most specifically, CBD features a severe tauopathy burden in the subcortical white matter, consisting of axonal threads and oligodendroglial coiled bodies. As shown in Fig. 432-2, patients with bvFTD, nonfluent/agrammatic PPA, and PSP-RS may also show CBD at autopsy, emphasizing the importance of distinguishing clinical and pathologic constructs and terminology. Treatment of CBS remains symptomatic; no disease-modifying therapies are available.

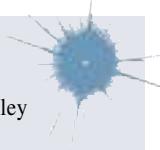
FURTHER READING

- I DJ et al: Frontotemporal lobar degeneration: Defining phenotypic diversity through personalized medicine. *Acta Neuropathol* 129:469, 2015.
- M I et al: Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: An update. *Acta Neuropathol* 119:1, 2010.
- O NT et al: Frontotemporal dementia. *Neurol Clin* 35:339, 2017.
- O CU, D -S J: The epidemiology of frontotemporal dementia. *Int Rev Psychiatry* 25:130, 2013.
- R ED: Mouse models of frontotemporal dementia. *Ann Neurol* 72:837, 2012.
- S WW: Behavioral variant frontotemporal dementia. *Continuum (Minneapolis Minn)* 25:76, 2019.

433

Vascular Dementia

Steven M. Greenberg, William W. Seeley



The term *vascular dementia* has traditionally been used to describe a subset of dementia cases due primarily to one or more symptomatic strokes. Considered as such, vascular dementia is usually ranked the second most frequent cause of dementia, exceeded only by Alzheimer's disease (Chap. 431), and is especially common in populations with limited access to medical care, where vascular risk factors are under-treated. More recently, this relatively narrow definition of vascular dementia has been substantially broadened to encompass the full impact of cerebrovascular disease on age-related cognitive decline. The term *vascular contributions to cognitive impairment and dementia* (VCID) reflects the observation that pathologic changes involving the cerebral vasculature are highly prevalent in the elderly and contribute to cognitive impairment, whether occurring in isolation or—more commonly—in conjunction with other neurodegenerative processes. The concept of VCID is one facet of the contemporary understanding of age-related cognitive decline as due to cumulative effects of distinct and overlapping neuropathologic changes. Multifactorial or “mixed” dementias appear to be more prevalent than single-etiiology dementias and thus represent the rule rather than the exception.

Symptomatic stroke and asymptomatic vascular lesions, most commonly detected with brain magnetic resonance imaging (MRI) scans, both contribute importantly to cognitive impairment. At least some cognitive impairment is present in approximately half of stroke survivors and progressively increases with longer periods of follow-up.

3382 Population-based studies also demonstrate substantially increased risk of cognitive impairment among individuals without symptomatic stroke but with MRI evidence of cerebrovascular disease. The high risk for subsequent cognitive impairment or dementia conferred by MRI markers of otherwise silent vascular brain injury highlights the cumulative impact of small distributed brain injuries—often associated with small-vessel brain disease—on compromising brain function. Further support for this framework comes from the correlation of cognitive performance during life with postmortem neuropathology. Analysis of large community-based samples demonstrates independent contributions to cognitive dysfunction and decline from both grossly visible infarcts and pathologic markers of overall cerebrovascular disease severity such as atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy scores. The Religious Orders Study and Memory and Aging Project analysis of 1079 community-based participants, for example, found each of these cerebrovascular entities to be moderate to severe in >30% of postmortem brains and, when present, to each account for ~20% of an individual's premortem cognitive decline.

Recent epidemiologic evidence of a decline in age-adjusted dementia incidence hints at the potential public impact of improving vascular health. The population-based Framingham Study reported 5-year age- and sex-adjusted cumulative hazard rates for dementia of 3.6 per 100 persons during the late 1970s to early 1980s, 2.8 in the late 1980s to early 1990s, 2.2 in the late 1990s to early 2000s, and 2.0 in the late 2000s to early 2010s. These time intervals coincide with parallel trends in hypertension control and stroke prevention, though the associations do not prove causation. Evidence supporting a potential causative effect of blood pressure control came from the SPRINT-MIND trial targeting systolic blood pressure (SBP) of <120 mmHg versus 140 mmHg in hypertensive individuals aged ≥50 years. The study ended prematurely because of effective prevention of cardiovascular outcomes in the lower SBP target group but nonetheless demonstrated that SBP reduction reduced rates of mild cognitive impairment (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.69–0.95) and combined mild cognitive impairment or probable dementia (HR, 0.85; 95% CI, 0.74–0.97), although not dementia alone (HR, 0.83; 95% CI, 0.67–1.04). It is notable that both these studies measured all-cause cognitive impairment rather than just a vascular dementia subset, underlining the potential importance of VCID as a target for dementia prevention.

■ GLOBAL CONSIDERATIONS

A review of data from across the globe indicates good evidence for variability in vascular dementia. Intracranial atherosclerosis, for example, is higher in Asians, Hispanics, and American blacks than it is in European and American whites, while whites may have more extracranial disease. The causes of these disparities remain under investigation but likely include access to health care, lifestyle factors such as diet, and possible genetic influences.

■ SUBTYPES OF CEREBROVASCULAR DISEASE ASSOCIATED WITH VCID

Large Cerebral Strokes Symptomatic strokes, whether ischemic (Chap. 427) or hemorrhagic (Chap. 428), reflect irreversible injury to discrete areas of cerebral cortex, subcortical white matter, or other subcortical and infratentorial structures and produce cognitive impairment as a function of their size and location. Rare individual infarcts in specific strategic locations such as thalamus, medial temporal cortex, anterior corpus callosum, or dominant-side angular gyrus can sufficiently impair episodic memory and functional skills to meet memory-based criteria for dementia. More commonly, strokes occur outside these strategic territories and affect various other aspects of cognition such as executive function, processing speed, and visuospatial performance that fall under the broader VCID concept. Multiple strokes and larger volumes of infarcted territory are associated with a higher likelihood of poststroke cognitive dysfunction.

Stroke patients who make good cognitive recovery nonetheless demonstrate accelerated poststroke cognitive decline. Community-based individuals in the longitudinal Reasons for Geographic and Racial Differences in Stroke study, for example, changed trajectory from an average prestroke cognitive gain of 0.021 points/year to poststroke

cognitive loss of −0.035 points/year on the six-item screener global cognitive function scale. Mechanisms for poststroke cognitive decline likely include ongoing effects of the cerebrovascular disease that gave rise to the index stroke as well as loss of cognitive reserve that makes the brain less resilient to any additional age-related disorders.

Cerebral Small-Vessel Disease Diseases of the brain's small vessels (Chap. 427) can also cause symptomatic ischemic or hemorrhagic stroke but are more often clinically asymptomatic and recognized only during evaluation for cognitive decline or other symptoms. The two common age-related cerebral small-vessel pathologies are arteriolosclerosis and cerebral amyloid angiopathy. *Arteriolosclerosis* represents thickening of arterioles due to infiltration of plasma proteins into the vessel wall. The primary risk factors for this process are age, hypertension, and diabetes mellitus. Cerebrovascular arteriolosclerosis can present as a cause of ischemic or hemorrhagic symptomatic stroke, both most commonly centered in territories supplied by deep penetrating vessels such as thalamus, basal ganglia, or brainstem. *Cerebral amyloid angiopathy* is defined by deposition of the β-amyloid peptide in the walls of small cerebral arteries, arterioles, and capillaries, with consequent loss of normal wall structure. Its primary risk factor is advancing age. Cerebral amyloid angiopathy is most often recognized symptomatically as a cause of intracerebral hemorrhage (Chap. 428), commonly located in cerebral cortex, subcortical white matter (collectively known as lobar hemorrhages), or the cerebral convexity subarachnoid space. The distinction between the deep penetrating territories most commonly affected by arteriolosclerosis and superficial lobar brain regions affected by cerebral amyloid angiopathy often allows the two small-vessel diseases to be radiographically distinguished.

Despite differences in their underlying pathogenic mechanisms, the two cerebral small-vessel diseases produce a similar range of ischemic and hemorrhagic brain lesions detectable by histopathology at autopsy or MRI scan during life (Fig. 433-1). *Small (lacunar) infarcts* are a common feature of arteriolosclerosis and less commonly of cerebral amyloid angiopathy. Chronic lacunar infarcts can appear on MRI fluid-attenuated inversion recovery (FLAIR) sequences as a hyperintense rim surrounding a hypointense cavitated core with diameters typically 3–15 mm (Fig. 433-1A), but this characteristic appearance evolves in only a subset of small infarcts, and many cannot be readily identified in the chronic stage. *Microinfarcts* <3 mm are characteristic of both small-vessel diseases. They are substantially more numerous than lacunar infarcts but less easily visualized. Acute microinfarcts may be visible as punctate hyperintensities on diffusion-weighted MRI images (Fig. 433-1B), whereas a small subset of chronic microinfarcts is detectable on high-resolution T2-weighted MRI sequences as hyperintense lesions in the cerebral cortex. *Cerebral microbleeds* are less numerous than lacunes or microinfarcts but readily detected in their chronic stage because of the paramagnetic effects of iron products. These appear as round hypointense lesions on T2-weighted MRI, primarily in deep penetrating brain regions if caused by arteriolosclerosis (Fig. 433-1C) or lobar regions if caused by cerebral amyloid angiopathy (Fig. 433-1D).

Other MRI markers of small-vessel disease identify diffuse injury of the white matter. *White matter hyperintensities* on T2-weighted or FLAIR MRI sequences (Fig. 433-1E) are an almost ubiquitous feature of aging. Although these lesions are readily visible on clinical MRI, they represent a nonspecific marker of white matter gliosis, demyelination, or increased water content. Extremely severe diffuse white matter vascular injury is commonly referred to as *Binswanger's disease* or subcortical arteriosclerotic encephalopathy, recognized as a clinical syndrome with gradual cognitive deterioration and notable white matter changes of small-vessel ischemic disease. On neuroimaging, a progressive confluent subcortical and periventricular white matter disease is seen (see Fig. 29-2), with hypoperfusion and hypometabolism. More subtle alterations in white matter structure can be sensitively and quantitatively detected by *diffusion tensor MRI* (Chap. 423) as increased water diffusivity or decreased diffusion directionality. Diffusion tensor measures of white matter structural integrity show a consistent association with cognitive performance and gait speed, reflecting the central role of disconnection of key brain networks in mediating the effects of

cerebral small-vessel disease. These diffusion tensor–based methods often require complex processing and are typically used in research rather than clinical settings. A relatively simple diffusion tensor–based metric defined by the peak width of the skeletonized mean diffusivity (PSMD) histogram has emerged as a candidate method for quantifying white matter disconnection.

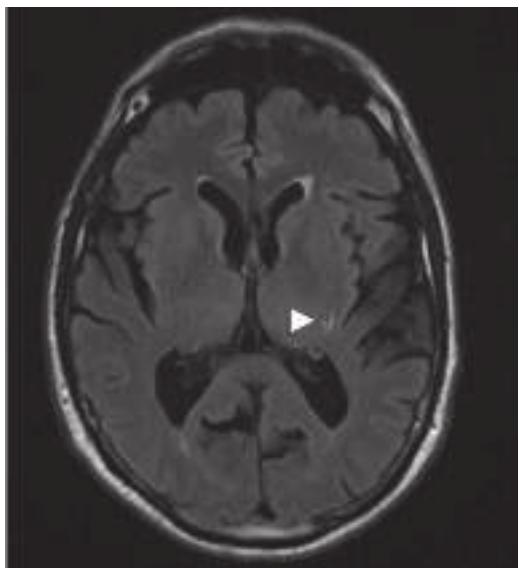
Role of Accompanying Brain Pathologies The concept of VCID posits that large strokes and small-vessel disease often occur in combination with neurodegenerative brain diseases, most commonly Alzheimer's disease (Chap. 431). Many clinicopathologic correlation studies have established that the co-occurrence of cerebrovascular and neurodegenerative lesions produces more cognitive and functional impairment than expected from the effects of each disease mechanism considered independently. Interactions between cerebrovascular and neurodegenerative processes may also contribute to dementia. Such

interactions might involve loss of blood-brain barrier integrity (possibly allowing brain penetration of neurotoxic or inflammatory agents) and impaired clearance of β -amyloid or other pathogenic molecules from the brain (postulated to occur along perivascular drainage pathways driven by physiologic vascular motion).

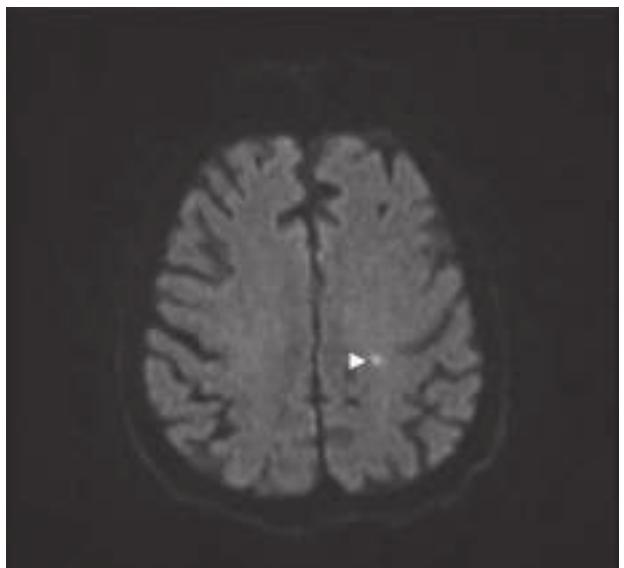
APPROACH TO THE PATIENT

Vascular Dementia

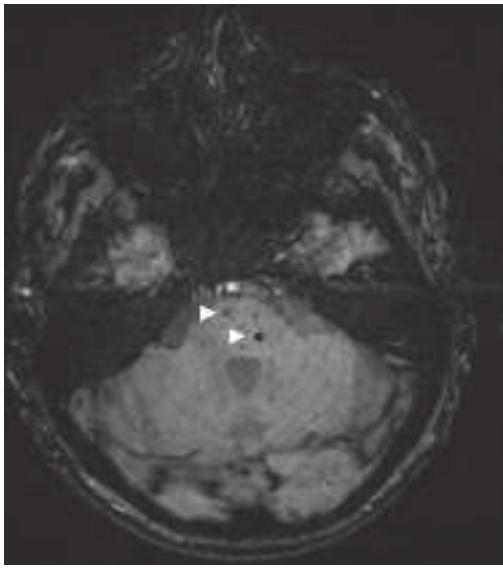
Identifying vascular contributors to a patient's cognitive impairment can clarify the etiologic diagnosis and point to specific interventions aimed at slowing progression. Clinical evaluation is focused on identifying vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, tobacco use, atrial fibrillation, coronary artery disease, or peripheral vascular disease), history of prior symptoms of stroke



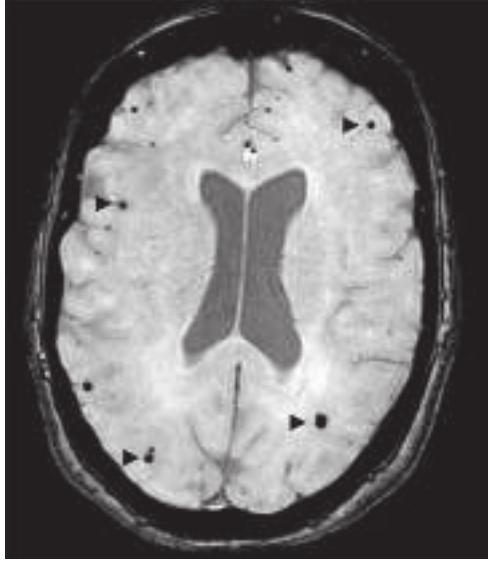
A



B



C



D

FIGURE 433-1 Magnetic resonance imaging (MRI) markers of cerebral small vessel disease. *A*. Lacunar infarct: fluid-attenuated inversion recovery (FLAIR) sequence showing hyperintense rim surrounding a hypointense cavitated core in the left thalamus (arrowhead). *B*. Acute microinfarct: diffusion-weighted sequence showing small hyperintense lesion in the left centrum semiovale (arrowhead). *C*. Cerebral microbleeds in deep penetrating brain region: T2*-weighted sequence showing multiple small hypointense lesions in the pons (arrowheads). *D*. Cerebral microbleeds in lobar brain regions: T2*-weighted sequence showing multiple small hypointense lesions lobar brain regions (arrowheads). *E* White matter hyperintensities: FLAIR sequence showing confluent diffuse hyperintensities in white matter.

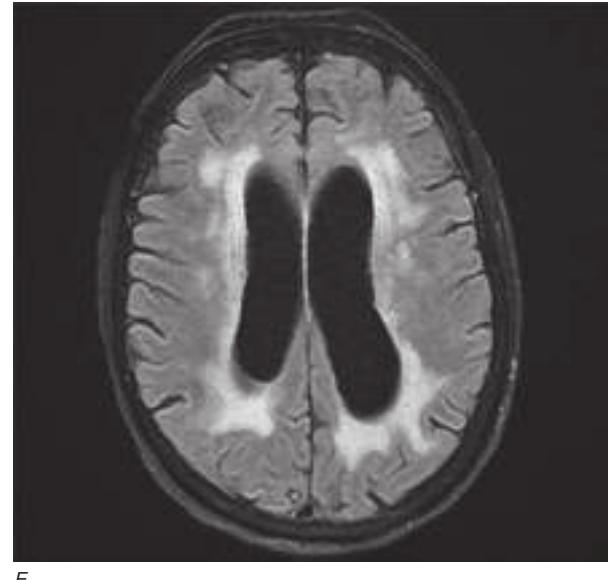


FIGURE 433-1 (Continued)

or transient ischemic attack, and family history of early stroke or vascular disease. Although stepwise progression and certain cognitive deficits such as loss of executive function are particularly suggestive, most individuals with VCID follow the more typical pattern of gradual progression of impaired episodic memory.

The mainstay for detection and subtyping of cerebrovascular disease is brain MRI. The MRI should include FLAIR, diffusion-weighted, and T2'-weighted sequences to detect the range of lesions noted above: large and small chronic infarcts, acute microinfarcts, microbleeds, and white matter hyperintensities. Vessel imaging studies such as computed tomography or magnetic resonance angiography are not required for initial evaluation of cognitive impairment though may be useful for determining the cause of any macroscopic infarcts that are identified. Genetic testing for rare hereditary forms of VCID such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Chap. 427) or hereditary cerebral amyloid angiopathy can be considered for cases in which there is a particularly young onset, positive family history, or suggestive neuroimaging, but is otherwise unnecessary.

TREATMENT

Vascular Dementia

Very few trials have addressed the optimal treatment for individuals with asymptomatic large- or small-vessel cerebrovascular disease, leaving uncertainty as to whether to follow primary or secondary stroke prevention guidelines. At a minimum, treatment should assiduously follow primary stroke prevention guidelines. The American Heart Association recommends the prudent approach for vascular health of managing blood pressure, controlling cholesterol, reducing blood sugar, maintaining an active lifestyle, adhering to a heart-healthy diet, losing weight, and discontinuing smoking (Life's Simple 7, <https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7>). Blood pressure targets are <140/90 mmHg for all individuals and <130/80 mmHg for those with estimated 10-year cardiovascular disease risk ≥10%, which likely applies to many individuals with imaging evidence of asymptomatic brain infarcts or advanced small-vessel disease. The usefulness of other treatments for secondary stroke prevention such as antiplatelet or statin therapy has not been established for

asymptomatic infarcts. These agents are reasonable to consider, however, when the imaging appearance suggests embolic or large-vessel-related strokes. All individuals with asymptomatic infarcts should be screened for atrial fibrillation, and those with embolic-appearing infarcts can be considered for prolonged cardiac monitoring. Similarly, patients with infarcts in the territories of large arteries should be considered for vascular imaging.

The few trials of symptomatic medications for cognitive impairment due to vascular etiologies have suggested modest cognitive benefits comparable to those found in Alzheimer's disease patients. Therefore, it may be reasonable in VCID to consider agents such as the cholinesterase inhibitors donepezil, rivastigmine, or galantamine for mild to moderate cognitive impairment and high-dose donepezil or the N-methyl-D-aspartate receptor antagonist memantine for moderate to severe impairment (Chap. 431). A shared decision-making approach in considering these medications is useful, given their relatively small impact on daily function.

FURTHER READING

- B PA et al: Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 83:74, 2018.
- C RA et al: The science of vascular contributions to cognitive impairment and dementia (VCID): A framework for advancing research priorities in the cerebrovascular biology of cognitive decline. Cell Mol Neurobiol 36:281, 2016.
- D M, L D: Vascular cognitive impairment. Circ Res 120:573, 2017.
- G SM et al: Cerebral amyloid angiopathy and Alzheimer disease: One peptide, two pathways. Nat Rev Neurol 16:30, 2020.
- L DA et al: Trajectory of cognitive decline after incident stroke. JAMA 314:41, 2015.
- S EE et al: Prevention of stroke in patients with silent cerebrovascular disease: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 48:e44, 2017.
- S DA et al: Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 277:813, 1997.
- V SE et al: Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 348:1215, 2003.
- W JM et al: Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12:822, 2013.

434 Dementia with Lewy Bodies

Irene Litvan, William W. Seeley,
Bruce L. Miller

Lewy body disease (LBD), manifesting as Parkinson's disease and dementia (PDD) or dementia with Lewy bodies (DLB), is the second most common cause of neurodegenerative dementia, after Alzheimer's disease (AD) (Chap. 431). Approximately 10% of patients with PD develop PDD per year, with the majority of PD patients developing PDD over time. The incidence of DLB is approximately 7 per 100,000 person-years. The prevalence of both PDD and DLB increases with aging, and both affect men more often than women.

CLINICAL MANIFESTATIONS

Most researchers conceptualize PDD and DLB as points on a spectrum of LBD pathology. Cognitively, PDD and DLB usually manifest with severe executive, attentional, and visuospatial deficits but preserved episodic memory. Cognitive decline in LBD affects performance of daily living activities beyond other PD symptoms. Early psychosis including well-formed visual hallucinations, fluctuating cognition, rapid eye movement sleep behavior disorder (RBD), and parkinsonism are the main diagnostic features in DLB. The sense of a presence behind the person may precede well-formed hallucinations. Delusions are less frequent than hallucinations and are usually related to misidentification, infidelity, theft, or persecution. Fluctuating attention and concentration are other characteristic features. Minor day-to-day variation in cognitive functioning is common across dementias, but in DLB these fluctuations can be marked, with short periods of confusion or severe lethargy that may rapidly resolve. Patients with PDD and DLB are highly sensitive to infectious or metabolic disturbances. The first manifestation of DLB in some patients is delirium, often precipitated by an infection, new medicine, or other systemic disturbance. Parkinsonism in DLB is usually associated with early postural instability and can present early or later in the course. RBD is a characteristic, often prodromal, feature. Normally, dreaming is accompanied by skeletal muscle paralysis, but patients with RBD enact dreams, often violently, leading to injuries to themselves or their bed partners. Both PDD and DLB may be accompanied or preceded by anosmia, constipation, RBD, depression, and anxiety.

The symptom profile in DLB and PDD can provide clues for the differential diagnosis at the clinic. Clinically, the time interval between parkinsonism and dementia differentiate PDD and DLB. PDD presents in patients with long-standing PD, who manifest dementia often with visual hallucinations, fluctuating attention or alertness, and RBD. On the other hand, when the dementia and the neuropsychiatric symptoms precede or co-emerge with the parkinsonism, the patient is diagnosed with DLB. Patients with DLB, more frequently than those with PDD, also have AD co-pathology, making the prediction of underlying pathology challenging for clinicians. Episodic memory disturbance points to the diagnosis of comorbid AD. Orthostatic hypotension that can lead to syncopal events, erectile dysfunction, and constipation can be present early in DLB, at times making it challenging to differentiate DLB from multiple system atrophy (MSA). In MSA the autonomic disturbances occur early and are usually more severe than in DLB, and cognition is relatively preserved. Anosmia is also more characteristic of LBD than MSA.

■ PRODRMAL PHASE

Both PDD and DLB have a prodromal phase where patients have a mild cognitive impairment (MCI), with cognitive deficits that do not have a substantial impact on daily life. PD-MCI is characterized by deficits in executive, attention, and visuospatial disturbances, but can also present with an amnestic or multiple-domain MCI. Prodromal DLB is also characterized by similar cognitive disturbances but is also

TABLE 434-1 Distinguishing MCI Due to Lewy Body Disease or Alzheimer's Disease

CLINICAL FEATURES	PRODRMAL MCI-LB PATHOLOGY	PRODRMAL MCI-AD PATHOLOGY
MCI	MCI usually affecting executive, attention, and/or visuospatial functions	MCI with impaired memory and semantic naming
Fluctuating cognition with variations in attention	Frequent and severe	Rare or not severe
Sleep	REM sleep behavior disorder	Insomnia, frequent awakenings
Recurrent visual hallucinations	Frequent	Rare
Biomarkers		
Polysomnogram	REM sleep behavior disorder with atonia	Normal
CSF	Decreased CSF α -synuclein by RT-QuIC	Decreased CSF β -amyloid and increased phospho-tau. This can be performed in blood now.
MRI	Atrophy of the amygdala	Atrophy of the parahippocampal/hippocampal areas
18F-deoxyglucose PET scan	Hypometabolism in occipital lobe and increased in posterior cingulate (cingulate island sign)	Hypometabolism in parieto-temporal lobes
Amyloid PET scan	Normal, unless associated with AD	Abnormal parieto-temporal areas
MIBG myocardial scintigraphy	Post-ganglionic sympathetic denervation	Normal
DAT scan or PET dopamine scan	Reduced dopamine transporter in the basal ganglia, particularly putamen	Normal

AD, Alzheimer's disease; CSF, cerebrospinal fluid; DAT, dopamine transporter; LB, Lewy bodies; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; RT-QuIC, real-time quaking-induced conversion.

associated with either hallucinations unrelated to medications, RBD, fluctuations in attention, or parkinsonism. It is at times challenging to differentiate prodromal MCI-DLB and PD-MCI when the major features are RBD and parkinsonism, for which the term *prodromal MCI-Lewy body* (MCI-LB) was recently proposed. RBD may precede the development of an LBD-related syndrome by many years, usually evolving into either PD or DLB. The clinical profile and several biomarkers can help differentiate MCI due to LBD vs. AD pathology (Table 434-1).

PATHOLOGY

The key neuropathologic feature in LBD is the presence of Lewy bodies and Lewy neurites throughout specific brainstem nuclei, substantia nigra, amygdala, cingulate gyrus, and, ultimately, the neocortex. Lewy bodies are intraneuronal cytoplasmic inclusions that stain with periodic acid-Schiff (PAS) and ubiquitin but are now identified with antibodies to the presynaptic protein α -synuclein. Lewy bodies are composed of straight neurofilaments 7–20 nm long with surrounding amorphous material and contain epitopes recognized by antibodies against phosphorylated and nonphosphorylated neurofilament proteins, ubiquitin, and α -synuclein. The presence of α -synuclein aggregates in neurons and glia in PDD and DLB molecularly classifies these diseases as synucleinopathies. In general, neuronal and synaptic loss, rather than Lewy pathology per se, best predicts the clinical deficits.

Formal criteria identify three stages of progression: (1) Brainstem predominant; (2) transitional limbic; and (3) diffuse neocortical. Importantly, healthy older individuals may also show isolated scattered Lewy body pathology in the substantia nigra, amygdala, or olfactory bulb. Pathologic studies have shown that PD usually starts in the

enteric nervous system and spreads through the vagus nerve to the heart, lower brainstem, substantia nigra, limbic system, and lastly the cerebral cortex. PD may also begin in the olfactory bulb and spread through olfactory system connections or start independently in enteric and olfactory bulb areas. Evidence from human anatomic pathology and animal models suggests that LBD may similarly propagate via a prion-like mechanism. Abnormally folded α -synuclein aggregates propagate transneuronally following connection pathways of the nervous system. This pathologic propagation from the periphery to the brain correlates with the evolution of clinical symptoms; PD usually manifests first with nonmotor features characterized by constipation and/or hyposmia, followed by anxiety, depression, RBD, parkinsonism, and lastly dementia. PDD is manifested clinically when limbic and cortical areas are involved.

A profound cholinergic deficit, owing to basal forebrain and pedunculopontine nucleus involvement, is present in most patients with DLB and may be associated with the characteristic fluctuations, inattention, and visual hallucinations. Adrenergic deficits from locus coeruleus involvement further undermine arousal and alerting.

PATHOGENESIS

Both genes and environmental factors are thought to contribute to the development of LBD. The presence of alpha-synuclein aggregates in Lewy bodies led to the discovery of α -synuclein duplications and triplications that manifest clinically as PD or DLB. There are multiple genes associated with PD, but mutations of glucocerebrosidase (GBA) particularly lead to PDD or DLB presentations (Chap. 435).

The origins of LBD in gastrointestinal and olfactory areas suggest that environmental toxins acting on a susceptible genetic background may contribute to the LBD pathogenesis (a “double-hit” hypothesis). Several toxins have been associated with PD (Chap. 435), but epidemiologic studies of risk factors in DLB remain inconclusive.

LABORATORY FEATURES

In patients presenting with cognitive disturbances, it is always necessary to rule out treatable causes of dementia such as drugs, infections, or metabolic disturbances (Chap. 29). MRI of the brain can be helpful to rule out vascular parkinsonism or subdural hematomas, or support the diagnosis of other disorders such as MSA (i.e., pontine “hot-cross buns” sign; Chap. 440).

Biomarkers that support the diagnosis of LBD include polysomnogram showing RBD with atonia, CSF showing either α -synuclein oligomers (RT-QuIC) or CSF or blood levels of phospho-tau217, iodine-123-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy showing cardiac postganglionic sympathetic denervation, and dopamine transporter imaging using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) (Table 434-1).

TREATMENT

Dementia with Lewy Bodies

Although there are currently no disease-modifying agents to prevent, slow, or cure LBD-related dementias, several symptomatic treatments are available. By addressing the substantial cholinergic deficit in DLB, cholinesterase inhibitors such as rivastigmine (target dose 6 mg twice daily or 9.5 mg patch daily) or donepezil (target dose 10 mg daily) often improve cognition, reduce hallucinations, and stabilize delusional symptoms. The atypical antipsychotic pimavanserin is frequently helpful to treat the psychosis and does not worsen parkinsonism; it is approved by the FDA for patients with PDD and is often used off-label for DLB. Pimavanserin is a selective inverse agonist of the serotonin 5-HT_{2A} receptor that does not block dopamine receptors but carries an FDA warning regarding an increase in risk of death, especially in older patients. Low-dose clozapine (begin at 6.25 mg, increasing up to 25 mg, daily) is also effective for treating hallucinations and delusions, but requires frequent blood draws due to the risk of agranulocytosis. Patients with LBD are sensitive to dopaminergic medications, which must be carefully titrated; tolerability may be improved with concomitant

use of a cholinesterase inhibitor. Patients with DLB should not be exposed to typical neuroleptics that can lead to a neuroleptic malignant syndrome and death, or anticholinergics or dopamine agonists that can exacerbate their symptoms.

RBD usually responds to melatonin, requiring at times 20 mg/day. If melatonin is not effective, clonazepam, gabapentin, or codeine can be used with caution due to the possibility of worsening cognition or falls. Antidepressants, especially those with strong anxiolytic properties (escitalopram, paroxetine, duloxetine, or venlafaxine; see Chap. 452), are often necessary for mood and anxiety symptoms. Orthostatic hypotension may require treatment with nonpharmacologic measures (diet high in salt and liquids, a 30° elevation of the head of the bed) or pharmacologic therapies (i.e., fludrocortisone, midodrine, droxidopa). Physical therapy can maximize motor function and protect against fall-related injury. Home safety assessments and transfer instruction should also be provided. Education for patients and caregivers and social worker support are also important. Therefore, the care of patients with LBD requires a multidisciplinary approach.

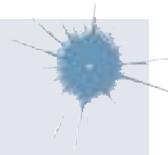
FURTHER READING

- E M et al: Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 22:1689, 2007.
- L I et al: Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 27:349, 2012.
- M IG et al: Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 89:88, 2017.
- M IG et al: Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology* 94:743, 2020.
- R M et al: Ultrasensitive RT-QuIC assay with high sensitivity and specificity for Lewy body-associated synucleinopathies. *Acta Neuropathol* 140:49, 2020.
- S I et al: Clinical validity of presynaptic dopaminergic imaging with 123I-ioflupane and noradrenergic imaging with 123I-MIBG in the differential diagnosis between Alzheimer's disease and dementia with Lewy bodies in the context of a structured 5-phase development framework. *Neurobiol Aging* 52:228, 2017.

435

Parkinson's Disease

C. Warren Olanow,
Anthony H.V. Schapira



PARKINSON'S DISEASE AND RELATED DISORDERS

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, exceeded only by Alzheimer's disease (AD). Its cardinal clinical features were first described by the English physician James Parkinson in 1817. James Parkinson was a general physician who captured the essence of this condition based on a visual inspection of a mere handful of patients, several of whom he only observed walking on the street and did not formally examine. It is estimated that the number of people with PD in the most populous nations worldwide is ~5 million persons, and this number is expected to double within 20 years based on the aging of the population. The mean age of onset of PD is about 60 years, and the lifetime risk is ~3% for men and 2% for women. The frequency of PD increases with age, but cases can be seen in individuals in their twenties and even younger, particularly when associated with a gene mutation.

Clinically, PD is characterized by rest tremor, rigidity (stiffness), bradykinesia (slowing), and gait dysfunction with postural instability.

TABLE 435-1 Clinical Features of Parkinson's Disease

CARDINAL MOTOR FEATURES	OTHER MOTOR FEATURES	NONMOTOR FEATURES
Bradykinesia	Micrographia	Anosmia
Rest tremor	Masked facies (hypomimia)	Sensory disturbances (e.g., pain)
Rigidity	Reduced eye blinking	Mood disorders (e.g., depression)
Postural instability	Drooling	Sleep disturbances (e.g., fragmented sleep, RBD)
	Soft voice (hypophonia)	Autonomic disturbances
	Dysphagia	Orthostatic hypotension
	Freezing	Gastrointestinal disturbances
	Falling	Genitourinary disturbances
		Sexual dysfunction
		Cognitive impairment/dementia

Abbreviation: RBD, rapid eye movement sleep behavior disorder.

These are known as the classical or “cardinal” features of the disease. Additional clinical features can include freezing of gait, speech difficulty, swallowing impairment, and a series of nonmotor features that include autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia (see Table 435-1 and discussion below).

Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNC), reduced striatal dopamine, and intraneuronal proteinaceous

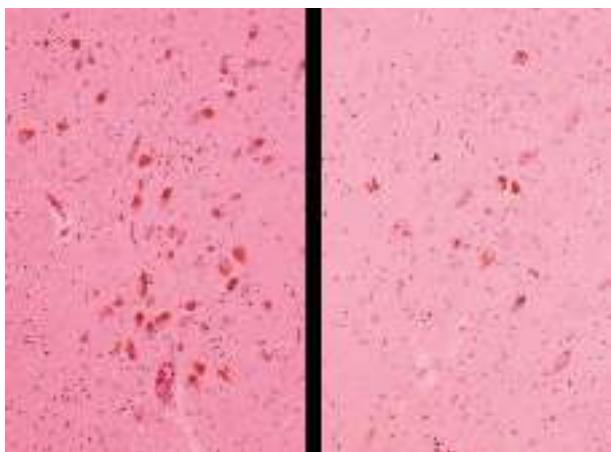
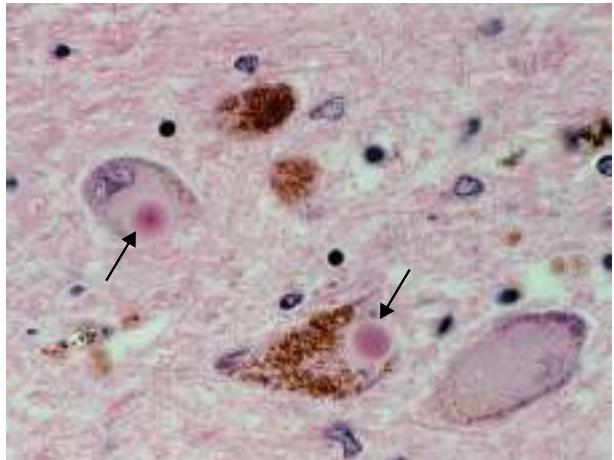
inclusions in cell bodies and axons that stain for α -synuclein (known as Lewy bodies and Lewy neurites, collectively as Lewy pathology) (Fig. 435-1). While interest has focused on the dopamine system, neuronal degeneration with Lewy pathology can also affect cholinergic neurons of the nucleus basalis of Meynert (NBM), norepinephrine neurons of the locus coeruleus (LC), serotonin neurons in the raphe nuclei of the brainstem, and neurons of the olfactory system, cerebral hemispheres, spinal cord, and peripheral autonomic nervous system. This “nondopaminergic” pathology is likely responsible for the nonmotor clinical features listed above and in Table 435-1. It has been postulated that Lewy pathology can begin in the peripheral autonomic nervous system, olfactory system, and dorsal motor nucleus of the vagus nerve in the lower brainstem, and then spread in a predictable and sequential manner to affect the SNC and cerebral hemispheres (Braak staging). These studies thus suggest that the classic degeneration of SNC dopamine neurons and the cardinal motor features of PD develop at a midstage of the illness. Indeed, epidemiologic studies suggest that clinical symptoms reflecting early involvement of nondopaminergic neurons such as constipation, anosmia, rapid eye movement (REM) behavior sleep disorder, and cardiac denervation can precede the onset of the classic motor features of PD by several years if not decades. Originally it was considered that these are risk factors for developing PD, but based on pathological findings it is now considered likely that they represent an early premotor form of the disease. Intense efforts are underway to accurately define a premotor stage of PD with high sensitivity and specificity. This will be of particular importance when a neuroprotective therapy is available as it would be desirable to initiate disease-modifying treatment at the earliest possible stage of the disease.



A



C



B

FIGURE 435-1 Pathologic specimens from a patient with Parkinson's disease (PD) compared to a normal control demonstrating (A) reduction of pigment in SNC in PD (right) versus control (left), (B) reduced numbers of cells in SNC in PD (right) compared to control (left), and (C) Lewy bodies (arrows) within melanized dopamine neurons in PD. SNC, substantia nigra pars compacta.

TABLE 435-2 Differential Diagnosis of Parkinsonism

Parkinson's Disease	Atypical Parkinsonism	Secondary Parkinsonism	Neurodegenerative disorders that are associated with parkinsonism
Sporadic	Multiple-system atrophy (MSA)	Drug-induced	Wilson's disease
Genetic	Cerebellar type (MSA-c)	Tumor	Huntington's disease
Dementia with Lewy bodies	Parkinson type (MSA-p)	Infection	Neurodegeneration with brain iron accumulation
	Progressive supranuclear palsy	Vascular	SCA 3 (spinocerebellar ataxia)
	Parkinsonism variant	Normal-pressure hydrocephalus	Fragile X-associated ataxia-tremor-parkinsonism
	Richardson variant	Trauma	Prion diseases
	Corticobasal syndrome	Liver failure	X-linked dystonia-parkinsonism
	Frontotemporal dementia	Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide)	Alzheimer's disease with parkinsonism
			Dopa-responsive dystonia

Abbreviation: MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.

■ DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Parkinsonism is a generic term that is used to define a syndrome manifest by bradykinesia with rigidity and/or tremor. It has a differential diagnosis (Table 435-2) that reflects differences in the site of involvement within the basal ganglia, the nature of the pathology, and the clinical picture. The basal ganglia are comprised of a group of subcortical nuclei that include the striatum (putamen and caudate nucleus), subthalamic nucleus (STN), globus pallidus pars externa (GP_e), globus pallidus pars interna (GP_i), and the SNC (Fig. 435-2). Among the different forms of parkinsonism, PD is the most common (~75% of cases). Historically, PD was diagnosed based on the presence of two of three parkinsonian features (tremor, rigidity, bradykinesia). However, postmortem studies found a 24% error rate when diagnosis was based solely on these criteria. Clinicopathologic correlation studies subsequently determined that parkinsonism (bradykinesia and rigidity) associated with rest tremor, asymmetry of motor impairment, and a good response to levodopa is much more likely to predict the correct pathologic diagnosis. With these revised criteria (known as the U.K. Brain Bank Criteria), a clinical diagnosis of PD could be confirmed pathologically in >90% of cases. Imaging of the dopamine system (see below) further increases diagnostic accuracy. The International Parkinson's Disease and Movement Disorder Society (MDS) has suggested revised clinical criteria for PD (known as the MDS Clinical Diagnostic Criteria for Parkinson's disease), which are thought to increase diagnostic accuracy even further, particularly in early cases where levodopa has not yet been tried. While motor parkinsonism has been retained as the core feature of the disease, the diagnosis of PD as the specific type of parkinsonism relies on three additional categories of diagnostic features: supportive criteria (features that increase confidence in the diagnosis of PD), absolute exclusion criteria, and red flags (which must

be counterbalanced by supportive criteria to permit a diagnosis of PD). Utilizing these criteria, two levels of certainty have been delineated; clinically established PD and clinically probable PD (see Berg et al. Movement Disorders 30:1591, 2015 in Further Reading).

Imaging of the brain dopamine system in patients with PD can be performed using positron emission tomography (PET) or single-photon emission computed tomography (SPECT). These studies typically show reduced and asymmetric uptake of striatal dopaminergic biomarkers, particularly in the posterior putamen with relative sparing of the caudate nucleus (Fig. 435-3). These findings reflect the degeneration of nigrostriatal dopaminergic neurons and the loss of their striatal terminals. Imaging can be useful in patients where there is diagnostic uncertainty (e.g., early stage, essential tremor, dystonic tremor, psychogenic tremor) or in research studies in order to ensure accuracy, but is not necessary in routine practice. This may change in the future when there is a disease-modifying therapy and it is critically important to make a correct diagnosis as early as possible. There is also some evidence that the diagnosis of PD, and even pre-PD, may be made based on the presence of increased iron in the SNC using transcranial sonography or special MRI protocols.

Genetic testing can be helpful for establishing a diagnosis but is not routinely employed as monogenic forms of PD are relatively rare and likely account for no more than 10% of cases (see discussion below). A genetic form of PD should be considered in patients with a strong positive family history, early age of onset (<40 years), a particular ethnic background (see below), and in research studies. Genetic variants of the glucocerebrosidase gene (*GBA*) are the most common genetic association with PD. They are present in 5–15% of PD patients, and in 25% of Ashkenazi PD patients. However, only about 30% of people with *GBA* variants will develop PD by age 80 years. Genetic variants

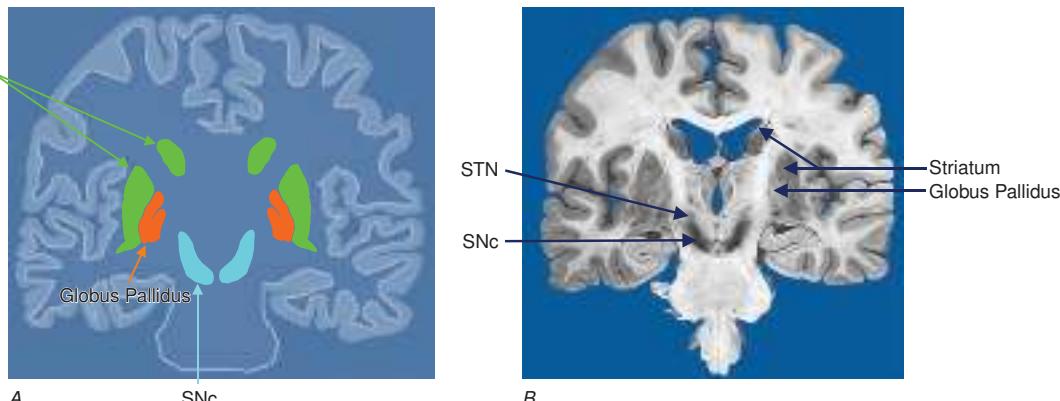


FIGURE 435-2 Basal ganglia nuclei. Schematic (A) and postmortem (B) coronal sections illustrating the various components of the basal ganglia. SNC, substantia nigra pars compacta; STN, subthalamic nucleus.

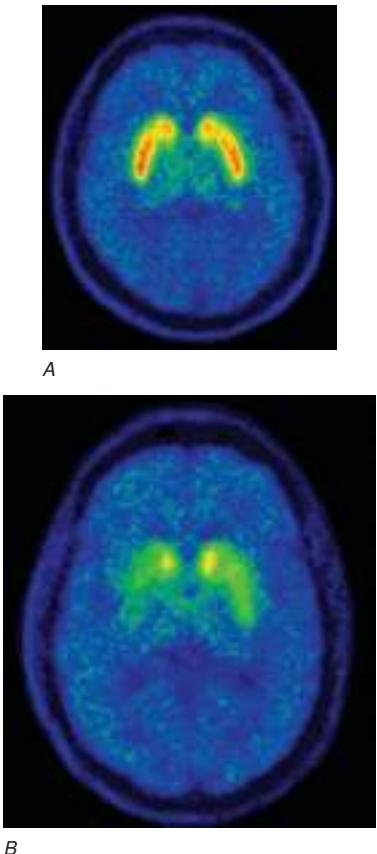


FIGURE 435-3 [^{18}F]Dihydrotnabenazine positron emission tomography (a marker of VMAT2) in healthy control (A) and Parkinson's disease (B) patient. Note the reduced striatal uptake of tracer, which is most pronounced in the posterior putamen and tends to be asymmetric. (Courtesy of Dr. Jon Stoessl.)

of the *LRRK2* gene have also attracted particular interest as they are responsible for ~1% of typical sporadic cases of the disease. *LRRK2* mutations are a particularly common cause of PD (~25%) in Ashkenazi Jews and North African Berber Arabs; however, there is considerable variability in penetrance and many carriers never develop clinical features of PD. Genetic testing is of particular interest for identifying at-risk individuals in a research setting and for defining enriched populations for clinical trials of therapies directed at a particular mutation.

Atypical, Secondary, and Other Forms of Parkinsonism
Atypical parkinsonism refers to a group of neurodegenerative conditions that are usually associated with more widespread pathology than found in PD (e.g., degeneration of striatum, globus pallidus, cerebellum, and brainstem, as well as the SNc). These conditions include multiple system atrophy (MSA; *Chap. 440*), progressive supranuclear palsy (PSP; *Chap. 432*), and corticobasal syndrome (CBS; *Chap. 432*). As a group, they tend to present with parkinsonism (rigidity and bradykinesia) but manifest clinical differences from PD reflecting their more widespread pathology. These include early involvement of speech and gait, absence of rest tremor, lack of motor asymmetry, poor or no response to levodopa, and a more aggressive clinical course. In the early stages, some cases may show a modest benefit from levodopa and can be difficult to distinguish from PD, but the diagnosis becomes clearer as the disease evolves over time. Neuroimaging of the dopamine system is usually not helpful, as striatal dopamine depletion can be seen in both PD and atypical parkinsonism. By contrast, metabolic imaging of the basal ganglia/thalamus network (using 2-F-deoxyglucose) may be helpful, showing a pattern of decreased activity in the GPi with increased activity in the thalamus, the reverse of what is seen in PD.

MSA manifests as a combination of the atypical parkinsonian features described above, as well as cerebellar and autonomic features. Clinical syndromes can be divided into a predominantly parkinsonian (MSA-p) or cerebellar (MSA-c) form. Clinically, MSA is suspected when a patient presents with features of atypical parkinsonism in conjunction with cerebellar signs and/or prominent autonomic dysfunction, usually orthostatic hypotension (*Chap. 440*). Pathologically, MSA is characterized by degeneration of the SNc, striatum, cerebellum, and inferior olfactory nuclei coupled with characteristic glial cytoplasmic inclusions (GCIs) that stain positively for α -synuclein (Lewy bodies) particularly in oligodendrocytes rather than in SNc neurons as in PD. MRI can show pathologic iron accumulation in the striatum on T2-weighted scans, high signal change in the region of the external surface of the putamen (putaminal rim) in MSA-p, or cerebellar and brainstem atrophy (the pontine “hot cross bun” sign [*Fig. 440-2*]) in MSA-c. There is currently no established evidence for any gene mutation/genetic risk factor for MSA.

PSP is a form of atypical parkinsonism that is characterized by parkinsonism as noted above coupled with slow ocular saccades, eyelid apraxia, and restricted vertical eye movements with particular impairment of downward gaze. Patients frequently experience hyperextension of the neck with early gait disturbance and falls. In later stages, speech and swallowing difficulty and cognitive impairment may become evident. Two clinical forms of PSP have been identified; a “Parkinson” form that can closely resemble PD in the early stages and can include a positive response to levodopa, and the more classic “Richardson” form that is characterized by the features described above with little or no response to levodopa. MRI may reveal a characteristic atrophy of the midbrain with relative preservation of the pons on midsagittal images (the so-called hummingbird sign). Pathologically, PSP is characterized by degeneration of the SNc, striatum, STN, midline thalamic nuclei, and pallidum, coupled with neurofibrillary tangles and inclusions that stain for the tau protein. Mutations in the MAPT gene that encodes for the tau protein have been detected in some familial cases.

CBS is a relatively uncommon condition that usually presents with asymmetric dystonic contractions and clumsiness of one hand coupled with cortical sensory disturbances manifest as apraxia, agnosia, focal limb myoclonus, or alien limb phenomenon (where the limb assumes a position in space without the patient being aware of its location or recognizing that the limb belongs to them). Dementia may occur at any stage of the disease. Both cortical and basal ganglia features are required to make this diagnosis. MRI frequently shows asymmetric cortical atrophy, but this must be carefully sought and may not be obvious to casual inspection. Pathologic findings include achromatic neuronal degeneration with tau deposits. Considerable overlap may occur both clinically and pathologically between CBS and PSP, and they may be difficult to distinguish without pathologic confirmation.

Secondary parkinsonisms occur as a consequence of other etiologic factors such as drugs, stroke, tumor, infection, or exposure to toxins (e.g., carbon monoxide, manganese) that cause basal ganglia dysfunction. Clinical features reflect the region of the basal ganglia that has been damaged. For example, strokes or tumors that affect the SNc may have a clinical picture that is largely identical to the motor features of PD, whereas toxins such as carbon monoxide or manganese that damage the globus pallidus more closely resemble atypical parkinsonism. Dopamine-blocking agents such as neuroleptics are the most common cause of secondary parkinsonism. These drugs are most widely used in psychiatry, but physicians should be aware that drugs such as metoclopramide which are primarily used to treat gastrointestinal problems are also neuroleptic agents and may induce secondary parkinsonism. These drugs can also cause acute and tardive dyskinesias (see *Chap. 436*). Other drugs that can cause secondary parkinsonism include tetrabenazine, calcium channel blockers (flunarizine, cinnarizine), amiodarone, and lithium.

Parkinsonism can also be seen as a feature of dopa-responsive dystonia (DRD), a condition that results from a mutation in the *GTP-Cyclohydrolase 1* gene, which can lead to a defect in a cofactor for tyrosine hydroxylase with impairment in the manufacture of dopa and dopamine. While it typically presents as dystonia (*Chap. 436*), it can

TABLE 435-3 Features Suggesting an Atypical or Secondary Cause of Parkinsonism

SYMPTOMS/SIGNS	ALTERNATIVE DIAGNOSIS TO CONSIDER
History	
Early speech and gait impairment (lack of tremor, lack of motor asymmetry, early falls)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40 years	Genetic form of PD, Wilson's disease, DRD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired vertical gaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Examination	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Slow saccades with impaired downgaze	PSP
High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: DRD, dopa-responsive dystonia; MSA-c, multiple-system atrophy—cerebellar type; MSA-p, multiple-system atrophy—Parkinson's type; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

present as a biochemically based form of parkinsonism (due to reduced synthesis of dopamine) that closely resembles PD and responds to levodopa but is not associated with abnormalities on fluoro-dopa positron emission tomography (FD-PET) nor neurodegeneration. This diagnosis should be considered in individuals aged <20 years who present with parkinsonism particularly if there are dystonic features.

Finally, parkinsonism can be seen as a feature of a variety of other neurodegenerative disorders such as Wilson's disease, Huntington's disease (especially the juvenile form known as the Westphal variant), certain spinocerebellar ataxias, and neurodegenerative disorders with brain iron accumulation such as pantothenate kinase (PANK)-associated neurodegeneration (formerly known as Hallervorden-Spatz disease). It is particularly important to rule out Wilson's disease, as progression can be prevented with the use of copper chelators.

Some features that suggest that parkinsonism might be due to a condition other than classic PD are shown in Table 435-3.

■ ETIOLOGY AND PATHOGENESIS

Most PD cases occur sporadically (~85–90%) and are of unknown cause. Gene mutations (see below) are the only known causes of PD. Twin studies performed several decades ago suggested that environmental factors might play an important role in patients with an age of onset ≥50 years, with genetic factors being more important in younger-onset patients. However, the demonstration of later-onset genetic variants (e.g., *LRRK2* and *GBA*) argues against the emphasis on environmental factors, even in individuals >50 years of age. The environmental hypothesis received some support in the 1980s with the demonstration that MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a by-product of the illicit manufacture of a heroin-like drug, caused a PD syndrome in addicts in northern California. MPTP is transported into the central nervous system, where it is oxidized to form MPP⁺, a mitochondrial toxin that is selectively taken up by, and damages, dopamine neurons, but typically without the formation of Lewy bodies. Importantly, MPTP or MPTP-like compounds have not been linked to sporadic PD. Epidemiologic studies have reported an increased risk of developing PD in association with exposure to

pesticides, rural living, farming, and drinking well water. Dozens of other associations have also been reported in individual studies, but results have been inconsistent, and no environmental factor has yet been proven to be a cause or contributor to PD. Some possible protective factors have also been identified in epidemiologic studies including caffeine, cigarette smoking, intake of nonsteroidal anti-inflammatory drugs, and calcium channel blockers. The validity of these findings and the responsible mechanism remain to be established.

About 10% of PD cases are familial in origin, and mutations in several PD-linked genes have been identified (Table 435-4). While monogenic mutations have been shown to be causative of PD, several genetic risk factors that increase the risk of developing PD have also been identified. Large-size genome-wide association studies (GWASs) have identified more than 25 independent gene variants (single-nucleotide polymorphisms) as PD risk factors including variants in the *SNCA*, *LRRK2*, *MAPT*, and *GBA* genes as well as in the *HLA* region on chromosome 6. It has been proposed that many cases of PD may be due to a “double hit” involving an interaction between (a) one or more genetic risk factors that induce susceptibility coupled with (b) exposure to a toxic environmental factor that may induce epigenetic or somatic DNA alterations or has the potential to directly damage the dopaminergic system. In this scenario, both factors are required for PD to ensue, while the presence of either one alone is not sufficient to cause the disease. Notably, however, even if a genetic or environmental risk factor doubles the risk to develop PD, this results in a lifetime risk of only 4% or lower, and thus cannot presently be used for individual patient counseling.

Several factors have been implicated in the pathogenesis of cell death in PD, including oxidative stress, inflammation, excitotoxicity, mitochondrial dysfunction, lysosomal/proteasomal dysfunction, and the accumulation of misfolded proteins with consequent proteolytic stress. Studies also suggest that with aging, dopamine neurons switch from sodium to calcium pacing through calcium channels, potentially making these high-energy neurons vulnerable to calcium-mediated neurotoxicity. Whatever the pathogenic mechanism, cell death appears to occur, at least in part, by way of a signal-mediated apoptotic or “suicidal” process. Each of these mechanisms offers a potential target for putative neuroprotective drugs. In addition, a role for inflammation is implicated by the genetic association of PD with the class II HLA gene *DRB1* (variants of which are associated with either protection or risk for PD), and that autoreactive T-cells recognizing peptides derived from alpha-synuclein are present in PD patients. However, it is not clear which of these factors is primary, if they are the same in all cases or specific to individual (genetic) subgroups, if they act by way of a network such that multiple insults are required for neurodegeneration to ensue, or if the findings discovered to date merely represent epiphomena unrelated to the true cause of cell death that still remains undiscovered (Fig. 435-4).

Although gene mutations cause only a minority of cases of PD, they have been very helpful in pointing to specific pathogenic pathways and molecular mechanisms that are likely to be central to the neurodegenerative process in the sporadic form of the disease. To date, most interest has focused on pathways implicated by mutations in α -synuclein (*SNCA*), *GBA*, *LRRK2*, and *PINK1/Parkin*.

SNCA was the first PD-linked gene mutation and the most intensely investigated with respect to causative mutations, risk variants, as well as function of the gene and its encoded protein. Shared clinical features of patients with *SNCA* mutations include earlier age of disease onset than in nongenetic PD, a faster progression of motor signs that are mostly levodopa-responsive, early occurrence of motor fluctuations, and presence of prominent nonmotor features, particularly cognitive impairment. Intriguingly, *SNCA* constitutes the major component of Lewy bodies implicating the protein in sporadic forms of PD as well (Fig. 435-1). Importantly, duplication or triplication of the wild-type *SNCA* gene also causes PD with triplication carriers being more severely affected than carriers of duplications. These findings indicate that increased production of the normal protein alone can cause PD. Lewy pathology was discovered to have developed in healthy embryonic dopamine neurons that had been implanted into the striatum of

TABLE 435-4 Confirmed Genetic Causes of Parkinson's Disease*

DESIGNATION* AND REFERENCE	GENE REVIEWS AND OMIM REFERENCE	CLINICAL CLUES	INHERITANCE	PREVIOUS LOCUS SYMBOL
1. Classical PD				
PARK-SNCA	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 168601	Missense mutations cause classical parkinsonism. Duplication or triplication mutations in this gene cause early-onset parkinsonism with prominent dementia.	AD	PARK1
PARK-LRRK2	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1208/ OMIM 607060	Clinically typical PD	AD	PARK8
PARK-VPS35	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 614203	Clinically typical PD	AD	PARK17
PARK-GBA	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 168600/606463	Clinically typical PD—possibly faster progression and greater risk of cognitive impairment	AD	
2. Early-onset PD				
PARK-Parkin	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1155/ OMIM 600116	Often presents with dystonia, typically in a leg	AR	PARK2
PARK-PINK1	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 605909	Often presents with psychiatric features	AR	PARK6
PARK-DJ1	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 606324		AR	PARK7
3. Parkinsonism				
PARK-ATP13A2	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 606693	Kufor-Rakeb syndrome with parkinsonism and dystonia; additional features: Supranuclear gaze palsy, spasticity/pyramidal signs, dementia, facial-facial-finger mini-myoclonus, dysphagia, dysarthria, olfactory dysfunction	AR	PARK9
PARK-FBXO7	GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 260300	Early-onset parkinsonism with pyramidal signs	AR	PARK15
PARK-DNAJC6	GeneReviews: n/a OMIM 615528	May present with mental retardation and seizures	AR	PARK19
PARK-SYNJ1	GeneReviews: n/a OMIM 615530	May have seizures, cognitive decline, abnormal eye movements, and dystonia	AR	PARK20

According to the recommendations of the International Parkinson's and Movement Disorder Society (C Marras: Mov Disord 31:436, 2016).

PD patients, suggesting that the abnormal protein had transferred from affected cells to healthy unaffected dopamine neurons. Based on these findings, it has been proposed that the SNCA protein may be a prion, and PD a prion or prion-like disorder (Chaps. 424 and 438). Like the prion protein PrP^C, SNCA can misfold to form β-rich sheets, join to form toxic oligomers and aggregates, polymerize to form amyloid plaques (i.e., Lewy bodies), and cause neurodegeneration with spread to involve unaffected neurons. Indeed, injection of SNCA fibrils into the striatum of both transgenic and wild-type rodents leads to the development of Lewy pathology in host neurons, neurodegeneration, behavioral abnormalities, and spread of SNCA pathology to anatomically connected sites. Further support for this hypothesis comes from the demonstration that inoculation into the striatum of homogenates derived from human Lewy bodies induces dopamine cell degeneration and widespread Lewy pathology in mice and primates. Exciting new evidence also suggests that SNCA pathology might begin peripherally in the enteric nervous system within the GI tract and spread by way of the vagus nerve to the lower brainstem (dorsal motor nucleus of the vagus) and ultimately to the SNc to cause the motor features of PD. There is growing interest in the possibility that the gut microbiome in PD patients causes inflammatory changes that promote

alpha-synuclein misfolding and spread. The gut-brain axis might therefore offer a mechanism by which alpha-synuclein pathology might spread to the brain and cause PD, and therefore provides a novel target for therapeutic intervention.

Collectively, this evidence supports the concept that neuroprotective therapies for PD might be developed based on inhibiting the accumulation or accelerating the removal of SNCA aggregates, knocking down levels of host SNCA, preventing the spread of misfolded SNCA, or blocking the templating phenomenon whereby misfolded SNCA promotes misfolding of the native protein in a prion-like chain reaction. Many of these approaches are currently being tested in the laboratory and preliminary clinical trials have already been initiated.

Mutations in the GBA gene represent the most important risk factor in terms of effect size for the development of PD. GBA encodes for the enzyme glucocerebrosidase (GCase), which promotes lysosomal function and enhances the clearance of misfolded proteins such as SNCA. Experimentally, there is a direct pathophysiological link between increased levels of SNCA and reduced levels of GBA. The identification of GBA as a risk gene for PD resulted from the clinical observation that patients with Gaucher's disease (GD) and their relatives commonly show signs of parkinsonism. This clinical observation

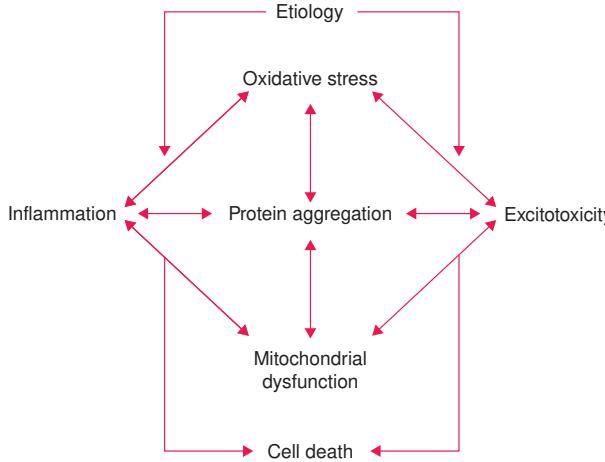


FIGURE 435-4 Schematic representation of how pathogenetic factors implicated in Parkinson's disease interact in a network manner, ultimately leading to cell death. This figure illustrates how interference with any one of these factors may not necessarily stop the cell death cascade. (Reproduced with permission from CW Chanow: The pathogenesis of cell death in Parkinson's disease—2007. *Mov Dis* 22:S335, 2007.)

led to the discovery that literally hundreds of mutations in *GBA* confer risk for the development of PD. Further, it has been shown that reduced levels of GCase activity due to *GBA* variants impair lysosomal function, which results in the accumulation of *SNCA*. Conversely, the accumulation of *SNCA* can lead to inhibition of lysosomal function and a further reduction in levels of *GBA*/GCase by interfering with endoplasmic reticulum-to-Golgi trafficking. Thus, experimentally there is a vicious cycle in which decreased *GBA* activity leads to the accumulation of *SNCA*, and increased levels of *SNCA* lead to a further impairment in lysosomal function. In this regard, it is noteworthy that lysosomal function is impaired and levels of GCase are reduced in patients with sporadic PD, and not just in those with *GBA* variants. These bidirectional effects of *SNCA* and *GBA* form a positive feedback loop that, after surpassing a theoretical threshold, could lead to self-propagating disease. These findings suggest that this molecular pathway may not only apply to patients with a *GBA* variant, but also to patients with sporadic PD or other synucleinopathies who have two normal wild-type *GBA* alleles. Some studies suggest that patients with *GBA* variants have a faster rate of progression and increased frequency of cognitive impairment. Studies of drugs that enhance GCase activity and promote lysosomal function are currently being tested in the clinic.

Multiple *LRRK2* mutations have also now been clearly linked to PD, with p.G2019S being the most common, possibly due to a founder effect in the Ashkenazi Jewish and North African Arab populations. Mutations in *LRRK2* account for 3–41% of familial PD cases (depending on the specific population) and are also found in apparently sporadic cases, albeit at a lower rate. The phenotype of *LRRK2* p.G2019S mutations is largely indistinguishable from that of sporadic PD, although tremor appears to be more common; leg tremor may be a useful diagnostic clue. The penetrance of *LRRK2* mutations is incomplete (30–74% depending on the ethnic group), and patients tend to run a more benign course. The mechanism responsible for cell death with this mutation is not conclusively known but is thought to involve enhanced kinase activity with altered phosphorylation of target proteins (including autophosphorylation) with possible impairment of lysosomal function. Kinase inhibitors can block toxicity associated with *LRRK2* mutations in laboratory models, and there has also been much interest in developing drugs directed at this target. However, nonselective kinase inhibitors are potentially toxic to the lungs and kidneys. Fortunately, *LRRK2* inhibitors have now been developed that have good preclinical safety and are currently being tested in PD populations.

Mutations in *Parkin* and *PINK1* have also been identified as a cause of PD. *Parkin* mutations are the more common, and the major cause of autosomal recessive and early-onset PD, accounting for up to 77%

of cases of juvenile PD with an age of onset <20 years, and for 10–20% of early-onset PD patients in general. The disease is slowly progressive, responds well to antiparkinsonian treatment, and is commonly complicated by dystonia, but very rarely by dementia. At pathology, neurodegeneration tends to be restricted to the SNc and LC in patients with *Parkin* mutations, and Lewy bodies are typically absent. The reason for these differences from classic PD is not known but may be related to impaired ubiquitination of damaged proteins (*Parkin* is a ubiquitin ligase that is required for Lewy body formation but may be impaired in the mutant form). The clinical phenotypes of *Parkin*- and *PINK1*-linked PD are similar. *Parkin* and *PINK1* proteins are involved in cell-protection mechanisms and in the turnover and clearance of damaged mitochondria (mitophagy). Mutations in *Parkin* and *PINK1* cause mitochondrial dysfunction in transgenic animals that can be corrected with overexpression of *Parkin*. Improving mitochondrial function is a particularly attractive potential therapeutic target because postmortem studies in PD patients show a defect in complex I of the respiratory chain in SNc neurons.

Thus, evidence is accumulating that genetic factors play an important role in both familial and "sporadic" forms of PD. It is anticipated that better understanding of the pathways responsible for cell death caused by these mutations will permit the development of more relevant animal models of PD and better-defined targets for the development of gene-specific neuroprotective drugs. A precision medicine approach in which therapies are directed specifically at patients who carry a mutation is of great interest, but it should also be appreciated that these same targets may also prove to be of importance for therapies directed at patients with sporadic PD.

■ PATHOPHYSIOLOGY OF PD

The classic model of the organization of the basal ganglia in the normal and PD states is provided in Fig. 435-5. With respect to motor function, a series of neuronal circuits with multiple feedback and feedforward loops link the basal ganglia nuclei with corresponding cortical and brainstem motor regions in a somatotopic manner. The striatum is the major input region of the basal ganglia, while the GPi and SNr are the major output regions. The input and output regions are connected via direct and indirect pathways that have reciprocal effects on the activity of the basal ganglia output. The output of the basal ganglia provides inhibitory (GABAergic) tone to thalamic and brainstem neurons that in turn connect to motor systems in the cerebral cortex and spinal cord that control motor function. An increase in neuronal activity in the output regions of the basal ganglia (GPi/SNr) is associated with poverty of movement or parkinsonism, while decreased output results in movement facilitation and involuntary movements such as dyskinesia. Dopaminergic projections from SNc neurons serve to modulate neuronal firing and to stabilize the basal ganglia network. Normal dopamine innervation thus serves to facilitate the selection of the desired movement and to suppress or reject unwanted movements. Cortical loops integrating the cortex and the basal ganglia are now thought to also play an important role in regulating other systems as well such as behavioral, emotional, and cognitive functions.

In PD, dopamine denervation with loss of dopaminergic tone leads to increased firing of neurons in the STN and GPi, excessive inhibition of the thalamus, reduced activation of cortical motor systems, and the development of parkinsonian features (Fig. 435-5). The current role of surgery in the treatment of PD is based on this model, which predicted that lesions or high-frequency stimulation of the STN or GPi might reduce this neuronal overactivity and improve PD features. The model has proven less useful in understanding the origins of dyskinesia (see Fig. 435-5).

TREATMENT

Parkinson's Disease

LEVODOPA

Since its introduction in the late 1960s, levodopa has been the mainstay of therapy for PD. Experiments in the late 1950s by

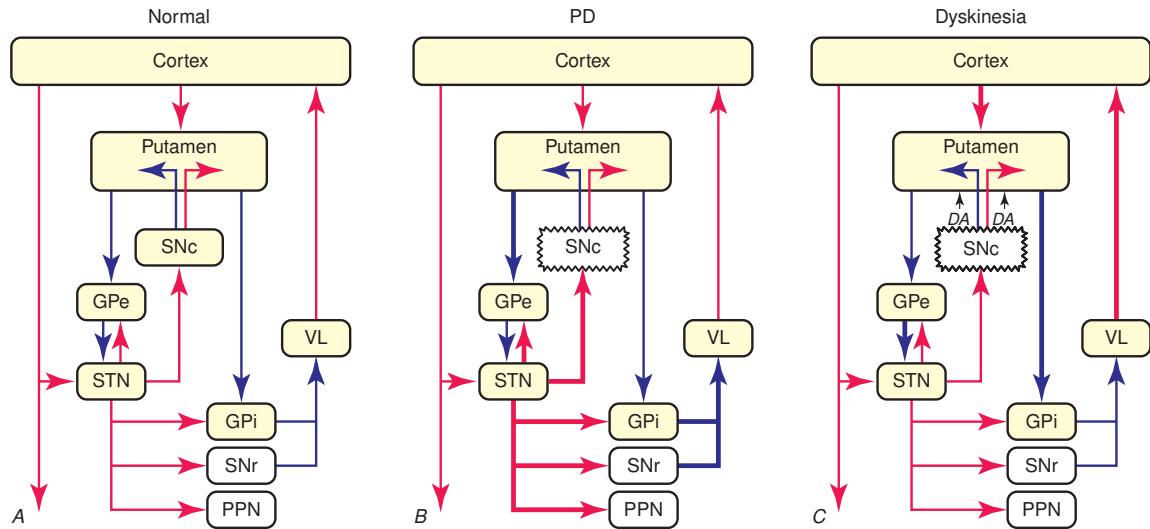


FIGURE 435-5 Basal ganglia organization. Classic model of the organization of the basal ganglia in the normal (A), Parkinson's disease (PD) (B), and levodopa-induced dyskinesia (C) state. Inhibitory connections are shown as blue arrows and excitatory connections as red arrows. The striatum is the major input region and receives its major input from the cortex. The GPI and SNr are the major output regions, and they project to the thalamocortical and brainstem motor regions. The striatum and GPI/SNr are connected by direct and indirect pathways. This model predicts that parkinsonism results from increased neuronal firing in the STN and GPI and that lesions or DBS of these targets might provide benefit. This concept led to the rationale for surgical therapies for PD. The model also predicts that dyskinesia results from decreased firing of the output regions, resulting in excessive cortical activation by the thalamus. This component of the model is not completely correct because lesions of the GPI ameliorate rather than increase dyskinesia in PD, suggesting that firing frequency is just one of the components that lead to the development of dyskinesia. DBS, deep brain stimulation; GPe, external segment of the globus pallidus; GPI, internal segment of the globus pallidus; PPN, pedunculopontine nucleus; SNC, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; STN, subthalamic nucleus; VL, ventrolateral thalamus. (Reproduced with permission from JA Obeso et al: Pathophysiology of the basal ganglia in Parkinson's disease. *Trends Neurosci* 23:S8, 2000.)

Carlsson and colleagues demonstrated that blocking dopamine uptake with reserpine caused rabbits to become parkinsonian; this could be reversed with the dopamine precursor, levodopa. Subsequently, Hornykiewicz demonstrated a dopamine deficiency in the striatum of PD patients and suggested the potential benefit of dopamine replacement therapy. Dopamine does not cross the blood-brain barrier (BBB), so clinical trials were initiated with levodopa, the precursor of dopamine. Studies over the course of the next decade confirmed the value of levodopa and revolutionized the treatment of PD.

Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea, vomiting, and orthostatic hypotension due to activation of dopamine receptors in the area postrema (the nausea and vomiting center) that are not protected by the BBB. In the United States, levodopa is combined with the decarboxylase inhibitor carbidopa (Sinemet), whereas in many other countries it is combined with benserazide (Madopar). Levodopa plus a decarboxylase inhibitor is also available in a methylated formulation, a controlled-release formulation (Sinemet CR or Madopar HP) and in combination with a catechol-O-methyltransferase (COMT) inhibitor (Stalevo). A long-acting formulation of levodopa (Rytary) and a levodopa carbidopa intestinal gel that is administered by continuous intraintestinal infusion via an implanted jejunal tube are also now available. An inhaled form of levodopa that is rapidly and reliably absorbed through the pulmonary alveoli has recently been approved as an on-demand therapy for the treatment of individual “off” episodes (see below).

Levodopa remains the most effective symptomatic treatment for PD and the gold standard against which new therapies are compared. No current medical or surgical treatment provides antiparkinsonian benefits superior to what can be achieved with levodopa. Levodopa benefits the classic motor features of PD, prolongs independence and employability, improves quality of life, and increases life span. Indeed, levodopa also benefits some “nondopaminergic” features such as anxiety, depression, and sweating. Almost all PD patients experience improvement, and failure to respond to an adequate trial of levodopa should cause the diagnosis to be questioned.

There are important limitations of levodopa therapy. Acute dopaminergic side effects include nausea, vomiting, and orthostatic hypotension. These are usually transient and can generally be avoided by starting with low doses and gradual titration. If they persist, they can be treated with additional doses of a peripheral decarboxylase inhibitor (e.g., carbidopa), administering with food, or adding a peripheral dopamine-blocking agent such as domperidone (not available in the United States). As the disease continues to progress, features such as falling, freezing, autonomic dysfunction, sleep disorders, and dementia may emerge that are not adequately controlled by levodopa. Indeed, these nondopaminergic features (especially falls and dementia) are the primary source of disability and the main reason for hospitalization and nursing home placement for patients with advanced PD in the levodopa era.

The major concern with levodopa is that chronic levodopa treatment is associated with the development of motor complications in the large majority of patients. These consist of fluctuations in motor response (“on” episodes when the drug is working and “off” episodes when parkinsonian features return as drug wears off) and involuntary movements known as dyskinesias, which typically complicate “on” periods (Fig. 435-6). When patients initially take levodopa, benefits are long-lasting (many hours) even though the drug has a relatively short half-life (60–90 min). With continued treatment, however, the duration of benefit following an individual dose becomes progressively shorter until it approaches the half-life of the drug. This loss of benefit is known as the *wearing-off effect*. Some patients may also experience a rapid and unpredictable switch from the “on” to the “off” state known as the *on-off phenomenon*. In advanced cases, because of variability in the bioavailability of standard oral levodopa, the response to a dose of levodopa may be variable and unpredictable with a given dose leading to a full-on response, a partial on-on response, a delay in turning on (delayed-on), or no response at all (no-on). Peak-dose dyskinesias can occur at the time of levodopa peak plasma concentration and maximal clinical benefit. They are usually choreiform but can manifest as dystonic movements, myoclonus, or other movement disorders. They are not troublesome when mild but can be disabling

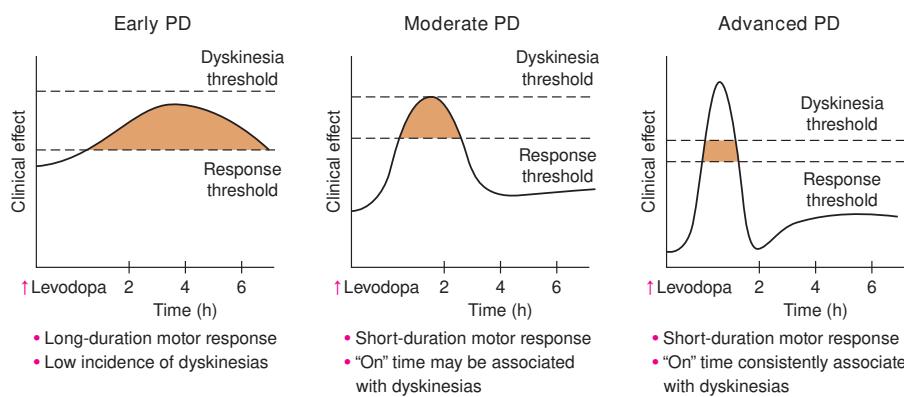


FIGURE 435-6 Changes in motor response associated with chronic levodopa treatment. Levodopa-induced motor complications. Schematic illustration of the gradual shortening of the duration of a beneficial motor response to levodopa (wearing off) and the appearance of dyskinesias complicating “on” time. PD, Parkinson’s disease.

when severe, and can limit the ability to use higher doses of levodopa to better control PD motor features. In more advanced states, patients may cycle between “on” periods complicated by disabling dyskinesias and “off” periods in which they suffer from severe parkinsonism and painful dystonic postures. Patients may also experience “diphasic dyskinesias,” which occur with lower plasma levodopa levels, and manifest as the levodopa dose begins to take effect and again as it wears off. These dyskinesias typically consist of transient, stereotypic, rhythmic movements that predominantly involve the lower extremities asymmetrically and are frequently associated with parkinsonism in other body regions. They can be relieved by increasing the dose of levodopa, although higher doses may induce more severe peak-dose dyskinesia and disappear as the concentration declines. Long-term double-blind studies show that the risk of developing motor complications can be minimized by using the lowest dose of levodopa that provides satisfactory benefit and through the use of polypharmacy to avoid the need for raising the dose of levodopa.

The cause of levodopa-induced motor complications is not precisely known. They are more likely to occur in younger individuals, with the use of higher doses of levodopa, in women, and in those with more severe disease. The classic model of the basal ganglia has been useful for understanding the origin of motor features in PD but has proved less valuable for understanding levodopa-induced dyskinesias (Fig. 435-5). The model predicts that dopamine replacement might excessively inhibit the pallidal output system, thereby leading to increased thalamocortical activity, enhanced stimulation of cortical motor regions, and the development of dyskinesia. However, lesions of the pallidum that dramatically reduce its output are associated with amelioration rather than induction of dyskinesia as would be suggested by the classic model. It is now thought that dyskinesia results from alterations in the GPi/SNr neuronal firing pattern (pauses, bursts, synchrony, etc.) and not simply the firing frequency alone. This leads to the transmission of “misinformation” from pallidum to thalamus/cortex that, along with firing frequency, contributes to the development of dyskinesia. Surgical lesions or high-frequency stimulation targeted at the GPi or STN presumably ameliorate dyskinesia by interfering with (blocking or masking) this abnormal neuronal activity and preventing the transfer of misinformation to motor systems.

A number of studies suggest that motor complications develop in response to nonphysiologic levodopa replacement. Striatal dopamine levels are normally maintained at a relatively constant level. In PD, where dopamine neurons and terminals have degenerated, striatal dopamine levels are dependent on the peripheral availability of levodopa. Intermittent oral doses of levodopa result in fluctuating plasma levels because of variability in the transit of the drug from the stomach to the duodenum where it is absorbed and the short half-life of the drug. This variability is translated to the brain and results in exposure of striatal dopamine receptors to alternating

high and low concentrations of dopamine. This in turn has been shown to induce molecular alterations in striatal neurons, neurophysiologic changes in pallidal output neurons, and ultimately the development of motor complications. It has been hypothesized that more continuous delivery of levodopa might be more physiologic and prevent the development of motor complications. Indeed, double-blind studies have demonstrated that continuous intraintestinal infusion of levodopa/carbidopa or subcutaneous infusion of apomorphine is associated with significant improvement in “off” time and in “on” time without dyskinesia in advanced PD patients compared with optimized standard oral levodopa. These benefits are superior to what has been observed in double-blind placebo-controlled studies with other dopaminergic agents. Intestinal infusion of levodopa is approved in the United States (Duopa) and Europe (Duodopa). The treatment is, however, complicated by potentially serious adverse events related to the surgical procedure, problems related to the tubing, and the inconvenience of having to wear an infusion system. SC apomorphine infusion is approved in Europe but not yet in the United States (see below). New approaches are currently being tested in which levodopa is continuously administered by a subcutaneous route, an intraoral infusion system, or by long-acting oral levodopa formulations in an effort to avoid the need for a surgical procedure.

Behavioral complications can also be associated with levodopa treatment. A dopamine dysregulation syndrome has been described where patients have a craving for levodopa and take frequent and unnecessary doses of the drug in an addictive manner. (In this regard, it is noteworthy that cocaine binds to the dopamine uptake receptor.) PD patients taking high doses of levodopa can also develop purposeless, stereotyped behaviors such as the assembly and disassembly or collection and sorting of objects. This is known as punding, a term taken from the Swedish description of the meaningless behaviors seen in chronic amphetamine users. Hypersexuality and other impulse-control disorders are occasionally encountered with levodopa, although these are more commonly seen with dopamine agonists.

Finally, because levodopa undergoes oxidative metabolism and has the potential to generate toxic free radicals, there has been long-standing concern that, independent of the drug’s ability to provide symptomatic benefits, it might accelerate neuronal degeneration. Alternatively, as levodopa improves long-term outcomes in comparison to the pre-levodopa era, it has been suggested that by restoring striatal dopamine, levodopa has the potential to have a disease-modifying or neuroprotective effect. Neither of these hypotheses has been established. A recent delayed-start study showed neither beneficial nor deleterious effects of levodopa on disease progression. Thus, it is generally recommended that levodopa be used solely based on its potential to provide symptomatic benefits balanced by the risk of inducing motor complications and other side effects.

DOPAMINE AGONISTS

Dopamine agonists are a diverse group of drugs that act directly on dopamine receptors. Unlike levodopa, they do not require metabolic conversion to an active product and do not undergo oxidative metabolism. Initial dopamine agonists were ergot derivatives (e.g., bromocriptine, pergolide, cabergoline) and were associated with potentially serious ergot-related side effects such as cardiac valvular damage and pulmonary fibrosis. They have largely been replaced by a second generation of non-ergot dopamine agonists (e.g., pramipexole, ropinirole, rotigotine). In general, dopamine agonists do not have comparable efficacy to levodopa. They were initially introduced as adjuncts to levodopa to enhance motor function and reduce “off” time in fluctuating patients. Subsequently, it was shown that dopamine agonists are less prone than levodopa to induce dyskinesia, possibly because they are relatively long-acting in comparison to levodopa. For this reason, many physicians initiate therapy with a dopamine agonist particularly in younger patients who are more prone to develop motor complications, although supplemental levodopa is eventually required in virtually all patients. This view has been tempered by the recognition that dopamine agonists are associated with potentially serious adverse effects such as unwanted sleep episodes and impulse-control disorders (see below). Both ropinirole and pramipexole are available as orally administered immediate (tid) and extended-release (qd) formulations. Rotigotine is administered as a once-daily transdermal patch and may be useful in managing surgical patients who are not able to be treated with an oral therapy. Apomorphine is the one dopamine agonist with efficacy thought to be comparable to levodopa, but it must be administered parenterally as it is rapidly and extensively metabolized if taken orally. It has a short half-life and duration of activity (45 min). It can be administered by subcutaneous injection as a rescue agent for the treatment of severe “off” episodes but can also be administered by continuous subcutaneous infusion where it has been demonstrated to reduce both “off” time and dyskinesia in advanced patients. This latter approach has been approved in Europe but not yet in the United States. A sublingual bilayer formulation of apomorphine has recently been approved as a rapid and reliable therapy for individual “off” periods that avoids the need for a subcutaneous (SC) injection (see below).

Dopamine agonist use is associated with a variety of side effects. Acute side effects are primarily dopaminergic and include nausea, vomiting, and orthostatic hypotension. These can usually be avoided or minimized by starting with low doses and using slow titration over weeks. Side effects associated with chronic use include hallucinations, cognitive impairment, and leg edema. Sedation with sudden unintended episodes of falling asleep that can occur in dangerous situations such as while driving a motor vehicle has been reported. Patients should be informed about this potential problem and should not drive when tired. Dopamine agonists can also be associated with impulse-control disorders, including pathologic gambling, hypersexuality, and compulsive eating and shopping. Patients should be advised of these risks and specifically questioned for their occurrence at follow-up examinations. The precise cause of these problems, and why they appear to occur more frequently with dopamine agonists than levodopa, remains to be resolved, but reward systems associated with dopamine and alterations in the ventral striatum and orbitofrontal regions have been implicated. In general, chronic side effects are dose-related and can be avoided or minimized with lower doses. Injections of apomorphine can be complicated by skin lesions at sites of administration, which can be minimized by proper cleaning and alteration of the injection site. The sublingual bilayer formulation of apomorphine is associated with a relatively high frequency of oropharyngeal side effects, which are generally mild and resolve either spontaneously or with treatment withdrawal.

MAO-B INHIBITORS

Inhibitors of monoamine oxidase type B (MAO-B) block central dopamine metabolism and increase synaptic concentrations of the

neurotransmitter. Selegiline and rasagiline are relatively selective suicide inhibitors of the MAO-B isoform of the enzyme. Clinically, these agents provide antiparkinsonian benefits when used as monotherapy in early disease stages and reduced “off” time when used as an adjunct to levodopa in patients with motor fluctuations. MAO-B inhibitors are generally safe and well tolerated. They may increase dyskinesia in levodopa-treated patients, but this can usually be controlled by down-titrating the dose of levodopa. Inhibition of the MAO-A isoform prevents metabolism of tyramine in the gut, leading to a potentially fatal hypertensive reaction known as a “cheese effect” because it can be precipitated by foods rich in tyramine such as some cheeses, aged meats, and red wine. Selegiline and rasagiline do not functionally inhibit MAO-A and are not associated with a cheese effect with doses used in clinical practice. There are theoretical risks of a serotonin reaction in patients receiving concomitant selective serotonin reuptake inhibitor (SSRI) antidepressants, but these are rarely encountered. Safinamide (Xadago) is a reversible MAO-B inhibitor that has been approved as an adjunct to levodopa for treating advanced PD patients with motor fluctuations. The drug also acts to block activated sodium channels and inhibit glutamate release, and therefore has the potential to provide anti-dyskinetic as well as anti-parkinsonian effects.

Interest in MAO-B inhibitors has also focused on their potential to have disease-modifying effects. MPTP toxicity can be prevented experimentally by coadministration of a MAO-B inhibitor that blocks its oxidative conversion to the toxic pyridinium ion MPP⁺ that is taken up by and selectively damages dopamine neurons. MAO-B inhibitors also have the potential to block the oxidative metabolism of dopamine and prevent oxidative stress. In addition, both selegiline and rasagiline incorporate a propargyl ring within their molecular structure that provides antiapoptotic effects in laboratory models. The DATATOP study showed that in untreated PD patients, selegiline significantly delayed the time until the emergence of disability necessitating the introduction of levodopa. However, it could not be definitively determined whether this benefit was due to a neuroprotective effect that slowed disease progression or a symptomatic effect that merely masked ongoing neurodegeneration. The ADAGIO study used a two-period delayed-start design and demonstrated that early treatment with rasagiline 1 mg/d provided benefits that could not be achieved when treatment with the same drug was initiated at a later time point, consistent with the drug having a disease-modifying effect. However, this benefit was not seen with the 2-mg dose, and it has not received regulatory approval for this indication.

COMT INHIBITORS

When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized in the periphery by the catechol-O-methyl transferase (COMT) enzyme. Inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability. Combining levodopa with a COMT inhibitor reduces “off” time and prolongs “on” time in fluctuating patients while enhancing motor scores. Two COMT inhibitors, tolcapone and entacapone, have been available for more than a decade; tolcapone is administered three times daily while entacapone is administered in combination with each dose of levodopa. More recently opicapone, a long-acting COMT inhibitor that requires only once-daily administration, has been approved in both Europe and the United States. A combination tablet of levodopa, carbidopa, and entacapone (Stalevo) is also available.

Side effects of COMT inhibitors are primarily dopaminergic (nausea, vomiting, increased dyskinesia) and can usually be controlled by down-titrating the dose of levodopa by 20–30% if required. Severe diarrhea has been described with tolcapone, and to a lesser degree with entacapone, and necessitates stopping the medication in 5–10% of individuals. Rare cases of fatal hepatic toxicity have been reported with tolcapone. It is still used because it is the most effective of the COMT inhibitors, but periodic monitoring of liver function is required. Liver problems have not been

encountered with entacapone or opicapone. Discoloration of urine can be seen with COMT inhibitors due to accumulation of a metabolite, but it is of no clinical concern.

It has been proposed that initiating levodopa in combination with a COMT inhibitor to enhance its elimination half-life could provide more continuous levodopa delivery and reduce the risk of motor complications. While this result has been demonstrated in a preclinical MPTP model of PD, and continuous infusion reduces both “off” time and dyskinesia in advanced PD patients, no benefit of initiating levodopa with a COMT inhibitor compared to levodopa alone was detected in early PD patients in the STRIDE-PD study. This may have been because the combination was not administered at frequent enough intervals to provide continuous levodopa availability. For now, the main value of COMT inhibitors continues to be in patients who experience motor fluctuations.

OTHER MEDICAL THERAPIES

Adenosine A_{2A} receptor antagonists are a class of drugs that inhibit A_{2A} receptors, which form heterodimers with D2 dopamine receptors on medium spiny striatal D2-bearing neurons of the indirect pathway. Blockade of A_{2A} receptors decreases the excessive activation of the indirect pathway in PD and theoretically restores balance in the basal ganglia-thalamocortical circuit, providing a dopaminergic effect without the need to increase levodopa doses. These agents are generally used in combination with low doses of levodopa and provide modest anti-parkinsonian effects with a reduced risk of motor complications. Three A_{2A} antagonists have been studied in PD but development in two has been discontinued; preladenant because it failed in phase 3 studies and tozadenant because of agranulocytosis in a few patients. Istradefylline is the only agent which is currently approved for use. Clinical trials in advanced PD patients showed improvement in “off” time comparable to other available agents but not in dyskinesia. The drug is generally well tolerated with adverse events similar to dopaminergic agents. Interestingly, caffeine is a potent A_{2A} antagonist, and large epidemiologic studies suggest that drinking coffee is associated with a reduced frequency of PD. This has raised the question as to whether this class of agent might be neuroprotective, but this has not been established in clinical trials.

Amantadine was originally introduced as an antiviral agent but the drug was appreciated to also have antiparkinsonian effects, likely due to N-methyl-aspartate (NMDA) receptor antagonism. While some physicians use amantadine in patients with early disease for its mild symptomatic effects, it is most widely used as an antidyskinesia agent in patients with advanced PD. Indeed, it is the only oral agent that has been demonstrated in controlled studies to reduce dyskinesia without worsening parkinsonian features (indeed, motor benefits have been reported). Cognitive impairment is a major concern particularly with high doses. Other side effects include livedo reticularis and weight gain. Amantadine should always be discontinued gradually because patients can experience withdrawal-like symptoms. An extended-release formulation of amantadine has recently been approved in the United States.

Central-acting anticholinergic drugs such as trihexyphenidyl and benzotropine were used historically for the treatment of PD, but they lost favor with the introduction of levodopa. Their major clinical effect is on tremor, although it is not certain that this benefit is superior to what can be obtained with agents such as levodopa and dopamine agonists. Still, they can be helpful in individual patients with severe tremor. Their use is limited particularly in the elderly, due to their propensity to induce a variety of side effects including urinary dysfunction, glaucoma, and particularly cognitive impairment.

The anticonvulsant zonisamide has also been shown to have antiparkinsonian effects and is approved for use in Japan. Its mechanism of action is unknown. Several classes of drugs are currently being investigated in an attempt to enhance antiparkinsonian effects, reduce “off” time, and treat or prevent dyskinesia.

TABLE 435-5 Drugs Commonly Used for Treatment of Parkinson’s Disease^a

AGENT	AVAILABLE DOSAGES	TYPICAL DOSING
Levodopa ^a		
Carbidopa/levodopa	10/100, 25/100, 25/250 mg	200–1000 mg levodopa/day
Benserazide/levodopa	25/100, 50/200 mg	
Carbidopa/levodopa CR	25/100, 50/200 mg	
Benserazide/levodopa MDS	25/200, 25/250 mg	
Parcopa	10/100, 25/100, 25/250 mg	
Ratyry (carbidopa/levodopa)	23.75/95, 36.25/145, 48.75/195, 61.25/245	See conversion tables
Carbidopa/levodopa/entacapone	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg	
Dopamine agonists		
Pramipexole	0.125, 0.25, 0.5, 1.0, 1.5 mg	0.25–1.0 mg tid
Pramipexole ER	0.375, 0.75, 1.5, 3.0, 4.5 mg	1–3 mg/d
Poprinrole	0.25, 0.5, 1.0, 3.0 mg	6–24 mg/d
Poprinrole XL	2, 4, 6, 8 mg	6–24 mg/d
Rotigotine patch	2-, 4-, 6-, 8-mg patches	4–24 mg/d
Apomorphine SC	2–8 mg	2–8 mg
COMT inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100, 200 mg	100–200 mg tid
Opicapone	50 mg	50 mg HS
MAO-B inhibitors		
Selegiline	5 mg	5 mg bid
Pasagiline	0.5, 1.0 mg	1 mg QAM
Safinamide	100 mg	100 mg QAM
On-demand therapy for off periods		
Inhaled levodopa	5–40 mg	Up to 5 doses per day
Apomorphine sublingual strip		Up to 5 doses per day
Others		
A _{2A} antagonist—Istradefylline	20, 40 mg	20 or 40 mg per day
Amantadine—immediate, extended-release	100–400 mg	

^aTreatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose.

Note: Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.

Abbreviations: COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase type B; QAM, every morning.

These include nicotinic agonists, glutamate antagonists, and 5-HT_{1A} agonists.

A list of the major drugs and available dosage strengths currently available to treat PD is provided in Table 435-5.

ON-DEMAND THERAPIES FOR “OFF” PERIODS

Despite all available therapies, many patients continue to experience “off” periods. “Off” periods represent a return of parkinsonian features following the benefit of a levodopa dose administration and can be disabling for patients, causing them to be at risk for falling and choking. As noted above, taking an additional levodopa tablet does not reliably treat individual “off” episodes, and some patients may continue in the “off” state for hours despite more frequent levodopa use. This inability to reliably and rapidly treat “off” episodes causes many patients to become depressed, withdrawn,

and unwilling to participate in social activities. Three therapies have now been approved as specific on-demand treatments for “off” periods: inhaled levodopa, subcutaneous injections of apomorphine, and sublingual apomorphine. Each of these avoids the variable bioavailability seen with levodopa and provides relatively predictable return to the “on” state.

NEUROPROTECTION

Despite the many therapeutic agents available for the treatment of PD, patients continue to progress and to develop intolerable disability. A neuroprotective or disease-modifying therapy that slows or stops disease progression remains the major unmet therapeutic need. Some trials have shown positive results (e.g., selegiline, rasagiline, pramipexole, ropinirole) consistent with a disease-modifying effect. However, it has not been possible to determine with certainty if the positive results were due to neuroprotection with slowing of disease progression or confounding symptomatic or pharmacologic effects that mask disease progression. Based on genetic and laboratory findings described above, several novel targets for a putative neuroprotective therapy have been discovered and multiple candidate therapies are currently being investigated. The most exciting targets among these etiopathogenic factors include agents that interfere with *SNCA* accumulation, LRRK2 inhibitors, *GBA* and *GCase* enhancers and anti-inflammatory agents that inhibit activation of microglia and cytokine production. Many of these agents have already shown promise in relevant animal models of PD and are currently in clinical trials in PD patients.

SURGICAL TREATMENT

Surgical treatments for PD have been used for more than a century. Lesions were initially placed in the motor cortex and improved tremor but were associated with motor deficits, and this approach was abandoned. Subsequently, it was appreciated that lesions placed into the ventral intermediate (VIM) nucleus of the thalamus reduced contralateral tremor without inducing hemiparesis, but these lesions did not meaningfully help other more disabling features of PD. In the 1990s, it was shown that lesions placed in the posteroverentral portion of the GPi (motor territory) improved rigidity and bradykinesia as well as tremor. Importantly, pallidotomy was also associated with marked improvement in contralateral dyskinesia. This procedure gained favor with greater understanding of the pathophysiology of PD (see above). However, this procedure is not optimal, because bilateral lesions are associated with side effects such as dysphagia, dysarthria, and impaired cognition. Lesions of the STN are also associated with antiparkinsonian benefit and reduced levodopa requirement, but there is a concern about the risk of hemiballismus, and this procedure is not commonly performed.

Most surgical procedures for PD performed today use deep brain stimulation (DBS). Here, an electrode is placed into the target area and connected to a stimulator inserted subcutaneously over the chest wall. DBS simulates the effects of a lesion without needing to make a brain lesion. The precise mechanism whereby DBS works is not fully resolved but may act by disrupting the abnormal neurophysiologic signals associated with PD and motor complications. The stimulation variables can be adjusted with respect to electrode configuration, voltage, frequency, and pulse duration in order to maximize benefit and minimize adverse side effects. The procedure does not require making a lesion in the brain and is thus suitable for performing bilateral procedures with relative safety. In cases with intolerable side effects, stimulation can be stopped and the system removed.

DBS for PD primarily targets the STN or the GPi. It provides dramatic results, particularly with respect to tremor and reducing both “off” time and dyskinesias but does not provide superior clinical benefits to levodopa. The procedure is thus primarily indicated for patients who suffer disability resulting from levodopa-induced motor complications that cannot be satisfactorily controlled with drug manipulation or those with severe tremor. Side effects can result from the surgical procedure (hemorrhage, infarction,

infection), DBS system (infection, lead break, lead displacement, skin ulceration), or the stimulation itself (ocular and speech abnormalities, muscle twitches, paresthesias, depression, and rarely suicide). Recent studies indicate that benefits following DBS of the STN and GPi are comparable, but that GPi stimulation may be associated with a reduced frequency of depression. Although not all PD patients are candidates, the procedure can be profoundly beneficial for many. Long-term studies demonstrate continued benefits with respect to the classic motor features of PD, but DBS does not prevent the development of nondopaminergic features, which continue to evolve and are a source of disability. Studies continue to evaluate the optimal way to use DBS (low- vs high-frequency stimulation, closed-loop systems, etc.). Trials of DBS in early PD patients show benefits that may be superior to best medical therapy, but this must be weighed against the cost of the procedure and the risk of side effects in patients who might otherwise be well controlled with medical therapies for many years. Additionally, the PD landscape is changing with the availability of on-demand therapies for treating “off” periods and the likelihood that future therapies may provide continuous levodopa availability with reduced risk of motor complications. Controlled studies comparing DBS to other therapies aimed at improving motor function without causing dyskinesia, such as Duodopa and apomorphine infusions, remain to be performed. The utility of DBS may also be reduced in future years if new medical therapies are developed that provide the benefits of levodopa without motor complications. New targets for DBS are also being actively explored, as well as “smart” closed-loop devices that sense the patient’s need for stimulation, to provide greater benefits against gait dysfunction, depression, and cognitive impairment (Chap. 487).

MRI-guided ultrasound is also now being used as a means of damaging critical target regions such as the GPi or STN in PD patients with motor complications in a noninvasive manner that avoids the needs for a surgical procedure. Preliminary results suggest good target localization and safety.

OTHER EXPERIMENTAL THERAPIES FOR PD

There has been considerable scientific and public interest in a number of novel interventions that are being investigated as possible treatments for PD. These include cell-based therapies (such as transplantation of fetal nigral dopamine cells or dopamine neurons derived from stem cells), gene therapies, trophic factors, and therapies directed against gene-specific targets. Transplant strategies are based on the concept of implanting dopaminergic cells into the striatum to replace degenerating SNc dopamine neurons. Fetal nigral mesencephalic cells have been demonstrated to survive implantation, re-innervate the striatum in an organotypic manner, and restore motor function in PD models. However, two double-blind studies failed to show significant benefit of fetal nigral transplantation in comparison to a sham operation with respect to their primary endpoints. Additionally, grafting of fetal nigral cells is associated with a previously unrecognized form of dyskinesia (graft-induced dyskinesia) that persists after lowering or even stopping levodopa. This has been postulated to be related to suboptimal release of dopamine from grafted cells leading to a sustained form of diphasic dyskinesia. In addition, there is evidence that after many years, transplanted healthy embryonic dopamine neurons from unrelated donors develop PD pathology and become dysfunctional, suggesting transfer of α -synuclein from affected to unaffected neurons in a prion-like manner (see discussion above). Perhaps most importantly, it is not clear how replacing dopamine cells alone will improve nondopaminergic features such as falling and dementia, which are the major sources of disability for patients with advanced disease. While stem cells, and specifically induced pluripotent stem cells (iPSCs) derived from the recipient, may overcome problems related to immunity, type and number of cells, and physiologic integration, many of these same concerns still apply. To date, stem cells have not yet been properly tested in PD patients and bear the additional concern of tumors and other unanticipated side effects.

While there remains a need for scientifically based studies attempting to evaluate the potential role of cell-based therapies in PD, there is no scientific basis to warrant routine treatment of PD patients with stem cells as is being marketed in some countries.

Trophic factors are a series of proteins that enhance neuronal growth and restore function to damaged neurons. Several different trophic factors have been demonstrated to have beneficial effects on dopamine neurons in laboratory studies. Glial-derived neurotrophic factor (GDNF) and neurturin have attracted particular attention as possible therapies for PD. However, double-blind trials of intraventricular and intraputaminal infusions of GDNF failed to show benefits compared to placebo in PD patients, possibly because of inadequate delivery of the trophic molecule to the target region.

Gene therapy offers the potential of providing long-term expression of a therapeutic protein with a single procedure. Gene therapy involves placing the nucleic acid of a therapeutic protein into a viral vector that can then be taken up and incorporated into the genome of host cells and then synthesized and released on a continual basis. The AAV2 virus has been most often used as the vector because it does not promote an inflammatory response, is not incorporated into the host genome, does not induce insertional mutagenesis, and is associated with long-lasting transgene expression. Clinical trials of AAV2 delivery of the trophic factor neurturin showed promising results in open-label trials but failed in double-blind trials, even when injected into both the putamen and the SNc. Nonetheless, long-term postmortem studies have demonstrated transgene survival with biological effects as long as 10 years after treatment. Still, the degree of putaminal coverage was very small and it is likely that much higher gene doses will be required if this type of therapy is to provide positive results. Gene delivery is also being explored as a means of delivering aromatic amino acid decarboxylase with or without tyrosine hydroxylase to the striatum to facilitate the conversion of orally administered levodopa to dopamine. Animal studies suggest that this approach can provide antiparkinsonian benefits with reduced motor complications, and clinical trials in PD patients are underway. Gene therapy is also being studied as a way to enhance GBA and the gene product GCase in an attempt to promote clearance of toxic alpha synuclein. Importantly, no clinically significant adverse events have been encountered in gene therapy studies to date, but there remains a risk of unanticipated side effects. Further, it is not clear how current approaches, even if successful, will address the nondopaminergic features of the illness.

MANAGEMENT OF THE NONMOTOR AND NONDOPAMINERGIC FEATURES OF PD

Although PD treatment has primarily focused on the dopaminergic features of the illness, management of the nondopaminergic features should not be ignored. Some nonmotor features, although they likely reflect nondopaminergic pathology, nonetheless benefit from dopaminergic drugs. For example, problems such as anxiety, panic attacks, depression, pain, sweating, sensory problems, freezing, and constipation all tend to be worse during “off” periods and have been reported to improve with better dopaminergic control. Approximately 50% of PD patients suffer depression during the course of the disease, and depression is frequently underdiagnosed and undertreated. Antidepressants should not be withheld, particularly for patients with major depression, although dopaminergic agents such as pramipexole may prove helpful for both depression and PD motor features. Anxiety is also a common problem, and if not adequately managed with better antiparkinsonian control, can be treated with short-acting benzodiazepines.

Psychosis can be a problem for some PD patients and is often a harbinger of developing dementia. In contrast to AD, hallucinations are typically visual, formed, and nonthreatening. Importantly, they can limit the use of dopaminergic agents necessary to obtain satisfactory motor control. They can be associated with the use of dopaminergic drugs, and the first approach is typically to withdraw agents that are less effective than levodopa such as anticholinergics,

amantadine, and dopamine agonists followed by lowering the dose of levodopa if possible. Psychosis in PD often responds to low doses of atypical neuroleptics and may permit higher doses of levodopa to be tolerated. Clozapine is an effective drug, but it can be associated with agranulocytosis, and regular monitoring is required. Quetiapine avoids these problems, but it has not been established to be effective in placebo-controlled trials. Pimavanserin (Nuplazid) differs from other atypical neuroleptics in that it is also an inverse agonist of the serotonin 5-HT_{2A} receptor. It has been shown to be effective in double-blind trials with a relatively good safety profile, and was recently approved for use in the United States.

Dementia in PD (PDD) is common, ultimately affecting as many as 80% of patients. Its frequency increases with aging and, in contrast to AD, primarily affects executive functions and attention, with relative sparing of language, memory, and calculation domains. When dementia precedes, develops coincident with, or occurs within 1 year after onset of motor dysfunction, it is by convention referred to as dementia with Lewy bodies (DLB; Chap. 434). These patients are particularly prone to experience hallucinations and diurnal fluctuations. Pathologically, DLB is characterized by Lewy bodies distributed throughout the cerebral cortex (especially the hippocampus and amygdala) and is more likely to be associated with AD pathology. It is likely that DLB and PD with dementia represent a spectrum of PD rather than separate disease entities. It is notable that variants of the GBA gene are a significant risk factor for both PD and DLB. Mild cognitive impairment (MCI) frequently precedes the onset of dementia and is a more reliable index of impending dementia than in the general population. Indeed, many PD patients demonstrate abnormalities in cognitive testing even at the earliest stages of the disease despite having no overt clinical dysfunction. Drugs used to treat PD can worsen cognitive function and should be stopped or reduced to try to provide a compromise between antiparkinsonian benefit and preserved cognitive function. Drugs are usually discontinued in the following sequence: anticholinergics, amantadine, dopamine agonists, COMT inhibitors, and MAO-B inhibitors. Eventually, patients with cognitive impairment should be managed with the lowest dose of standard levodopa that provides meaningful antiparkinsonian effects and does not worsen mental function. Anticholinesterase agents such as memantine and cholinesterase inhibitors such as rivastigmine improve measures of cognitive function and can improve attention in PD, but do not improve cognition or quality of life in any meaningful way. More effective therapies that treat or prevent dementia are a critical unmet need in the therapy of PD.

Autonomic disturbances are common and frequently require attention. Orthostatic hypotension can be problematic and contribute to falling. Initial treatment should include adding salt to the diet and elevating the head of the bed to prevent overnight sodium natriuresis. Low doses of fludrocortisone (Florinef) or midodrine provide control for most cases. The norepinephrine precursor 3-O-methylDOPA (Droxidopa) has been shown to provide mild and transient benefits for patients with orthostatic hypotension and was recently approved by the U.S. Food and Drug Administration. Vasopressin and erythropoietin can be used in more severe or refractory cases. If orthostatic hypotension is prominent in early parkinsonian cases, a diagnosis of MSA should be considered (Chap. 440). Sexual dysfunction may be helped with sildenafil or tadalafil. Urinary problems, especially in males, should be treated in consultation with a urologist to exclude prostate problems. Anticholinergic agents, such as oxybutynin (Ditropan), may be helpful. Constipation can be a very important problem for PD patients. Mild laxatives or enemas can be useful, but physicians should first ensure that patients are drinking adequate amounts of fluid and consuming a diet rich in bulk with green leafy vegetables and bran. Agents that promote gastrointestinal (GI) motility can also be helpful. Several recent studies are evaluating the effect on constipation of agents that interfere with inflammation and alpha synuclein misfolding in the GI tract.

Sleep disturbances are common in PD patients, with many experiencing fragmented sleep with excess daytime sleepiness. Restless leg syndrome, sleep apnea, and other sleep disorders also occur with increased frequency and should be treated as appropriate. REM behavior disorder (RBD) is a syndrome composed of violent movements and vocalizations during REM sleep, possibly representing acting out of dreams due to a failure of motor inhibition that typically accompanies REM sleep (Chap. 31). Many PD patients have a history of RBD preceding the onset of the classic motor features of PD by many years, and most cases of RBD eventually go on to develop an α -synucleinopathy (PD or MSA). Low doses of clonazepam (0.5–1 mg at bedtime) are usually effective in controlling this problem. Consultation with a sleep specialist and polysomnography may be necessary to identify and optimally treat sleep problems. Excess daytime sleepiness can be problematic for PD patients, and therapies such as Xyrem that are effective in narcolepsy are currently being evaluated in PD.

NONPHARMACOLOGIC THERAPY

Gait dysfunction with falling is an important cause of disability in PD. Dopaminergic therapies can help patients whose gait is worse in “off” times, but there are currently no specific therapies for gait dysfunction. Canes and walkers may become necessary to increase stability and reduce the risk of falling. An effective therapy for gait impairment is an important unmet need in PD.

Freezing, where patients suddenly become stuck in place for seconds to minutes as if their feet were glued to the ground, is a major cause of falling. Freezing may occur during “on” or “off” periods. Freezing during “off” periods may respond to dopaminergic therapies, but there are no specific treatments for on-period freezing and the mechanism is not well understood. Some patients will respond to sensory cues such as marching in place, singing a song, or stepping over an imaginary line or obstacle.

Speech impairment is another source of disability for many advanced PD patients. Speech therapy programs may be helpful, but benefits are generally limited and transient.

Exercise has been shown to maintain and even improve function for PD patients, and active and passive exercises with full range of motion reduce the risk of arthritis and frozen joints. Some laboratory studies suggest the possibility that exercise might also have neuroprotective effects, but this has not been confirmed in PD patients. Exercise is generally recommended for all PD patients. It is less clear that any specific type of physical therapy or exercise programs such as tai chi or dance offer any specific advantage. It is important for patients to maintain social and intellectual activities to the extent possible. Education, assistance with financial planning, social services, and attention to home safety are important elements of the overall care plan. Information is available through numerous PD foundations and on the Internet but should be reviewed with physicians to ensure accuracy. The needs of the caregiver should not be neglected. Caring for a person with PD involves a substantial work effort and there is an increased incidence of depression among caregivers. Support groups for patients and caregivers may be useful.

CURRENT MANAGEMENT OF PD

The management of PD should be tailored to the needs of the individual patient, and there is no single treatment approach that is universally accepted and applicable to all individuals. Clearly, if an agent could be demonstrated to have disease-modifying effects, it should be initiated at the time of diagnosis. Indeed, recent studies suggest that dopamine terminal degeneration may be complete within 4 years of diagnosis. Epidemiologic and pathologic studies suggest that constipation, RBD, and anosmia may represent premotor features of PD and, along with imaging of the dopamine system, could permit diagnosis and the initiation of a disease-modifying therapy even prior to the onset of the classical motor features of the disease. However, no therapy has been conclusively proven to be a disease-modifying agent as yet, although rasagiline 1 mg per day met

all three prespecified primary endpoints consistent with a disease-modifying effect. For now, physicians must use their judgment in deciding whether or not to introduce a drug such as rasagiline for its possible disease-modifying effects based on available preclinical and clinical information.

The next important issue to address is when to initiate symptomatic therapy and which agent to use. Several studies suggest that it may be best to start therapy at the time of diagnosis in order to preserve beneficial compensatory mechanisms and possibly provide functional benefits with improved quality of life even in the early stage of the disease. Levodopa remains the most effective symptomatic therapy for PD, and some recommend starting it immediately using low doses (≤ 400 mg/d), as motor complications have now clearly been shown to be dose-related. Others, however, prefer to delay introduction of levodopa treatment, particularly in younger patients, in order to reduce the risk of inducing motor complications. An alternate approach is to begin with an MAO-B inhibitor and/or a dopamine agonist, and reserve levodopa for later stages when these drugs no longer provide satisfactory control. In making this decision, the age, degree of disability, and side effect profile of the drug must all be considered. In patients with more severe disability, the elderly, and those with cognitive impairment, significant comorbidities, or in whom the diagnosis is uncertain, most physicians would initiate therapy with levodopa. Regardless of initial choice, most patients ultimately require polypharmacy (combination of levodopa, an MAO-B inhibitor, and a dopamine agonist) in order to minimize the total daily levodopa dose and reduce the risk of motor complications. While it is important to use low doses of each agent to reduce the risk of side effects, it is important not to deny patients levodopa when they cannot be adequately controlled with alternative medications. It is important to discuss the risks and benefits of the different therapeutic options with patients so that they have informed opinions as to whether they wish to start therapy and if so which drug to start.

If motor complications develop, patients can initially be treated by adjusting the frequency and dose of levodopa or by combining lower doses of levodopa with a dopamine agonist, a COMT inhibitor, or an MAO-B inhibitor. More recently the A_{2A} antagonist istradefylline has been approved in the United States as an additional medical therapy for treating “off” periods. Amantadine is the only drug that has been demonstrated to treat dyskinesia without worsening parkinsonism, but benefits may decline over time and there are important side effects related to cognitive function. In advanced cases where patients suffer motor complications that cannot be adequately controlled with medical therapies, it may be necessary to consider a surgical procedure such as DBS or Duodopa, but as described above, these procedures have their own set of complications. The use of DBS in early PD patients has been advocated by some, but there is considerable skepticism about this approach considering the costs and potential side effects, when inexpensive, well-tolerated, and effective medical alternatives are available. Continuous intraintestinal infusion of levodopa/carbidopa intestinal gel (Duodopa) offers similar benefits to DBS, but also requires a surgical intervention with potentially serious complications. Continuous infusion of apomorphine is a treatment option that does not require surgery but is associated with potentially troublesome skin nodules. Well-controlled comparative studies of these approaches are awaited. There are ongoing efforts aimed at developing systems that provide continuous delivery of levodopa or a long-acting formulation of levodopa that mirror the pharmacokinetic properties of a levodopa infusion. Such a formulation might provide all of the benefits of levodopa without motor complications and avoid the need for polypharmacy and surgical intervention. Treatment for the nonmotor features of PD should be instituted as deemed appropriate, and exercise therapy is recommended for all patients.

A decision tree that considers the various treatment options and decision points for the management of PD is provided in Fig. 435-7.

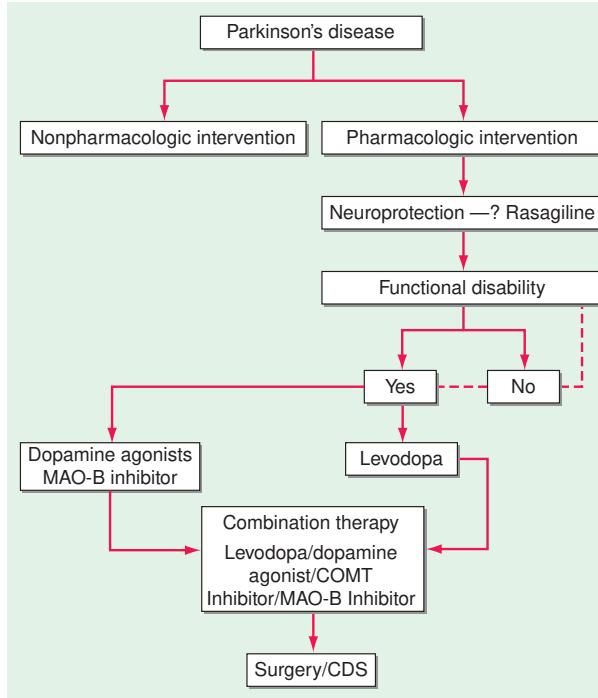


FIGURE 435-7 Treatment options for the management of Parkinson's disease (PD). Decision points include: (1) Introduction of a neuroprotective therapy: no drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this potential based on laboratory and preliminary clinical studies (e.g., rasagiline 1 mg/d, coenzyme Q10 1200 mg/d, the dopamine agonist ropinirole, and pramipexole). (2) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because patients may have some disability even at an early stage, and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy. (3) What therapy to initiate: many experts favor starting with a monoamine oxidase type B (MAO-B) inhibitor in mildly affected patients because of the good safety profile of the drug and the potential for a disease-modifying effect; dopamine agonists for younger patients with functionally significant disability to reduce the risk of motor complications; and levodopa for patients with more advanced disease, the elderly, or those with cognitive impairment. Recent studies suggest the early employment of polypharmacy using low doses of multiple drugs to avoid side effects associated with high doses of any one agent. (4) Management of motor complications: motor complications are typically approached with combination therapy to try to reduce dyskinesia and enhance the "on" time. When medical therapies cannot provide satisfactory control, surgical therapies such as DBS or continuous infusion of levodopa/carbidopa intestinal gel can be considered. (5) Nonpharmacologic approaches: interventions such as exercise, education, and support should be considered throughout the course of the disease. CDS, continuous dopaminergic stimulation; COMT, catechol-O-methyltransferase. (Reproduced with permission from CW Olanow et al: *The scientific and clinical basis for the treatment of Parkinson disease* (2009). *Neurology* 72(21 Suppl 4):S1, 2009.)

FURTHER READING

- A A, S MA: The epidemiology of Parkinson's disease: Risk factors and prevention. *Lancet Neurol* 15:1257, 2016.
- B D et al: MDS research criteria for prodromal Parkinson's disease. *Mov Disord* 12:1600, 2015.
- B C et al: The genetic architecture of Parkinson's disease. *Lancet Neurol* 19:170, 2020.
- D ER et al: Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 68:384, 2007.
- H GU et al: Clinical diagnosis of progressive supranuclear palsy: The Movement Disorder Society criteria. Movement Disorder Society-endorsed PSP Study Group. *Mov Disord* 32:853, 2017.

JA et al: A specific amino acid motif of HLA-DRB1 mediates risk and interacts with smoking history in Parkinson's disease. *Proc Natl Acad Sci U S A* 116:7419, 2019.

K K et al: A new approach to the development of disease-modifying therapies for PD; treating another pandemic. *Mov Disord* 36:59, 2021.

M C et al: Nomenclature of genetic movement disorders: Recommendations of the International Parkinson and Movement Disorder Society task force. *Mov Disord* 32:724, 2017.

O JA et al: Past, present and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy. *Mov Disord* 32:1264, 2017.

O CW, P SB: Is Parkinson's disease a prion disorder? *Proc Natl Acad Sci* 106:12571, 2009.

O CW et al: A double-blind delayed-start study of rasagiline in early Parkinson's disease. *N Engl J Med* 361:1268, 2009.

O CW et al: Scientific and clinical basis for the treatment of PD—2009. *Neurology* 72:S1, 2009.

P RB et al: MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 12:1591, 2015.

S AH et al: Slowing of neurodegeneration in Parkinson's disease and Huntington's disease: Future therapeutic perspectives. *Lancet* 384:545, 2014.

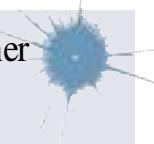
S AHV et al: Non-motor features of Parkinson disease. *Nat Rev Neurosci* 18:435, 2017.

V CVM et al: Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med* 380:315, 2019.

436

Tremor, Chorea, and Other Movement Disorders

C. Warren Olanow, Christine Klein



HYPERKINETIC MOVEMENT DISORDERS

Hyperkinetic movement disorders are characterized by involuntary movements unaccompanied by weakness (Table 436-1). This term is somewhat arbitrary and potentially misleading as hypokinetic disorders such as Parkinson's disease (PD) are often accompanied by tremor, which is a hyperkinetic feature, and hyperkinetic disorders such as dystonia may manifest slow or restricted movement because of the severe muscle contractions. Nonetheless, the terms continue to be used because of convention. The major hyperkinetic movement disorders and the diseases with which they are associated are considered in this section.

TREMOR

CLINICAL FEATURES

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part with alternating contractions of agonist and antagonist muscles. It can be most prominent at rest (rest tremor), on assuming a posture (postural tremor), on actively reaching for a target (kinetic tremor), or on carrying out a movement (action tremor). Tremor may also be characterized based on its distribution, frequency, amplitude, and related neurologic dysfunction. Tremor is classified along two axes: Axis 1 covers the clinical characteristics, including historical features (age at onset, family history, temporal evolution), tremor characteristics (body distribution, activation condition), associated signs (systemic, neurologic), and laboratory tests (electrophysiology, imaging). Axis 2 relates to the etiology of the tremor and distinguishes acquired, genetic, or idiopathic origins.

PD ([Chap. 427](#)) is characterized by a predominant resting tremor, essential tremor (ET) characterized by a tremor that typically occurs while trying to sustain a posture coupled with an action tremor, and

TABLE 436-1 Hyperkinetic Movement Disorders

Tremor	Rhythmic oscillation of a body part due to intermittent muscle contractions
Dystonia	Involuntary, patterned, sustained, or repeated muscle contractions often associated with twisting movements and abnormal posture
Athetosis	Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands (this represents a form of dystonia with increased mobility)
Chorea	Rapid, semipurposeful, graceful, dance-like nonpatterned involuntary movements involving distal or proximal muscle groups. When the movements are of large amplitude and predominant proximal distribution, the term <i>ballism</i> is used.
Myoclonus	Sudden, brief (<100 ms), jerk-like, arrhythmic muscle twitches
Tic	Brief, repeated, stereotyped muscle contractions that can often be suppressed for a short time. These can be simple and involve a single muscle group or complex and affect a range of motor activities.

cerebellar dysfunction characterized by a kinetic tremor (brought out by trying to touch an object) and is usually associated with hypotonia and past pointing. Normal individuals can have a physiologic tremor that typically manifests as a mild, high-frequency (10–12 Hz), postural, or action tremor typically affecting the upper extremities. This tremor is usually of no clinical consequence and often is only appreciated with an accelerometer or under stress. An enhanced physiologic tremor (EPT) can be seen in up to 10% of the population, and tends to occur in association with anxiety, fatigue, a metabolic disturbance (e.g., hyperthyroidism, electrolyte abnormalities), drugs (e.g., valproate, lithium), or toxins (e.g., caffeine, smoking, alcohol). Treatment is initially directed at control of any underlying disorder and, if necessary, can often be improved with a beta blocker.

■ ESSENTIAL TREMOR

ET is the most common movement disorder, affecting ~5% of the population (an estimated 5–10 million persons in the United States or Western Europe). It can present in childhood but dramatically increases in prevalence in those aged >70 years. ET is characterized by a high-frequency tremor (6–10 Hz) that predominantly affects the upper extremities. The tremor is most often manifest as a postural or action tremor and, in severe cases, can interfere with functions such as eating and drinking. It is typically bilateral and symmetric but may begin on one side and remain asymmetric. Patients with severe ET can have an intention tremor with overshoot and slowness of movement suggesting the possibility of a cerebellar origin. Tremor involves the head in ~30% of cases, voice in ~20%, tongue in ~20%, face/jaw in ~10%, and lower limbs in ~10%. Multiple body parts are involved in at least 50% of cases. The tremor is characteristically improved by alcohol and worsened by stress. Usually the neurologic examination is normal aside from tremor, but subtle impairment of coordination or tandem walking may be present, and disturbances of hearing, cognition, personality, mood, and olfaction have also been described. The differential diagnosis includes dystonic tremor (see below) or PD. PD can usually be differentiated from ET because the former stops at the onset of a voluntary action and is typically associated with bradykinesia with progressive slowing of sequential movements (sequence effect), rigidity, gait and postural instability, and other parkinsonian features. However, the examiner should be aware that PD patients may have a postural tremor and ET patients may develop a rest tremor, but that these typically only begin after a latency of a few seconds (emergent tremor). In contrast to the micrographia of PD, ET patients have relatively large handwriting with evidence of the effect of tremor. The examiner must also differentiate the effect of tremor when assessing tone in order to distinguish the tremor of ET from the cogwheel rigidity found in PD.

■ ETIOLOGY AND PATHOPHYSIOLOGY

The etiology and pathophysiology of ET are not known. Approximately 50% of cases have a positive family history with an autosomal dominant pattern of inheritance. Linkage studies have detected possibly

linked loci in large ET families. Recently, expansion of GGC repeat in the human-specific NOTCH2NLC gene has been found to be associated with ET, but no independently confirmed causative genes have been identified to date. It is likely that there are undiscovered genes for ET that have escaped detection to date because of the heterogeneity of the syndrome and the high population frequency of ET likely resulting in a large number of phenocopies, (i.e., family members with a similar clinical syndrome, but not carrying the causative mutation). The cerebellum and inferior olive have been implicated as possible sites of a “tremor pacemaker” based on the presence of cerebellar signs in about 10% of ET patients, and increased metabolic activity and blood flow in these regions in some patients. Some pathologic studies have described cerebellar pathology with a loss of Purkinje cells and axonal torpedoes, but these findings are controversial, and the precise pathologic correlate of ET remains to be defined. It is likely that multiple causes of ET will ultimately be identified.

■ TREATMENT

Many cases are mild, do not cause any functional impairment, and require no treatment other than reassurance. Occasionally, tremor can be severe and interfere with eating, writing, and activities of daily living. This is more likely to occur as the patient ages and is often associated with a reduction in tremor frequency. Beta blockers and primidone are the standard drug therapies for ET and are useful in about 50% of cases. Propranolol (20–120 mg daily, given in divided doses) is usually effective at relatively low doses, but higher doses may be needed in some patients. The drug is contraindicated in patients with bradycardia or asthma. Hand tremor tends to be most improved, while head tremor is often refractory. Primidone can be helpful but should be started at low doses (12.5 mg) and gradually increased (125–250 mg tid) to avoid sedation, nausea, and dizziness. Benefits have also been reported with gabapentin and topiramate, but these drugs have not been widely employed. Botulinum toxin injections may be helpful for limb or voice tremor, but treatment can be associated with muscle weakness. Surgical therapies targeting the ventro-intermediate (VIM) nucleus of the thalamus can be very effective for severe and drug-resistant cases. Recently, focal ultrasound (which is a procedure that does not require surgery) has also been shown to be an effective therapy against tremor in ET.

DYSTONIA

■ CLINICAL FEATURES

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions of agonist/antagonist muscles causing abnormal, often repetitive movements and postures. Dystonic movements are typically patterned and twisting and may be associated with a “dystonic” tremor in which the tremor is most pronounced when the body part is moved in the direction of the dystonia. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation. Dystonia can range from focal minor contractions affecting only an individual muscle group to severe and disabling involvement of multiple muscle groups. The frequency is estimated to be 16 per 100,000 (~50,000 cases in the United States) but is likely to be much higher because many cases are not recognized. Dystonia is often brought out by voluntary movements (action dystonia) and can extend to involve other muscle groups and body regions not required for the intended action (overflow). It can be aggravated by stress and fatigue and attenuated by relaxation and sensory tricks such as touching the affected body part (*geste antagoniste*).

Historically, dystonia has been described as primary or secondary. However, because of a confusing and not always congruent combination of phenotypic and etiologic features, the older terms are no longer recommended. A Movement Disorder Society Task Force charged with redefining dystonia recommends classifying dystonia along the same main axes as ET: clinical and etiologic. On clinical grounds, dystonia can be categorized by age of onset (infancy, childhood, adolescence, early and late adulthood), body distribution (focal, segmental, multifocal, and generalized), temporal pattern (static or progressive,

action-specific [diurnal and paroxysmal]), and association with additional features. Clinical description along these lines enables formulating specific dystonia syndromes (e.g., early-onset generalized isolated dystonia). From an etiologic point of view, dystonia primarily reflects genetic abnormalities, although occasionally there may be other causes such as dystonia following trauma and stroke. Genetic features used for classification include mode of inheritance or identification of a specific genetic defect. More than 200 genes have been linked to different, mainly childhood-onset and generalized forms of dystonia. These include forms in which dystonia is the only disease manifestation with the exception of tremor ("isolated dystonia"), forms in which dystonia co-occurs with another movement disorder such as parkinsonism or myoclonus ("combined dystonia"), and disorders in which dystonia is one of several clinical manifestations and may be a less prominent or even inconsistent feature ("complex dystonia"). Most of the genetic forms belong to the latter phenotypic group, which also represents the most heterogeneous class in terms of clinical expression.

■ ISOLATED DYSTONIAS

Focal, Multifocal, and Segmental Dystonia Adult-onset, focal dystonia is by far the most frequent form of isolated dystonia, with women being affected about twice as often as men. Focal dystonia typically presents in the fourth to sixth decade of life. The major clinical phenotypes are as follows: (1) *Cervical dystonia*—dystonic contractions of neck muscles causing the head to deviate to one side (*laterocollis*), twist (*torticollis*), move in a forward direction (*anterocollis*), or move in a backward direction (*retrocollis*). Muscle contractions can be painful and occasionally can be complicated by a secondary cervical radiculopathy. (2) *Blepharospasm*—dystonic contractions of the eyelids with increased blinking that can interfere with reading, watching television, working on a computer, and driving. This can sometimes be severe enough to cause functional blindness. (3) *Oromandibular dystonia* (OMD)—contractions of muscles of the lower face, lips, tongue, and jaw (opening or closing). Meige's syndrome is a combination of OMD and blepharospasm that predominantly affects women aged >60 years. (4) *Spasmodic dysphonia*—dystonic contractions of the vocal cords during phonation, causing impaired speech. Most cases affect the adductor muscles and cause speech to have a choking or strained quality. Less commonly, the abductors are affected, leading to speech with a breathy or whispering quality. (5) *Limb dystonias*—these can be present in either arms or legs and are often brought out by task-specific activities such as handwriting (writer's cramp), playing a musical instrument (musician's cramp), or putting in golf (the yips). The vast majority of patients with this class of dystonia have cervical dystonia (~50%) or blepharospasm (~20%). Focal hand or leg dystonia (~5%), spasmodic dysphonia (~2%), musician's dystonia (~3%), or OMD (~1%) are much less common. Focal dystonias can extend to involve other body regions (about 30% of cases) and are frequently misdiagnosed as psychiatric or orthopedic in origin. Their cause is usually not known. They are rarely monogenic (~1%); autoimmunity and trauma have been suggested as other possible etiologies. Focal dystonias are often associated with a high-frequency tremor that can resemble ET. Dystonic tremor can usually be distinguished from ET because it tends to occur in conjunction with the dystonic contraction and disappears when the dystonia is relieved (e.g., turning the head in the opposite direction of the dystonia).

Generalized Dystonia Generalized dystonia is often hereditary in nature and, unlike focal dystonia, typically has an age of onset in childhood or adolescence. There are currently at least seven well-established genes that, when mutated, can cause a generalized dystonia; *TOR1A*, *THAP1*, *ANO3*, *GNAL*, *KMT2B*, *PRKRA*, and *HPCA*. While *PRKRA* and *HPCA* mutations are recessively inherited, all others are transmitted in an autosomal dominant fashion. According to the recommendations of the International Parkinson's Disease and Movement Disorder Society, monogenic forms of dystonia are classified according to the absence or presence of accompanying additional clinical features and preceded by a "DYT" prefix, e.g., DYT-TOR1A. These genetic forms are primarily inherited in an autosomal dominant fashion and are found in <5% of dystonia patients. Further, not all mutation carriers

develop generalized dystonia; about 35% remain unaffected despite harboring a pathogenic mutation (reduced penetrance), and rarely they present with dystonia that remains focal or segmental in nature.

Mutations in the *TOR1A* gene (torsin family 1 member A—formerly known as the *DYT1* gene) are the most common cause of early-onset generalized dystonia. The first, and currently the only clearly established mutation, is a 3-base pair deletion in the *TOR1A* gene. The mutation is frequently found among Ashkenazi Jewish patients due to a founder effect. Mutation carriers usually present with dystonia in an extremity in childhood that later progresses to other body parts, but typically spares the face and neck. Rare carriers of two mutated alleles have been described and are characterized by a severe neurodevelopmental syndrome and arthrogryposis.

Mutations in the *THAP1* (*THAP domain containing, apoptosis associated protein 1*) gene have been linked to adolescent-onset dystonia with mixed phenotype. About 100 different mutations have been reported in *THAP1*. Mutations typically manifest with dysphonia or writer's cramp beginning in late childhood or adolescence. Over the course of the disease, dystonia can spread to other body parts with prominent craniocervical involvement.

Mutations in the *ANO3* (*anoctamin 3*) gene were first reported in patients with predominantly craniocervical dystonia with a broad range of ages of onset. While a large number of missense variants can be found in healthy individuals, a pathogenic role of *ANO3* mutations has been confirmed by the description of additional families with dystonia and myoclonic jerks.

Mutations in the *GNAL* (*guanine nucleotide-binding protein subunit alpha L*) gene are a rare cause of cervical or cranial dystonia, with a few patients developing a generalized dystonia. Mean age of onset is in the thirties. About 30 different *GNAL* mutations have been reported in dystonia patients.

In addition to the above, missense mutations in *KMT2B* (*lysine methyltransferase 2B*) have been confirmed to be a cause of an early-onset generalized dystonia that may be accompanied by other syndromic features including intellectual disability, microcephaly, psychiatric features, dysmorphia, or skin lesions. The majority of the mutations occurred de novo. *KMT2B* mutations may account for up to 10% of early-onset generalized dystonia, but further validation is warranted, and placement into the group of isolated vs complex dystonias is currently under debate.

The vast majority of *PRKRA* mutation carriers develop a generalized dystonia, frequently with laryngeal involvement. Likewise, all patients described to carry *HPCA* mutations are characterized by generalized dystonia.

■ COMBINED DYSTONIAS

A number of other well-established genes have been described that are associated with combined forms of dystonia in which dystonia occurs in conjunction with a different movement disorder, such as parkinsonism or myoclonus.

Dopa-responsive dystonia (DRD; also known as Segawa syndrome) is caused by mutations in the *GCH1* (*GTP cyclohydrolase-I*) gene that encodes the rate-limiting enzyme in the biosynthesis of dopamine via the biopterin pathway. It is manifest as a childhood-onset form of dystonia with diurnal fluctuations and is important to recognize as the condition dramatically responds to low doses of levodopa. Parkinsonism can be a major, or even the only, finding, and there may be a pre-synaptic dopaminergic deficit as evidenced by SPECT. To date, more than 100 different mutations have been reported with a penetrance of around 50%, which is considerably higher in women compared to men. Recessively inherited (biallelic) mutations in *GCH1* result in a much more severe clinical phenotype with developmental delay and infantile onset. Due to the enzymatic defect in levodopa biosynthesis, there is a lifelong and dramatic response to levodopa therapy. Younger patients are frequently misdiagnosed as having cerebral palsy, and all young-onset forms of dystonia should be tested with levodopa to exclude the possibility of DRD. Importantly, since the dopamine neuronal network is anatomically preserved, these patients do not develop dyskinesia with chronic levodopa treatment.

X-linked dystonia-parkinsonism (Lubag) is a combined form of dystonia and parkinsonism that is found exclusively in patients of Filipino origin due to a founder effect and seems to be fully penetrant. Patients usually develop focal (cranial) dystonia first that rapidly generalizes and, after 5–10 years, is gradually replaced by a form of L-dopa-unresponsive parkinsonism. A retrotransposon insertion in the *TAFI* (*TATA-box binding protein associated factor 1*) gene is the cause of the disease, and 50% of the age-at-onset variability is explained by the variable length of a hexameric repeat expansion within the retrotransposon.

Mutations in the *ATPIA3* (*ATPase Na⁺/K⁺ transporting subunit alpha 3*) gene present with a characteristic, sudden-onset dystonia usually in adolescence or young adulthood, often triggered by high fever, physical exertion, or emotional stress. Dystonic symptoms frequently show a rostrocaudal gradient with a strong involvement of the bulbar region, often accompanied by parkinsonian features such as bradykinesia. In addition, mutations in *ATPIA3* have been linked to a variety of clinical syndromes (pleiotropy), including epileptic or hemiplegic attacks, ataxia, cognitive decline, and other neurologic disorders, often with a more severe course and an earlier age at onset.

Myoclonic-dystonia is characterized by action-induced, alcohol-responsive myoclonic jerks predominantly involving the upper body half. Onset is usually in childhood or adolescence. Many individuals also develop psychiatric features such as depression, anxiety-related disorders, and alcohol dependence. The disorder is primarily related to mutations in the *SGCE* (*sarcoglycan epsilon*) gene, which codes for the ε member of the sarcoglycan family. About 80 different mutations have been reported in *SGCE* including deletions of the entire gene. The latter type of mutation often also involves loss of adjacent genes leading to additional clinical features such as joint problems. *SGCE* mutations are incompletely penetrant and only manifest when inherited from the father due to the epigenetic effect of maternal imprinting of *SGCE*. Another recently identified cause of myoclonus-dystonia is *KCTD17* mutation.

A number of additional monogenic causes have been suggested for isolated and combined forms of dystonia but still await independent confirmation. Table 436-2 provides a list of the confirmed monogenic forms of isolated and combined dystonias.

■ COMPLEX DYSTONIAS

In the complex dystonias, dystonia is a part of a syndrome that is characterized by multiple different clinical manifestations of the disease. Most frequently, they are hereditary such as Wilson's disease (WD), Huntington's disease (HD), Lesh Nyhan syndrome, corticobasal ganglionic disorders, and a variety of other neurologic, neurometabolic,

and mitochondrial disorders. Complex dystonias may also develop as a consequence of drugs or toxins (previously referred to as secondary dystonias). Drug-induced dystonia may be acute or chronic and is most commonly seen with neuroleptic drugs or after chronic levodopa treatment in PD patients. Dystonia can also be observed following discrete lesions in the striatum, and occasionally in the pallidum, thalamus, cortex, or brainstem due to infarction, hemorrhage, anoxia, trauma, tumor, infection, or toxins such as manganese or carbon monoxide. In these cases, dystonia often assumes a segmental distribution but may be generalized when lesions are bilateral or widespread. More rarely, dystonia can develop following peripheral nerve injury and be associated with features of complex regional pain syndrome (Chap. 17). A psychogenic origin is responsible for some cases of dystonia; these typically present with fixed, immobile dystonic postures (see below).

■ PATHOPHYSIOLOGY OF DYSTONIA

Even in cases with a known dystonia gene mutation, the pathophysiological basis of dystonia is not completely known. The phenomenon is characterized by co-contracting synchronous bursts of agonist and antagonist muscle groups with recruitment of muscle groups that are not required for a given movement (overflow). Dystonia is characterized by derangement of the basic physiologic principle of action selection, leading to abnormal recruitment of inappropriate muscles for a given action with inadequate inhibition of this undesired motor activity. Physiologically, loss of surround inhibition is observed at multiple levels of the motor system (e.g., cortex, brainstem, spinal cord) accompanied by increased cortical excitability and reorganization. Attention has focused on the basal ganglia as the site of origin of at least some types of dystonia because there are alterations in blood flow and metabolism in these structures. Further, lesions of the basal ganglia (particularly the putamen) can induce dystonia, and surgical ablation or deep brain stimulation (DBS) of specific regions of the globus pallidus may ameliorate dystonia. The dopamine system has also been implicated, because dopaminergic therapies can both induce and treat some forms of dystonia in different circumstances. Interestingly, no specific pathology has been consistently identified to underlie dystonia.

TREATMENT

Dystonia

Treatment of dystonia is for the most part symptomatic except in rare cases where correction of a primary underlying condition is possible. Wilson's disease should be ruled out, particularly in young patients with dystonia. Levodopa should be tried in all cases of

TABLE 436-2 Confirmed Monogenic Forms of Isolated and Combined Dystonia^a

FORM OF DYSTONIA	GENE	LOCUS NAME	DESIGNATION AND PHENOTYPIC SUBGROUP ^b	ADDITIONAL DISTINGUISHING FEATURES	MOI
Isolated	<i>TOR1A</i>	DYT1	DYT-TOR1A	Childhood or adolescent-onset, generalized	AD
	<i>THAP1</i>	DYT6	DYT-THAP1	Adolescent-onset, cranial or generalized	AD
	<i>ANO8</i>	DYT24	DYT-ANO3	Adult-onset, focal or segmental	AD
	<i>GNAL</i>	DYT25	DYT-GNAL	Mostly adult-onset, focal or segmental	AD
	<i>KMT2B^c</i>	DYT28	DYT-KMT2B	Early-onset, generalized, mild syndromic features	AD
Combined	Dystonia plus parkinsonism	<i>GCH1</i>	DYT-GCH1 ^a	Dopa-responsive	AD
		<i>TAF1</i>	DYT-TAF1	Neurodegeneration	XL
		<i>PRKRA</i>	DYT-PRKRA	Dystonia with mild parkinsonism	AR
		<i>ATP1A3</i>	DYT-ATP1A3	Rapid-onset	AD
	Dystonia plus myoclonus	<i>SGCE</i>	DYT-SGCE	Psychiatric disease	AD

^aAccording to CMarras et al: Mov Disord 31:436, 2016. ^bSeveral, but not all, patients show syndromic features; DYT-KMT2B may thus be better placed with the complex dystonias.

^cAbbreviations: AD, autosomal dominant; AR, autosomal recessive; MOI, mode of inheritance; XL, X-linked.

childhood-onset dystonia to test for DRD. High-dose anticholinergics (e.g., trihexyphenidyl 20–120 mg/d) may be beneficial in children, but adults can rarely tolerate high doses because of side effects related to cognitive impairment and hallucinations. Oral baclofen (20–120 mg) may also be helpful, but benefits, if present, are usually modest, and side effects of sedation, weakness, and memory loss can be problematic. Intrathecal infusion of baclofen is more likely to be useful, particularly for leg and trunk dystonia, but benefits are frequently not sustained, and complications can be serious and include infection, seizures, and coma. Tetrabenazine is another consideration; the usual starting dose is 12.5 mg/d and the average treating dose is 25–75 mg/d, but its use may be limited by sedation and the development of parkinsonism. Parkinsonian side effects can be minimized with deuterated tetrabenazine. Neuroleptics can both improve and induce dystonia, but they are typically not recommended because of their potential to induce parkinsonism and other movement disorders, including tardive dystonia. Clonazepam and diazepam are sometimes effective.

Botulinum toxin has become the preferred treatment for patients with focal and segmental dystonia, particularly where involvement is limited to small muscle groups such as in blepharospasm, torticollis, and spasmodic dysphonia. Botulinum toxin acts by blocking the release of acetylcholine at the neuromuscular junction, leading to reduced dystonic muscle contractions. However, treatment with botulinum toxin can be complicated by excessive weakness that can be troublesome, particularly if it involves neck and swallowing muscles. No systemic side effects are encountered with the doses typically used, but benefits are transient, and repeat injections are required at 2- to 5-month intervals. Some patients fail to respond after having experienced an initial benefit. This has been attributed to development of neutralizing antibodies, but improper muscle selection, injection technique, and inadequate dose should be excluded.

Surgical therapy is an alternative for patients with severe dystonia who are not responsive to other treatments. Peripheral procedures such as rhizotomy and myotomy were used in the past to treat cervical dystonia but are now rarely employed. DBS of the pallidum can provide dramatic benefits for some patients with various forms of hereditary and nonhereditary generalized dystonia. This represents a major therapeutic advance because previously there was no consistently effective therapy, especially for patients with severe disability. Benefits tend to be obtained with a lower frequency of stimulation than used in PD or ET, and often occur only after a relatively long latency. Better results are typically obtained in younger patients with shorter disease duration and in those with certain monogenic forms, such as DYT-Tor1A. Recent studies suggest that DBS may also be valuable for patients with focal and secondary dystonias, although results are less consistent. Supportive treatments such as physical therapy and education should be a part of the treatment regimen for all types of dystonia.

Physicians should be aware of dystonic storm, a rare but potentially fatal condition that can occur in response to a stress situation such as a surgical procedure or a systemic infection in patients with preexisting dystonia. It consists of the acute onset of generalized and persistent dystonic contractions that can involve the vocal cords or laryngeal muscles, leading to airway obstruction. Patients may experience rhabdomyolysis with renal failure and should be managed in an intensive care unit with airway protection if required. Treatment can be instituted with one or a combination of anticholinergics, diphenhydramine, baclofen, benzodiazepines, and dopaminergic agents. Spasms may be difficult to control, and anesthesia with muscle paralysis may be required.

CHOREAS

HUNTINGTON'S DISEASE

HD is a progressive, fatal, highly penetrant autosomal dominant disorder characterized by motor, behavioral, oculomotor, and cognitive dysfunction. The disease is named for George Huntington, a family

physician who described cases on Long Island, New York, in the nineteenth century. Onset is typically between the ages of 25 and 45 years (range, 3–70 years) with a prevalence of 2–8 cases per 100,000 and an average age at death of 60 years. It is prevalent in Europe, North America, South America, and Australia but is rare in African blacks and Asians. HD is characterized by rapid, nonpatterned, semipurposeful, involuntary choreiform movements, and for this reason was formerly referred to as Huntington's chorea. However, dysarthria, gait disturbance, oculomotor abnormalities, behavioral disturbance, and cognitive impairment with dementia are also common features; thus the condition is currently referred to as Huntington's disease. In the early stages, chorea tends to be focal or segmental, but progresses over time to involve multiple body regions. With advancing disease, there tends to be a reduction in chorea and the emergence of dystonia, rigidity, bradykinesia, and myoclonus. Functional decline is often predicted by progressive weight loss despite adequate calorie intake. In younger patients (~10% of cases), HD can present as an akinetic-rigid parkinsonian syndrome (Westphal variant). HD patients eventually develop behavioral and cognitive disturbances, and the majority progress to dementia. Depression with suicidal tendencies, aggressive behavior, and psychosis can be prominent features. HD patients may also develop non-insulin-dependent diabetes mellitus and neuroendocrine abnormalities (e.g., hypothalamic dysfunction). A clinical diagnosis of HD can be strongly suspected in cases of chorea with a positive family history, but genetic testing provides the ultimate confirmation of the diagnosis.

The disease predominantly affects the striatum but progresses to involve the cerebral cortex and other brain regions. Progressive atrophy of the head of the caudate nucleus, which forms the lateral margin of the lateral ventricle, can be visualized on MRI (Fig. 436-1), but the putamen can be equally or even more severely affected. More diffuse cortical atrophy can be seen in the middle and late stages of the disease. Supportive studies include reduced metabolic activity in the caudate nucleus and putamen, and reduced brain metabolites on MR spectroscopy. Genetic testing can be used to confirm the diagnosis and to detect at-risk individuals in the family but must be performed with caution and in conjunction with trained counselors, because positive results can worsen depression and even generate suicidal reactions. Indeed, genetic counseling is a requirement in some regions. The neuropathology of HD consists of prominent neuronal loss and gliosis in the caudate nucleus and putamen; similar changes are also widespread in the cerebral cortex. Intraneuronal inclusions containing aggregates of ubiquitin and the mutant protein huntingtin are found in the nuclei of affected neurons.

In anticipation of developing neuroprotective therapies, there has been an intensive effort to define the premanifest stage of HD. Subtle motor impairment, cognitive alterations, and imaging changes can be detected in at-risk individuals who later go on to develop the manifest form of the disease. Defining the rate of progression of these features is paramount for future studies of putative disease-modifying therapies designed to slow the rate of disease progression and the development of cumulative disability.

ETIOLOGY

HD is caused by an increase in the number of polyglutamine (CAG) repeats (>40) in the coding sequence of the *huntingtin* gene located on the short arm of chromosome 4. The larger the number of repeats, the earlier the disease is manifest. Intermediate forms of the disease with 36–39 repeats are described in some patients, typically with less severe clinical involvement. Acceleration of the process tends to occur, particularly in males, with subsequent generations having larger numbers of repeats and earlier age of disease onset, a phenomenon referred to as anticipation. There is also evidence of somatic gene expansion that occurs over time.

The *huntingtin* gene encodes the highly conserved cytoplasmic protein huntingtin (HTT), which is widely distributed in neurons throughout the central nervous system (CNS). Mutated HTT RNA is toxic. Mutant HTT disrupts transcription, impairs immune and mitochondrial function, and is aberrantly modified post-translationally.

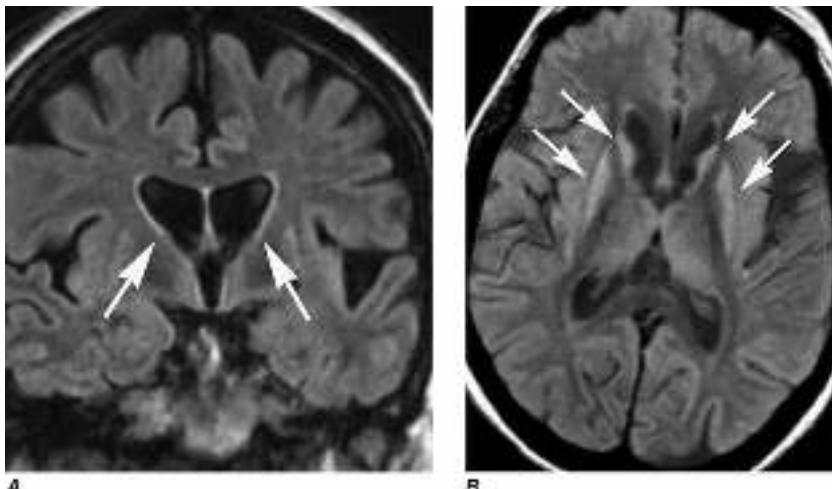


FIGURE 436-1 Huntington's disease. **A.** Coronal fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging shows enlargement of the lateral ventricles reflecting typical atrophy (arrows). **B.** Axial FLAIR image demonstrates abnormal high signal in the caudate and putamen (arrows).

Genome-wide association studies have nominated DNA repair pathways as modifiers of somatic instability and disease course in HD. Fragments of the mutant HTT can also be toxic, possibly by translocating into the nucleus and interfering with transcriptional regulation of proteins. Neuronal inclusions found in affected regions in HD may represent a protective mechanism aimed at segregating and facilitating the clearance of these toxic proteins. There is also interest in the possibility that protein accumulation and aggregation in HD, like Alzheimer's disease (Chap. 431) and PD (Chap. 435), may be critical to the disease process and reflect a prion-like disorder (Chap. 438; see also Chap. 424). Models of HD with striatal pathology can be induced in multiple transgenic animals that express the mutant gene and by excitotoxic agents such as kainic acid and 3-nitropropionic acid, which promote calcium entry into the cell and cytotoxicity.

TREATMENT

Huntington's Disease

Although the gene for HD was identified more than 25 years ago, there is still no disease-modifying therapy for this disorder, and symptomatic treatment is limited. Current treatment involves a multidisciplinary approach, with medical, neuropsychiatric, social, and genetic counseling for patients and their families. Dopamine-blocking agents may control the choreatic movements. Tetrabenazine (a presynaptic dopamine-depleting agent) has been approved for the treatment of chorea but can cause secondary parkinsonism. Deuterated tetrabenazine (Austedo) has also been approved as a treatment for chorea in HD. Deuteration interferes with the metabolism of tetrabenazine and avoids a high Cmax, which is thought to contribute to adverse effects. In clinical trials, deuterated tetrabenazine has been shown to have fewer dose-related side effects than tetrabenazine and therefore can be administered in higher doses with potentially superior clinical benefits. Neuroleptics are generally not recommended because of their potential to induce other troubling movement disorders and because HD chorea tends to be self-limited and is usually not disabling. These drugs may be used, however, in patients with severe and disabling chorea. Depression and anxiety can be major problems, and patients should be treated with appropriate antidepressant and antianxiety drugs and monitored for mania and suicidal ideations. Psychosis can be treated with atypical antipsychotics such as clozapine (50–600 mg/d), quetiapine (50–600 mg/d), and risperidone (2–8 mg/d).

A neuroprotective therapy that slows or stops disease progression is the major unmet medical need in HD. Strategies to reduce mutant HTT focus on inhibiting mRNA synthesis either by

blocking transcription (zinc finger motif protein), preventing post-transcriptional processes, and promoting early mRNA degradation (antisense oligonucleotides; ASO) or inhibiting translation with short-interfering RNA. The most advanced of these experimental therapeutic approaches investigated intrathecal administration of an ASO in patients with early HD in a randomized, placebo-controlled, double-blind phase 1–2a clinical trial. While a dose-dependent reduction in concentrations of mutant HTT was observed and there were no side effects, the study was prematurely terminated, presumably because no clinical benefit was detected. Drugs that enhance mitochondrial function and increase the clearance of defective mitochondria are also being tested as possible disease-modifying therapies. Other investigative approaches include immunotherapy, dietary supplements (Resveratrol), lipid-lowering medication (Fenofibrate), and anaplerotic therapy (Triheptanoin), and DBS of the globus pallidus pars interna (GPi). Perhaps most promising at this time is the sigma 1 receptor agonist pridopidine. While previous 6-month trials with this drug showed no significant benefit with respect to total motor function, significant benefits were observed in total functional capacity after 1 year, particularly in patients with relatively mild disease. Double-blind studies are currently underway.

HUNTINGTON'S DISEASE LIKE DISORDERS

A group of rare inherited conditions that can mimic HD, designated HD-like (HDL) disorders, has also been identified. HDL-1, 2, and 4 are autosomal dominant conditions that typically present in adulthood. HDL-3 is recessively inherited, presents in early childhood, and differs markedly from HD and the other HDLs. HDL-1 is due to expansion of an octapeptide repeat in *PRNP*, the gene encoding the prion protein (Chap. 438). Thus HDL-1 is properly considered a prion disease. Patients exhibit onset of personality change in the third or fourth decade of life, followed by chorea, rigidity, myoclonus, ataxia, and epilepsy. HDL-2 manifests in the third or fourth decade of life with a variety of movement disorders, including chorea, dystonia, or parkinsonism and dementia. Most patients are of African descent. Acanthocytosis can sometimes be seen in these patients, and this condition must be distinguished from neuroacanthocytosis (below). HDL-2 is caused by an abnormally expanded CTG/CAG trinucleotide repeat expansion in the *junctophilin-3 (JPH3)* gene. The pathology of HDL-2 consists of intranuclear inclusions immunoreactive for ubiquitin and expanded polyglutamine repeats. HDL-4, the most common condition in this group, is caused by expansion of trinucleotide repeats in *TBP*, the gene that encodes the TATA box-binding protein involved in regulating transcription; this condition is identical to spinocerebellar ataxia

3406 (SCA) 17 (Chap. 439), and most patients present primarily with ataxia rather than chorea. Mutations of the *C9orf72* gene associated with amyotrophic lateral sclerosis (Chap. 437) have also been reported in some individuals with an HDL phenotype.

■ OTHER CHOREAS

Chorea can be seen in a number of additional disorders related to genetic mutations or other disease states.

Among the hereditary forms of childhood-onset chorea, mutations in the *NKX2-1* gene cause a benign hereditary chorea. Mutations in the *ADCY5* (adenylyl cyclase 5) gene are an increasingly recognized and relatively common cause of childhood-onset chorea, often in combination with dystonia and developmental delay. Characteristic perioral movements are a hallmark of the disorder.

Chorea-acanthocytosis (neuroacanthocytosis) is a progressive and typically fatal autosomal recessive disorder that is characterized by chorea coupled with red cell abnormalities on peripheral blood smear (acanthocytes). The chorea can be severe and associated with self-mutilating behavior, dystonia, tics, seizures, and a polyneuropathy. Mutations in the *VPS13A* gene encoding chorein have been described. A phenotypically similar X-linked form of the disorder has been described in older individuals who have reactivity with Kell blood group antigens (McLeod syndrome). A benign hereditary chorea of childhood (BHC1) due to mutations in the gene for thyroid transcription factor 1 and a late-onset benign senile chorea (BHC2) have also been reported. It is important to ensure that patients with these types of choreas do not have HD.

Chorea may also occur in association with a variety of infections and degenerative disorders as well as vascular diseases and hypo- and hyperglycemia. Sydenham's chorea (originally called St. Vitus' dance) is more common in females and is typically seen in childhood (5–15 years). It often develops in association with prior exposure to group A streptococcal infection (Chap. 148) and is thought to be autoimmune in nature. It is characterized by the acute onset of choreiform movements and behavioral disturbances. With the reduction in the incidence of rheumatic fever, the incidence of Sydenham's chorea has fallen, but it can still be seen in developing countries. The chorea generally responds to dopamine-blocking agents, valproic acid, and carbamazepine, but is self-limited, and treatment is generally restricted to those with severe chorea. Chorea may recur in later life, particularly in association with pregnancy (chorea gravidarum) or treatment with sex hormones. Several reports have documented cases of chorea associated with N-methyl-D-aspartate (NMDA) receptor antibody-positive encephalitis (Chap. 94) following herpes simplex virus encephalitis, and in paraneoplastic syndromes associated with anti-CRMP-5 or anti-Hu antibodies (Chap. 90). Systemic lupus erythematosus (Chap. 356) is the most common systemic disorder that is associated with chorea. The chorea can last for days to years. Chorea can also be seen with hyperthyroidism, autoimmune disorders including Sjögren's syndrome, infectious disorders including HIV disease, metabolic alterations, and polycythemia rubra vera. Chorea has also been described following open-heart surgery in the pediatric population and in association with many medications (especially anticonvulsants, cocaine, CNS stimulants, estrogens, and lithium). Chorea is commonly seen as a side effect of chronic levodopa treatment in patients with PD (Chap. 435).

■ BALLISM/HEMIBALLISMUS

Ballism is a violent form of choreiform movement composed of wild, flinging, large-amplitude movements most frequently affecting proximal limb muscles on one side of the body (hemiballism). The movements may affect only one limb (monoballism) or, more exceptionally, both upper or lower limbs (paraballism). The movements may be so severe as to cause exhaustion, dehydration, local injury, and, in extreme cases, death. Fortunately, dopamine-blocking drugs can be very helpful, and importantly, hemiballismus is usually self-limiting and tends to resolve spontaneously after weeks or months. The most common cause is a partial lesion (infarct or hemorrhage) in the subthalamic nucleus (STN), but in 30–40% of cases the lesion is found in the putamen, thalamus, or parietal cortex. Hemiballismus is also a common feature of

the paroxysmal dyskinesias (see below). In extreme cases, pallidotomy or DBS of the GPi can be effective and abolish the involuntary movements. Interestingly, surgically induced lesions and DBS of the STN in PD patients are usually not associated with hemiballismus.

TICS

A tic is a brief, rapid, recurrent, stereotyped, and seemingly purposeless motor contraction. Motor tics can be simple, with movement only affecting an individual muscle group (e.g., blinking, twitching of the nose, jerking of the neck), or complex, with coordinated involvement of multiple muscle groups (e.g., jumping, sniffing, head banging, and echopraxia [mimicking movements]). Phonic (or vocal) tics can also be simple (e.g., grunting) or complex (e.g., echolalia [repeating other people's words], palilalia [repeating one's own words], and coprolalia [expression of obscene words]). Patients may also experience sensory tics, composed of unpleasant focal sensations in the face, head, or neck. These can be mild and of little clinical consequence or severe and disabling. Tics may present in adulthood and can be seen in association with a variety of disorders, including PD, HD, trauma, dystonia, drugs (e.g., levodopa, neuroleptics), and toxins.

■ TOURETTE'S SYNDROME

Tourette's syndrome (TS) is a neurobehavioral disorder named after the French neurologist Georges Gilles de la Tourette. It predominantly affects males, and the prevalence is estimated to be 0.03–1.6%, but it is likely that many mild cases do not come to medical attention. TS is characterized by multiple motor tics often accompanied by vocalizations (phonic tics). Patients characteristically can voluntarily suppress tics for short periods of time, but then experience an irresistible urge to express them. Tics vary in intensity and may be absent for days or weeks only to recur, occasionally in a different pattern. Tics tend to present between ages 2 and 15 years (mean 7 years) and often lessen or even disappear in adulthood, particularly in males. Associated behavioral disturbances include anxiety, depression, attention deficit hyperactivity disorder, and obsessive-compulsive disorder. Patients may experience personality disorders, self-destructive behaviors, difficulties in school, and impaired interpersonal relationships.

Etiology and Pathophysiology TS has a high heritability and is thus thought to be a genetic disorder, but no specific monogenic cause has yet been identified. Current evidence supports a complex inheritance pattern with an important contribution of *de novo*, likely gene-disrupting variants. Four likely risk genes with multiple *de novo* damaging variants in unrelated probands include *WWC1*, *CELSR3*, *NIPBL*, and *FNI*. The risk of a family with one affected child having a second is about 25%. The pathophysiology of TS is not known, but alterations in dopamine neurotransmission, opioids, and second-messenger systems have been proposed.

TREATMENT

Tics

Patients with mild disease often only require education and counseling (for themselves and family members). In a high proportion of patients, the severity of tics wanes in adult life, becoming less of a medical problem, thus arguing for conservative management if possible during the first decades of life. Drug treatment is indicated when the tics are disabling and interfere with quality of life and social interactions. Therapy is individualized, and there is no singular treatment regimen that has been properly evaluated in double-blind trials. Some physicians use the α -agonist clonidine, starting at low doses and gradually increasing the dose and frequency until satisfactory control is achieved. Guanfacine (0.5–2 mg/d) is an α -agonist that is preferred by some because it requires only once-daily dosing. Other physicians prefer to use neuroleptics. Atypical neuroleptics are usually used initially (risperidone, olanzapine, ziprasidone) because they are thought to be associated with a reduced risk of tardive dyskinesia. If they are not effective, low doses of classical neuroleptics such as haloperidol,

fluphenazine, pimozide, or tiapride can be tried because the risk of tardive dyskinesia in young people is relatively low. Tetrabenazine and deuterated tetrabenazine are currently being evaluated. Botulinum toxin injections can be effective in controlling focal tics that involve small muscle groups. Behavioral features, and particularly anxiety and compulsions, can be a disabling feature of TS and should be treated as appropriate. The potential value of DBS targeting the anterior portion of the internal capsule, the GPI, or the thalamus is currently being explored and a large-scale public database and registry for DBS in TS has been established.

MYOCLONUS

Myoclonus is a brief, rapid (<100 ms), shocklike, jerky movement consisting of single or repetitive muscle discharges. Myoclonic jerks can be focal, multifocal, segmental, or generalized and can occur spontaneously, in association with voluntary movement (action myoclonus), or in response to an external stimulus (reflex myoclonus). Negative myoclonus consists of a brief loss of muscle activity (e.g., asterixis in hepatic failure). Myoclonic jerks can be severe and interfere with normal movement or benign and of no clinical consequence as is commonly observed in normal people when waking up or falling asleep (hypnagogic jerks).

Myoclonic jerks differ from tics in that they are not typically repetitive, can severely interfere with normal voluntary movement, and are not suppressible. They can arise in association with abnormal neuronal discharges in cortical, subcortical, brainstem, or spinal cord regions, particularly in association with hypoxemia (especially following cardiac arrest), encephalopathy, and neurodegeneration. Reversible myoclonus can be seen with metabolic disturbances (renal failure, electrolyte imbalance, hypocalcemia), toxins, and many medications. Hereditary myoclonus syndromes can be grouped into three classes based on clinical features: prominent myoclonus syndromes, prominent myoclonus syndromes combined with another prominent movement disorder, and disorders that usually present with other phenotypes but can also manifest as a prominent myoclonus syndrome. An additional movement disorder is seen in nearly all myoclonus syndromes, most commonly ataxia or dystonia. Furthermore, cognitive decline and epilepsy are present in the vast majority of patients. The most common form of action myoclonus of cortical origin with ataxia and generalized epilepsy is myoclonic epilepsy type 1 (EPM-1) or Unverricht-Lundborg disease, which can have a variable but often progressive course. This is an autosomal recessive disease caused by mutations in the *CSBT* gene. Other causes are Lafora body epilepsy or progressive myoclonic epilepsy (PME-2) caused by mutations in the *EPM2A* gene or the *NHLRC1* gene and ceroid lipofuscinosi. In patients with less severe or absent epilepsy, mitochondrial disorders and neurodegenerative disorders affecting the cerebellum (i.e., SCAs) should be considered. Essential myoclonus is a relatively benign familial condition characterized by multifocal, very brief, lightning-like movements that are frequently alcohol-sensitive. Mutations in the *epsilon-sarcoglycan* gene have been associated with myoclonus seen in association with dystonia (myoclonic-dystonia).

TREATMENT

Myoclonus

Treatment primarily consists of managing the underlying condition or removing an offending agent. Pharmacologic therapy involves one or a combination of GABAergic agents such as valproic acid (800–3000 mg/d), piracetam (8–20 g/d), clonazepam (2–15 mg/d), levetiracetam (1000–3000 mg/d), or primidone (500–1000 mg/d). Treatment may be associated with striking clinical improvement in chronic cases (e.g., postanoxic myoclonus, progressive myoclonic epilepsy) in which a cortical origin for the myoclonic discharges has been identified. The serotonin precursor 5-hydroxytryptophan (plus carbidopa) may be useful in some cases of postanoxic myoclonus. DBS can be highly effective in myoclonus dystonia.

DRUG INDUCED MOVEMENT DISORDERS

This important group of movement disorders is primarily associated with drugs that block dopamine receptors (neuroleptics) or central dopaminergic transmission. These drugs are widely used in psychiatry, but it is important to appreciate that drugs used in the treatment of nausea or vomiting (e.g., prochlorperazine [Compazine]) or gastroesophageal disorders (e.g., metoclopramide) are neuroleptic agents and can also cause these disorders. Hyperkinetic movement disorders secondary to neuroleptic drugs can be divided into those that present acutely, subacutely, or after prolonged exposure (tardive syndromes). Dopamine-blocking drugs can also be associated with a reversible parkinsonian syndrome for which anticholinergics are often concomitantly prescribed, but these drugs are not effective antiparkinsonian agents, they are associated with cognitive side effects, and there is concern that this may increase the risk of developing a tardive syndrome.

■ ACUTE

Dystonia is the most common acute hyperkinetic drug reaction. It is typically generalized in children and focal in adults (e.g., blepharospasm, torticollis, or OMD). The reaction can develop within minutes of exposure and can be successfully treated in most cases with parenteral administration of anticholinergics (benztropine or diphenhydramine), benzodiazepines (lorazepam, clonazepam, or diazepam), or dopamine agonists. The abrupt onset of severe spasms may occasionally be confused with a seizure; however, there is no loss of consciousness, automatisms, EEG abnormalities, or postictal features typical of epilepsy. The acute onset of chorea, stereotypic behavior, and tics may also be seen, particularly following exposure to CNS stimulants such as methylphenidate, cocaine, or amphetamines.

■ SUBACUTE

Akathisia is the most common reaction in this category. It consists of motor restlessness with a need to move that is alleviated by movement. Therapy consists of removing the offending agent. When this is not possible, symptoms may be ameliorated with benzodiazepines, anticholinergics, beta blockers, or dopamine agonists.

■ TARDIVE SYNDROMES

These disorders develop months to years after initiation of the neuroleptic agent. Tardive dyskinesias (TD) are most common, and typically present with choreiform and/or dystonic movements involving the mouth, lips, and tongue. In severe cases, the trunk, limbs, and respiratory muscles may also be affected. In approximately one-third of patients, TD remit within 3 months of stopping the drug, and most patients gradually improve over the course of several years. However, abnormal movements may also develop, persist, or worsen after stopping the offending agent. The movements are thought to be often mild and more upsetting to the family than to the patient, but they can be severe and disabling, particularly in the context of an underlying psychiatric disorder. Atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) are associated with a lower risk of causing TD in comparison to traditional antipsychotics. Younger patients have a lower risk of developing neuroleptic-induced TD, whereas elderly people, females, and those with underlying organic cerebral dysfunction have been reported to be at greater risk. Chronic use is associated with increased risk of TD, and specifically, the U.S. Food and Drug Administration has warned that use of metoclopramide for >12 weeks increases the risk of TD. Because TD can be permanent and resistant to treatment, antipsychotics should be used judiciously, atypical neuroleptics should be the preferred agent when possible although there are now questions as to the risk of TD with atypical neuroleptics as well, and continued use should be regularly monitored and cease when possible.

Treatment primarily consists of stopping the offending agent. If the patient is receiving a traditional antipsychotic, and withdrawal is not possible, replacement with an atypical antipsychotic (e.g., clozapine) should be tried. Abrupt cessation of a neuroleptic should be avoided because acute withdrawal can induce worsening. TD can persist after withdrawal of antipsychotics and can be difficult to treat. Valbenazine

(Ingrezza) is an ester of tetrabenazine that is approved for the treatment of TD based on results of efficacy in double-blind trials, but it is associated with sleepiness and QT prolongation. It acts as a vesicular monoamine transporter type 2 (VMAT-2) inhibitor and blocks storage of dopamine. Deuterated tetrabenazine is also being studied for this indication. Benefits in open-label studies have been reported with valproic acid (750–3000 mg/d), anticholinergics, or botulinum toxin injections. Other approaches that have been tried include baclofen (40–80 mg/d) or clonazepam (1–8 mg/d). In some cases, where the abnormal movement is refractory to therapy, pallidal DBS may be a treatment option.

Chronic neuroleptic exposure can also be associated with tardive dystonia, with preferential involvement of axial muscles and characteristic rocking movements of the trunk and pelvis. Tardive dystonia can be more troublesome than tardive dyskinesia and frequently persists despite stopping medication. Valproic acid, anticholinergics, and botulinum toxin may occasionally be beneficial, but patients are frequently refractory to medical therapy. Tardive akathisia, tardive TS, and tardive tremor syndromes are rare but may also occur after chronic neuroleptic exposure.

Neuroleptic medications can also be associated with a neuroleptic malignant syndrome (NMS). NMS is characterized by the acute or subacute onset of muscle rigidity, elevated temperature, altered mental status, hyperthermia, tachycardia, labile blood pressure, renal failure, and markedly elevated creatine kinase levels. Symptoms typically evolve within days or weeks after initiating the drug. NMS can also be precipitated by the abrupt withdrawal of dopaminergic medications in PD patients. Treatment involves immediate cessation of the offending antipsychotic drug and the introduction of a dopaminergic agent (e.g., a dopamine agonist or levodopa), dantrolene, or a benzodiazepine. In very severe cases, when oral intake is not possible, a patch (delivering rotigotine subcutaneously) or an infusion pump (delivering apomorphine subcutaneously) may be the best approach to provide dopaminergic treatment. Treatment may need to be undertaken in an intensive care setting and include supportive measures such as control of body temperature (antipyretics and cooling blankets), hydration, electrolyte replacement, and control of renal function and blood pressure.

Drugs that have serotonin-like activity (tryptophan, MDMA or “ecstasy,” meperidine) or that block serotonin reuptake can induce a rare, but potentially fatal, serotonin syndrome that is characterized by confusion, hyperthermia, tachycardia, and coma as well as rigidity, ataxia, and tremor. Myoclonus is often a prominent feature, in contrast to NMS, which it resembles in other respects. Patients can be managed with propranolol, diazepam, diphenhydramine, chlorpromazine, or cyproheptadine as well as supportive measures.

A variety of drugs can also be associated with parkinsonism and other hyperkinetic movement disorders. Some examples include phenytoin (chorea, dystonia, tremor, myoclonus), carbamazepine (tics and dystonia), tricyclic antidepressants (dyskinesias, tremor, myoclonus), fluoxetine (myoclonus, chorea, dystonia), oral contraceptives (dyskinesia), β -adrenergics (tremor), buspirone (akathisia, dyskinesias, myoclonus), and digoxin, cimetidine, diazoxide, lithium, methadone, and fentanyl (dyskinesias).

PAROXYSMAL DYSKINESIAS

Paroxysmal dyskinesias are a group of rare disorders characterized by episodic, brief involuntary movements that can manifest as various types of hyperkinetic movements, including chorea, dystonia, tremor, myoclonus, and ballism. There are three main types: (1) *paroxysmal kinesigenic dyskinesia (PKD)*, where the involuntary movements are triggered by sudden movement, (2) *paroxysmal nonkinesigenic dyskinesias (PNKD)*, where the attacks are not induced by movement, and (3) rare cases of *paroxysmal exertion-induced dyskinesia (PED)*, where attacks are induced by prolonged exercise.

PKD is characterized by brief, self-limited attacks induced by movement onset such as running but also occasionally by unexpected sound or photic stimulation. Attacks may affect one side of the body, last seconds to minutes at a time, and recur several times a day. They

usually manifest as a mixed hyperkinetic movement disorder with dystonic posturing of a limb, ballismus, and chorea, which may also become generalized. PKD is most commonly familial with an autosomal dominant pattern of inheritance and mutations in the *proline-rich transmembrane protein 2 (PRRT2)* gene, but may also occur secondary to various brain disorders such as multiple sclerosis or hyperglycemia. PKD is more frequent in males (4:1), and the onset is typically in the first or second decade of life. About 70% report sensory symptoms such as tingling or numbness of the affected limb preceding the attack by a few milliseconds. The evolution is relatively benign, and there is a trend toward resolution of the attacks over time. Treatment with low-dose anticonvulsant therapy such as carbamazepine or phenytoin is advised when the attacks are frequent and interfere with daily life activities and is effective in about 80% of patients. Some clinical features of PKD (abrupt and short-lasting attacks preceded by an “aura”), the association with true seizure episodes, and its favorable response to anticonvulsant drugs have led to speculation that it is epileptic in origin, but this has not been established.

PNKD involves attacks of generalized dyskinesias precipitated by alcohol, caffeine, stress, or fatigue. In comparison with PKD, the episodes have a relatively longer duration (minutes to hours) and are less frequent (one to three per day). PNKD is inherited as an autosomal dominant condition with high (~80%) but incomplete penetrance. A missense mutation in the *myofibrillogenesis regulator (PNKD)* gene has been identified in several families. Recognition of the condition and elimination of the underlying precipitating factors, where possible, are the first priorities. Tetrabenazine, neuroleptics, dopamine-blocking agents, propranolol, clonazepam, and baclofen may be helpful. Treatment may not be required if the condition is mild and self-limited. Most patients with PNKD do not benefit from anticonvulsant drugs, but some may respond to clonazepam or other benzodiazepines.

The *SLC2A1* (solute carrier family 2 member 1) gene, previously linked to *GLUT1* (glucose transporter of the blood-brain barrier) deficiency syndrome, has been identified to also cause paroxysmal PED. The attacks in this disorder are characterized by a combination of chorea, athetosis, and dystonia in excessively exercised body regions with the legs being most frequently affected. A single attack lasts from a few minutes to an hour and occurs after prolonged physical exercise. In addition to the movement disorder, several patients have other disease manifestations between episodes such as epilepsy, hemolytic anemia, and migraine. A ketogenic diet is an effective therapeutic option.

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is a neurologic disorder that affects ~10% of the adult population (it is rare in Asians) and can cause significant morbidity in some individuals. It was first described in the seventeenth century by the English physician Thomas Willis but has only recently been recognized as a bona fide movement disorder. The four core symptoms required for diagnosis are: an urge to move the legs usually caused or accompanied by an unpleasant sensation in the legs; symptoms that begin or worsen with rest; partial or complete relief by movement; and worsening during the evening or night.

Symptoms most commonly begin in the legs but can spread to, or even begin in, the upper limbs. The unpleasant sensation is often described as a creepy-crawly feeling, paresthesia, or burning. In about 80% of patients, RLS is associated with periodic leg movements (PLMs) during sleep and occasionally while awake. These involuntary movements are usually brief, lasting no more than a few seconds, and recur every 5–90 s. The restlessness and PLMs are a major cause of sleep disturbance, leading to poor-quality sleep and daytime sleepiness.

Primary RLS has a strong genetic component; however, no causative gene has been identified. Genome association studies have identified variants associated with RLS risk, the strongest candidates in the *PTPRD*, *BTBD9*, and *MEIS1* genes. The mean age of onset in familial forms is in the third decade of life, although pediatric cases are recognized. The severity of symptoms is variable. Secondary RLS may be associated with pregnancy or a range of underlying disorders, including anemia, ferritin deficiency, renal failure, and peripheral

neuropathy. The pathogenesis probably involves disordered dopamine function, which may be peripheral or central, possibly in association with an abnormality of iron metabolism. Diagnosis is made on clinical grounds but can be supported by polysomnography and the demonstration of PLMs. The neurologic examination is normal. Secondary causes of RLS should be excluded, and ferritin levels, glucose, and renal function should be measured.

Most RLS sufferers have mild symptoms that do not require specific treatment. General measures to improve sleep hygiene and quality should be attempted first. If symptoms remain intrusive, low doses of dopamine agonists, e.g., pramipexole (0.25–0.5 mg), ropinirole (1–2 mg), or patch rotigotine (2–3 mg), taken 1–2 h before bedtime are generally effective. Levodopa may also be effective but is more likely to be associated with augmentation (spread and worsening of restlessness and its appearance earlier in the day) or rebound (reappearance sometimes with worsening of symptoms at a time related to the drug's short half-life). Augmentation can also be seen with dopamine agonists, particularly if higher doses are employed. Other drugs that can be effective include anticonvulsants, analgesics, and opiates. Management of secondary RLS should be directed to correcting the underlying disorder; for example, iron replacement for anemia.

OTHER DISORDERS THAT MAY PRESENT WITH A COMBINATION OF PARKINSONISM AND HYPERKINETIC MOVEMENTS

■ WILSON'S DISEASE SEE ALSO CHAP. 415

Wilson's disease (WD) is an inherited autosomal recessive disorder of copper metabolism that produces neurologic, psychiatric, and liver manifestations, alone or in combination. It is caused by mutations in the *ATP7B* gene encoding a P-type ATPase. The disease was first described by the English neurologist Kinnier Wilson at the beginning of the twentieth century, although at around the same time the German physicians Kayser and Fleischer separately noted the characteristic association of corneal pigmentation with hepatic and neurologic features. WD has a worldwide prevalence of ~1 in 30,000, with a mutation carrier frequency of 1 in 90. About half of WD patients (especially younger patients) present with liver abnormalities. The remainder present with neurologic disease (with or without underlying liver abnormalities), and a small proportion have hematologic or psychiatric problems at disease onset.

Neurologic onset usually manifests in the second decade of life with tremor, rigidity, and dystonia. The tremor is usually in the upper limbs, bilateral, and asymmetric. Tremor can be on intention or occasionally at rest and, in advanced disease, can take on a wing-beating characteristic (a flapping movement when the arms are held outstretched with the fingers opposed). Other features can include parkinsonism with bradykinesia, dystonia (particularly facial grimacing), dysarthria, and dysphagia. More than half of those with neurologic features have a history of psychiatric disturbances, including depression, mood swings, and overt psychosis. Kayser-Fleischer (KF) rings are seen virtually in all patients with neurologic features and 80% of those with hepatic presentations. KF rings represent the deposition of copper in Descemet's membrane around the cornea. They consist of a characteristic grayish rim or circle at the limbus of the cornea and are best detected by slit-lamp examination. Neuropathologic examination is characterized by neurodegeneration and astrogliosis in the basal ganglia, particularly in the striatum.

WD should always be considered in the differential diagnosis of a movement disorder in the first decades of life. Low levels of blood copper and ceruloplasmin and high levels of urinary copper may be present, but normal levels do not exclude the diagnosis. Brain imaging usually reveals generalized brain atrophy in established cases, and ~50% have signal hypointensity in the caudate head, putamen, globus pallidus, substantia nigra, and red nucleus on T2-weighted MRI scans. However, correlation of imaging changes with clinical features is not good. Liver biopsy with demonstration of high copper levels and genetic testing remain the gold standard for the diagnosis.

In the absence of treatment, the course is progressive and leads to severe neurologic dysfunction and early death in the majority of patients, although a small proportion experience a relatively benign course. Treatment is directed at reducing tissue copper levels and maintenance therapy to prevent reaccumulation. There is no clear consensus on optimal treatment, and patients should be managed in a unit with expertise in WD. Penicillamine is frequently used to increase copper excretion, but may lead to a worsening of symptoms in the initial stages of therapy. Side effects are common and can to some degree be attenuated by coadministration of pyridoxine. Tetrathiomolybdate blocks the absorption of copper and can be used instead of penicillamine. Trientine and zinc are useful drugs for maintenance therapy. Effective treatment can reverse the neurologic features in most patients, particularly when started early. However, some patients may still progress, especially those with hepatocerebral disease. KF rings tend to decrease after 3–6 months and disappear by 2 years. Adherence to maintenance therapy is a major challenge in long-term care. Patients with advanced hepatic disease may require a liver transplant, and the potential role of organ-specific chelation therapy is under investigation.

■ NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

Neurodegeneration with brain iron accumulation (NBIA) represents a group of inherited disorders characterized by iron accumulation in the basal ganglia. Clinically, they can manifest as progressive neurologic disorders with a variety of clinical features including parkinsonism, dystonia, neuropsychiatric abnormalities, and retinal degeneration. Cognitive disorders and cerebellar dysfunction may also be seen. Presentation is usually in childhood, but adult cases have been described. Multiple genes have been identified. Pantothenate kinase-associated neurodegeneration (PKAN), formerly known as Halleervorden-Spatz disease, is caused by a mutation in the *PANK2* gene, and is the most common form of NBIA, accounting for about 50% of cases. Onset is usually in early childhood and is manifest as a combination of dystonia, parkinsonism, and spasticity. MRI shows a characteristic low signal abnormality in the center of the globus pallidus on T2-weighted scans caused by iron accumulation and known as the "eye of the tiger" sign. Numerous other gene mutations have been described associated with iron accumulation including *PLA2G6*, *C19orf12*, *FA2H*, *ATP13A2*, *WDR45*, *FTL*, *CP*, *COASY*, and *DCAF17*. One must be cautious, however, not to assume that all cases with iron accumulation in the basal ganglia represent an NBIA, because iron accumulation in specific basal ganglia regions is normal, and excess iron accumulation may occur in the basal ganglia as a nonspecific secondary consequence of neurodegeneration unrelated to a defect in iron metabolism.

FUNCTIONAL PSYCHOGENIC DISORDERS

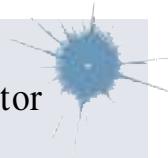
Virtually all movement disorders including tremor, tics, dystonia, myoclonus, chorea, ballism, and parkinsonism can be psychogenic in origin. The term *functional neurological symptom disorder (FND)/conversion disorder* has been suggested to replace the term *psychogenic disorder* in order to remove the criterion of psychological stress as a prerequisite for diagnosis; however, the terminology remains controversial and both terms are used. A diagnosis can be made by identifying neurologic signs that are specific to FNDs without reliance on psychological stressors or suggestive historical clues. Tremor affecting the upper limbs is the most common psychogenic movement disorder. Psychogenic movements can result from a somatoform or conversion disorder, malingering (e.g., seeking financial gain), or a factitious disorder (e.g., seeking psychological gain). Functional movement disorders are relatively common (estimated to be 2–3% of patients seen in a movement disorder clinic), more frequent in women, disabling for the patient and family, and expensive for society. Clinical features suggesting a functional or psychogenic movement disorder include an acute onset with a pattern of abnormal movement that is inconsistent with the phenotype of a known movement disorder. Diagnosis is based on the nonorganic quality of the movement, the absence of findings of an organic disease process, and positive features that specifically

point to a functional illness such as variability and distractibility. For example, in a functional or psychogenic disorder, the magnitude of tremor is increased with attention and diminishes or even disappears when the patient is distracted by being asked to perform a different task or is unaware that he or she is being observed. This is the opposite of what is seen with an organic tremor where the magnitude of tremor is increased with distraction and tends to be reduced when observed. Other positive features suggesting a psychogenic problem include variable tremor frequency, entrainment of frequency with the frequency of a designated movement in the contralateral limb such as tapping, and a response to placebo interventions. Associated features can include nonanatomic sensory findings, give-way weakness, astasia-abasia (an odd, gyrating gait or posture) (Chap. 26), and multiple somatic complaints with no underlying pathology (somatoform disorder). Comorbid psychiatric problems such as anxiety, depression, and emotional trauma may be present but are not necessary for the diagnosis, which is why some prefer to call the movement disorder functional rather than psychogenic. Functional movement disorders typically occur as an isolated entity but may also be seen in association with an underlying organic problem. The diagnosis can usually be made based on history and clinical features alone, and unnecessary tests or medications can be avoided. If there are underlying psychiatric problems, they should be identified and treated, but as noted many patients with functional movement disorders have no obvious psychiatric pathology. Treatment of FND starts with explaining the diagnosis to the patient in a nonthreatening manner, but many are resistant to accepting this diagnosis. Psychological therapies (especially cognitive-behavioral) are the method of choice. An increasing role of physiotherapy has recently been recognized; comorbid depression, anxiety, and pain may be treated pharmacologically. Patients with hypochondriasis, factitious disorders, and malingering have a poor prognosis.

FURTHER READING

- A A et al: Therapeutic advances in dystonia. *Mov Disord* 30:1547, 2015.
- B B, B KP: Dystonia: An update on phenomenology, classification, pathogenesis and treatment. *Curr Opin Neurol* 27:468, 2014.
- B KP et al: Consensus statement on the classification of tremors from the task force on tremor of the International Parkinson and Movement Disorder Society. *Mov Disord* 33:75, 2018.
- B A, J J: Current management of tics and Tourette syndrome: Behavioral, pharmacologic, and surgical treatments. *Neurotherapeutics* 17:1681, 2020.
- E AJ et al: Essential pitfalls in “essential” tremor. *Mov Disord* 32:325, 2017.
- E AJ et al: Current concepts in diagnosis and treatment of functional neurological disorders. *JAMA Neurol* 75:1132, 2018.
- K K et al: Huntington’s disease: Current and future therapeutic prospects. *Mov Disorders* 33:1033, 2018.
- K P et al: Current applications and limitations of surgical treatments for movement disorders. *Mov Disord* 32:36, 2017.
- M C et al: Nomenclature of genetic movement disorders: Recommendations of the International Parkinson and Movement Disorder Society task force. *Mov Disord* 32:724, 2017.
- M TA: Recent advances in the therapeutic development for Huntington disease. *Parkinsonism Relat Disord* 59:125, 2019.
- P L, F A: Huntington’s disease: New frontiers in therapeutics. *Curr Neurol Neurosci Rep* 21:10, 2021.
- T SJ et al: Targeting Huntington expression in patients with Huntington’s disease. *N Engl J Med* 380:2307, 2019.
- V D V S et al: Nomenclature of genetically determined myoclonus syndromes: Recommendations of the International Parkinson and Movement Disorder Society Task Force. *Mov Disord* 34:1602, 2019.

Robert H. Brown, Jr.



AMYOTROPHIC LATERAL SCLEROSIS ALS

ALS is the most common progressive motor neuron disease. It is a prime example of a neurodegenerative disease and is arguably the most devastating of the neurodegenerative disorders.

PATHOLOGY

The pathologic hallmark of motor neuron degenerative disorders is death of lower motor neurons (consisting of anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to synapse with lower motor neurons, either directly or indirectly via interneurons) (Chap. 24). Although at its onset ALS may involve selective loss of function of only upper or lower motor neurons, it ultimately causes progressive loss of both categories of motor neurons. Indeed, in the absence of clear involvement of both motor neuron types, the diagnosis of ALS is questionable. In a subset of cases, ALS arises concurrently with frontotemporal dementia (Chap. 432); in these instances, there is degeneration of frontotemporal cortical neurons and corresponding cortical atrophy.

Other motor neuron diseases involve only particular subsets of motor neurons (Tables 437-1 and 437-2). Thus, in bulbar palsy and spinal muscular atrophy (SMA; also called *progressive muscular atrophy*), the lower motor neurons of brainstem and spinal cord, respectively, are most severely involved. By contrast, pseudobulbar palsy, primary lateral sclerosis (PLS), and hereditary spastic paraparesis (HSP) affect only upper motor neurons innervating the brainstem and spinal cord.

In each of these diseases, the affected motor neurons undergo shrinkage, often with accumulation of the pigmented lipid (lipofuscin) that normally develops in these cells with advancing age. In ALS, the motor neuron cytoskeleton is typically affected early in the illness. Focal enlargements are frequent in proximal motor axons; ultrastructurally, these “spheroids” are composed of accumulations of neurofilaments and other proteins. Commonly in both sporadic and familial ALS, the affected neurons demonstrate ubiquitin-positive aggregates, typically associated with the protein TDP43 (see below). Also seen is proliferation of astroglia and microglia, the inevitable accompaniment of all degenerative processes in the central nervous system (CNS).

The death of the peripheral motor neurons in the brainstem and spinal cord leads to denervation and atrophy of the corresponding muscle fibers. Histochemical and electrophysiologic evidence indicates that in the early phases of the illness denervated muscle can be reinnervated by sprouting of nearby distal motor nerve terminals, although reinnervation in this disease is considerably less extensive than in most other disorders affecting motor neurons (e.g., poliomyelitis, peripheral neuropathy). As denervation progresses, muscle atrophy is readily recognized in muscle biopsies and on clinical examination. This is the basis for the term *amyotrophy*. The loss of cortical motor neurons results in thinning of the corticospinal tracts that travel via the internal capsule (Fig. 437-1) and pyramidal tracts in the brainstem to the lateral and anterior white matter columns of the spinal cord. The loss of fibers in the lateral columns and resulting fibrillary gliosis impart a particular firmness (*lateral sclerosis*). A remarkable feature of the disease is the selectivity of neuronal cell death. By light microscopy, the entire sensory apparatus and cerebellar structures that control the coordination of movement remain intact. Except in cases of frontotemporal dementia, the components of the brain required for cognitive processing are also preserved. However, immunostaining indicates that neurons bearing ubiquitin, a marker for degeneration, are also detected

TABLE 437-1 Etiology of Motor Neuron Disorders

DIAGNOSTIC CATEGORY	INVESTIGATION
Structural lesions	
Parasagittal or foramen magnum tumors	MRI scan of head (including foramen magnum and cervical spine)
Cervical spondylosis	
Chiari malformation of syrinx	
Spinal cord arteriovenous malformation	
Infections	CSF exam, culture
Bacterial—tetanus, Lyme	Lyme titer
Viral—poliomyelitis, herpes zoster	Antiviral antibody
Retroviral—myelopathy	HTLV-1 titers
Intoxications, physical agents	24-h urine for heavy metals
Toxins—lead, aluminum, others	Serum lead level
Drugs—strychnine, phenytoin	
Electric short, x-irradiation	
Immunologic mechanisms	Complete blood count ^a
Plasma cell dyscrasias	Sedimentation rate ^a
Autoimmune polyradiculopathy	Total protein ^a
Motor neuropathy with conduction block	Anti-GM 1 antibodies ^a
Paraneoplastic	Anti-Hu antibody
Paracarcinomatous	MRI scan, bone marrow biopsy
Metabolic	Fasting blood sugar ^a
Hypoglycemia	Routine chemistries including calcium ^a
Hyperparathyroidism	PTH
Hyperthyroidism	Thyroid function ^a
Deficiency of folate, vitamin B ₁₂ , vitamin E	Vitamin B ₁₂ , vitamin E, folate ^a
Malabsorption	Serum zinc, copper ^a
Deficiency of copper, zinc	24-h stool fat, carotene, prothrombin time
Mitochondrial dysfunction	Fasting lactate, pyruvate, ammonia
Hyperlipidemia	Lipid electrophoresis
Hyperglycinuria	Urine and serum amino acids CSF amino acids
Hereditary disorders	WBC or cheek swab DNA for mutational analysis
C9orf72	
Superoxide dismutase	
TDP43	
FUS/TLS	
Androgen receptor defect (Kennedy's disease)	

^aShould be obtained in all cases.

Abbreviations: CSF, cerebrospinal fluid; FUS/TLS, fused in sarcoma/translocated in liposarcoma; HTLV-1, human T-cell lymphotropic virus; MRI, magnetic resonance imaging; PTH, parathyroid; WBC, white blood cell.

in nonmotor systems. Moreover, studies of glucose metabolism in the illness also indicate that there is neuronal dysfunction outside of the motor system. Pathologic studies reveal proliferation of microglial cells and astrocytes in affected regions; in some cases, this phenomenon, designated neuroinflammation, can be visualized using positron emission tomography (PET) scanning for ligands that are recognized by activated microglia. Within the motor system, there is some selectivity of involvement. Thus, motor neurons required for ocular motility remain unaffected, as do the parasympathetic neurons in the sacral spinal cord (the nucleus of Onufrowicz, or Onuf) that innervate the sphincters of the bowel and bladder.

■ CLINICAL MANIFESTATIONS

The manifestations of ALS are somewhat variable depending on whether corticospinal neurons or lower motor neurons in the brainstem and spinal cord are more prominently involved. With lower

TABLE 437-2 Sporadic Motor Neuron Diseases

CHRONIC	ENTITY
Upper and lower motor neuron	Amyotrophic lateral sclerosis
Predominantly upper motor neuron	Primary lateral sclerosis
Predominantly lower motor neuron	Multifocal motor neuropathy with conduction block Motor neuropathy with paraproteinemia or cancer Motor predominant peripheral neuropathies
OTHER	
Associated with other neurodegenerative disorders	
Secondary motor neuron disorders (see Table 437-1)	
ACUTE	
Poliomyelitis	
Herpes zoster	
Coxsackie virus	
West Nile virus	

motor neuron dysfunction and early denervation, typically the first evidence of the disease is insidiously developing asymmetric weakness, usually first evident distally in one of the limbs. A detailed history often discloses recent development of cramping with volitional movements, typically in the early hours of the morning (e.g., while stretching in bed). Weakness caused by denervation is associated with progressive wasting and atrophy of muscles and, particularly early in the illness, spontaneous twitching of motor units, or fasciculations. In the hands, a preponderance of extensor over flexor weakness is common. When the initial denervation involves bulbar rather than limb muscles, the problem at onset is difficulty with chewing, swallowing, and movements of the face and tongue. Rarely, early involvement of the muscles of respiration may lead to death before the disease is far advanced

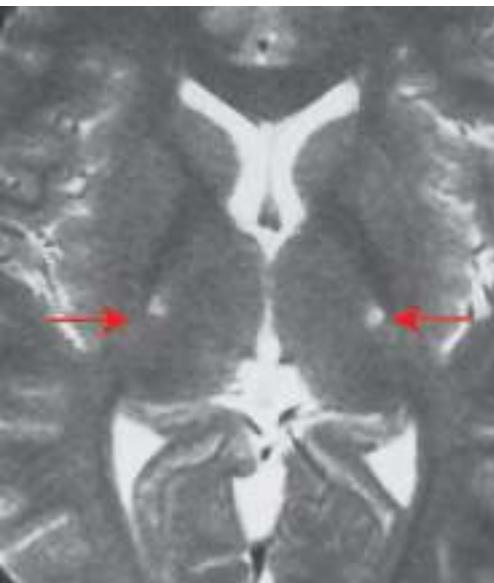


FIGURE 437-1 Amyotrophic lateral sclerosis. Axial T2-weighted magnetic resonance imaging (MRI) scan through the lateral ventricles of the brain reveals abnormal high signal intensity within the corticospinal tracts (arrows). This MRI feature represents an increase in water content in myelin tracts undergoing Wallerian degeneration secondary to cortical motor neuronal loss. This finding is commonly present in ALS but can also be seen in AIDS-related encephalopathy, infarction, or other disease processes that produce corticospinal neuronal loss in a symmetric fashion.

elsewhere. With prominent corticospinal involvement, there is hyperactivity of the muscle-stretch reflexes (tendon jerks) and, often, spastic resistance to passive movements of the affected limbs. Patients with significant reflex hyperactivity complain of muscle stiffness often out of proportion to weakness. Degeneration of the corticobulbar projections innervating the brainstem results in dysarthria and exaggeration of the motor expressions of emotion. The latter leads to involuntary excess in weeping or laughing (pseudobulbar affect).

Virtually any muscle group may be the first to show signs of disease, but, as time passes, more and more muscles become involved until ultimately the disorder takes on a symmetric distribution in all regions. It is characteristic of ALS that, regardless of whether the initial disease involves upper or lower motor neurons, both will eventually be implicated. Even in the late stages of the illness, sensory, bowel and bladder, and cognitive functions are preserved. Even when there is severe brainstem disease, ocular motility is spared until the very late stages of the illness. As noted, in some cases (particularly those that are familial), ALS develops concurrently with frontotemporal dementia, characterized by early behavioral abnormalities with prominent behavioral features indicative of frontal lobe dysfunction.

A committee of the World Federation of Neurology has established diagnostic guidelines for ALS. Essential for the diagnosis is simultaneous upper and lower motor neuron involvement with progressive weakness and the exclusion of all alternative diagnoses. The disorder is ranked as “definite” ALS when three or four of the following are involved: bulbar, cervical, thoracic, and lumbosacral motor neurons. When two sites are involved, the diagnosis is “probable,” and when only one site is implicated, the diagnosis is “possible.” An exception is made for those who have progressive upper and lower motor neuron signs at only one site and a mutation in the gene encoding superoxide dismutase (SOD1; see below).

It is now recognized that another clinical manifestation in most cases of ALS is the presence in cerebrospinal fluid (CSF) of markers of neurodegeneration, such as elevated levels of neurofilament light chains or phosphorylated neurofilament heavy chains; some markers of inflammation (e.g., monocyte chemoattractant protein 1) are also elevated. These CSF biomarkers are increasingly used as endpoints in clinical trials.

■ EPIDEMIOLOGY

The illness is relentlessly progressive, leading to death from respiratory paralysis; the median survival is from 3 to 5 years. There are very rare reports of stabilization or even regression of ALS. In most societies, there is an incidence of 1–3 per 100,000 and a prevalence of 3–5 per 100,000. It is striking that at least 1 in 1000 deaths in North America and Western Europe (and probably elsewhere) are due to ALS; this finding predicts that more than 300,000 individuals now alive in the United States will die of ALS. Several endemic foci of higher prevalence exist in the western Pacific (e.g., in specific regions of Guam or Papua New Guinea). In the United States and Europe, men are somewhat more frequently affected than women. Epidemiologic studies have incriminated risk factors for this disease including exposure to pesticides and insecticides, silica, smoking, and possibly service in the military. Although ALS is overwhelmingly a sporadic disorder, some 10% of cases are inherited as an autosomal dominant trait.

■ FAMILIAL ALS

Several forms of selective motor neuron disease are inheritable (Table 437-3). Familial ALS (FALS) involves both corticospinal and lower motor neurons. Apart from its inheritance as an autosomal dominant trait, it is clinically indistinguishable from sporadic ALS. Genetic studies have identified mutations in multiple genes, including those encoding the protein C9orf72 (open reading frame 72 on chromosome 9), cytosolic enzyme SOD1 (superoxide dismutase), the RNA binding proteins TDP43 (encoded by the TAR DNA binding protein gene), and fused in sarcoma/translocated in liposarcoma (FUS/TLS), as the most common causes of FALS. Mutations in C9orf72 account for ~45–50% of FALS and perhaps 5–10% of sporadic ALS cases. Mutations in SOD1

explain another 20% of cases of FALS, whereas TDP43 and FUS/TLS each represent about 5% of familial cases. Mutations in several other genes (such as optineurin, TBK1 and profilin-1) each cause about ~1% of cases.

Rare mutations in other genes are also clearly implicated in ALS-like diseases. Thus, a familial, dominantly inherited motor disorder that in some individuals closely mimics the ALS phenotype arises from mutations in senataxin, a helicase, cause an early-adult-onset, slowly evolving ALS variant. Kennedy’s syndrome is an X-linked, adult-onset disorder that may mimic ALS, as described below. Tau gene mutations usually underlie frontotemporal dementia, but in some instances may be associated with prominent motor neuron findings.

Genetic analyses are also beginning to illuminate the pathogenesis of some childhood-onset motor neuron diseases. For example, a slowly disabling degenerative, predominantly upper motor neuron disease that starts in the first decade is caused by mutations in a gene that expresses a novel signaling molecule with properties of a guanine-exchange factor, termed *alsin*.

■ DIFFERENTIAL DIAGNOSIS

Because ALS is currently untreatable, it is imperative that potentially remediable causes of motor neuron dysfunction be excluded (Table 437-1). This is particularly true in cases that are atypical by virtue of (1) restriction to either upper or lower motor neurons, (2) involvement of neurons other than motor neurons, and (3) evidence of motor neuronal conduction block on electrophysiologic testing. Compression of the cervical spinal cord or cervicomедullary junction from tumors in the cervical regions or at the foramen magnum or from cervical spondylosis with osteophytes projecting into the vertebral canal can produce weakness, wasting, and fasciculations in the upper limbs and spasticity in the legs, closely resembling ALS. The absence of cranial nerve involvement may be helpful in differentiation, although some foramen magnum lesions may compress the twelfth cranial (hypoglossal) nerve, with resulting paralysis of the tongue. Absence of pain or of sensory changes, normal bowel and bladder function, normal radiologic studies of the spine, and normal CSF all favor ALS. Where doubt exists, MRI scans and possibly contrast myelography should be performed to visualize the cervical spinal cord.

Another important entity in the differential diagnosis of ALS is *multiplex motor neuropathy with conduction block* (MMCB), discussed below. A diffuse, lower motor axonal neuropathy mimicking ALS sometimes evolves in association with hematopoietic disorders such as lymphoma or multiple myeloma. In this clinical setting, the presence of an M-component in serum should prompt consideration of a bone marrow biopsy. Lyme disease (Chap. 186) may also cause an axonal, lower motor neuropathy, although typically with intense proximal limb pain and a CSF pleocytosis.

Other treatable disorders that occasionally mimic ALS are chronic lead poisoning and thyrotoxicosis. These disorders may be suggested by the patient’s social or occupational history or by unusual clinical features. When the family history is positive, disorders involving the genes encoding C9orf72, cytosolic SOD1, TDP43, FUS/TLS, and adult hexosaminidase A or α -glucosidase deficiency must be excluded (Chap. 418). These are readily identified by appropriate laboratory tests; importantly, panels for simultaneous analysis of multiple ALS and FTD genes are now commercially available. Benign fasciculations are occasionally a source of concern because on inspection they resemble the fascicular twitchings that accompany motor neuron degeneration. The absence of weakness, atrophy, or denervation phenomena on electrophysiologic examination usually excludes ALS or other serious neurologic disease. Patients who have recovered from poliomyelitis may experience a delayed deterioration of motor neurons that presents clinically with progressive weakness, atrophy, and fasciculations. Its cause is unknown, but it is thought to reflect subtle prior injury to motor neurons by poliovirus (Chap. 204).

Rarely, ALS develops concurrently with features indicative of more widespread neurodegeneration. Thus, one infrequently encounters

TABLE 437-3 Selected Genetic Motor Neuron Diseases

DISEASE	GENE SYMBOL	GENE NAME	INHERITANCE	FREQUENCY (IN THE UNITED STATES)	USUAL ONSET	PROTEIN FUNCTION	UNUSUAL FEATURES
I. Upper and Lower Motor Neurons (Familial ALS)							
ALS1	SOD1	Cu/Zn superoxide dismutase 1	AD	20% FALS	Adult	Protein antioxidant	
ALS2	ALS2	Alsin	AR	<1% FALS	Juvenile	GEF signaling	Severe corticobulbar, corticospinal features may mimic PLS; childhood onset
ALS4	SETX	Senataxin	AD	~1% FALS	Late juvenile	DNA helicase	Late-childhood onset
ALS6	FUS/TLS	Fused in sarcoma/translocated in liposarcoma	AD	5% FALS	Adult	DNA, RNA binding	
ALS8/SMA	VAPB	Vesicle-associated protein B	AD	<1%	Adult	Vesicular trafficking	
ALS10	TARDBP	TAR DNA binding protein	AD	5% FALS	Adult	DNA, RNA binding	
ALS12	OPTN	Optineurin	AD/AR	~1% FALS	Adult	Attenuates NF-κB	
ALS14	VCP	Valosin-containing protein	AD	~ 1% FALS	Adult	ATPase	
ALS18	PFN1	Profilin 1	AD	~1% FALS	Adult	Involved in actin polymerization	
ALS20	HNRNPA1	Heterogeneous nuclear ribonucleoprotein A1	AD	<1%	Adult	Heteronuclear RNA binding protein	
ALS	DCTN1	Dynactin	AD	<1%	Adult	Axonal transport	May cause vocal cord paralysis or PLSe
ALS-FTD	TBK1	Tank-binding kinase 1	AD		Adult	NF-κB signaling	Also mimics PLS
ALS-FTD	UBQLN2	Ubiquilin 2	X-LD	<1%	Adult or juvenile	Protein degradation	
ALS-FTD	CHMP2B	Chromatin-modifying protein 2B	AD	<1% FALS	Adult	Chromatin-binding protein	
ALS-FTD	C9ORF72	Chromosome 9 open reading frame 72	AD	40–50% FALS	Adult	Regulates vesicle trafficking	May also be associated with parkinsonism, PLS
ALS-FTD	MAPT	Microtubule-associated protein Tau	AD		Adult	Cytoskeletal protein	Usually causes only FTD
II. Lower Motor Neurons							
Spinal muscular atrophies	SMN	Survival motor neuron	AR	1/10,000 live births	Infancy	RNA metabolism	
GM2-gangliosidosis							
1. Sandhoff's disease	HEXB	Hexosaminidase B	AR		Childhood	Ganglioside recycling	
2. AB variant	GM2A	GM2-activator protein	AR		Childhood	Ganglioside recycling	
3. Adult Tay-Sachs disease	HEXA	Hexosaminidase A	AR		Childhood	Ganglioside recycling	
X-linked spinobulbar muscular atrophy	AR	Androgen receptor	XR		Adult	Nuclear signaling	
III. Upper Motor Neuron (Selected HSPs)							
SPG3A	ATL1	Atlastin	AD	10% AD FSP	Childhood	GTPase—vesicle recycling	
SPG4	SPAST	Spastin	AD	50–60% AD FSP	Early adulthood	ATPase family—microtubule associate	Some sensory loss
SPG6	NIPA1	Nonimprinted in Prader-Willi/Angelman syndrome 1	AD		Early adulthood	Membrane transporter or receptor	Deleted in Prader-Willi, Angelman's
SPG8	WASHC5	Strumpellin	AD		Early adulthood	Ubiquitous, spectrin-like	
SPG10	KIF5A	Kinesin heavy-chain isoform 5A	AD	10% AD FSP	Second–third decade	Motor-associated protein	± Peripheral neuropathy, retardation
SPG31	REEP1	Receptor expression enhancing protein 1	AD	10% AD FSP	Early	Mitochondrial protein	Rarely, amyotrophy

(Continued)

TABLE 437-3 Selected Genetic Motor Neuron Diseases (Continued)

DISEASE	GENE SYMBOL	GENE NAME	INHERITANCE	FREQUENCY (IN THE UNITED STATES)	USUAL ONSET	PROTEIN FUNCTION	UNUSUAL FEATURES
SPG5	CYP7B1	Cytochrome P450	AR	5–10% AR FSP	Variable	Degrades endogenous substances	Sensory loss
SPG7	SPG7	Paraplegin	AR	5–10% AR FSP	Variable	Mitochondrial protein	Rarely, optic atrophy, ataxia, rarely PLS
SPG11	SPG11	Spatacsin	AR	20–70% AR FSP depends on ethnicity	Predominantly childhood	Cytosolic, ? membrane-associated	Some sensory loss, thin corpus callosum; may mimic ALS (ALS5)
SPG39	PNPLA6	Patatin-like phospholipase domain-containing protein 6 / neuropathy target esterase	AR		Early childhood	Esterase	May have PLS-like phenotype
SPG44	GJC2	Gap junction protein gamma 2/ Connexin 47	AR		Childhood	Gap junction protein	Possible mild CNS features
SPG2	PLP	Proteolipid protein	XR		Early childhood	Myelin protein	Sometimes multiple CNS features
SPG1	L1-CAM	Neural cell adhesion molecule L1 precursor	XR		Infancy	Cell adhesion molecule	
Adrenoleukodystrophy	ABCD1	Adrenoleukodystrophy protein	XR		Early adulthood	ATP binding transporter protein	Possible adrenal insufficiency, CNS inflammation

Abbreviations: AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; BSCL2, Bernadelli-Seip congenital lipodystrophy 2B; CNS, central nervous system; FUS/TLS, fused in sarcoma/translocated in liposarcoma; GEF, Guanidine nucleotide exchange factor; HSP, hereditary spastic paraparesis; TDP43, Tar DNA binding protein 43 kd; XR, X-linked recessive.

otherwise-typical ALS patients with a parkinsonian movement disorder or frontotemporal dementia, particularly in instances of C9orf72 mutations, which strongly suggests that the simultaneous occurrence of two disorders is a direct consequence of the gene mutation. As another example, prominent amyotrophy has been described as a dominantly inherited disorder in individuals with bizarre behavior and a movement disorder suggestive of parkinsonism; many such cases have now been ascribed to mutations that alter the expression of tau protein in the brain (Chap. 432). In other cases, ALS develops simultaneously with a striking frontotemporal dementia. An ALS-like disorder has also been described in some individuals with chronic traumatic encephalopathy, associated with deposition of TDP43 and neurofibrillary tangles in motor neurons.

PATHOGENESIS

The cause of sporadic ALS is not well defined. Several mechanisms that impair motor neuron viability have been elucidated in rodents induced to develop motor neuron disease by SOD1 or profilin-1 transgenes with ALS-associated mutations. One may loosely group the genetic causes of ALS into three categories. In one group, the primary problem is inherent instability of the mutant proteins, with subsequent perturbations in protein degradation (SOD1, ubiquilin-1 and 2, p62). In the second category, the causative mutant genes perturb RNA processing, transport, and metabolism (C9orf73, TDP43, FUS). In the case of C9orf72, the molecular pathology is an expansion of an intronic hexanucleotide repeat (-GGGGCC-) beyond an upper normal of 30 repeats to hundreds or even thousands of repeats. As observed in other intronic repeat disorders such as myotonic dystrophy (Chap. 449) and spinocerebellar atrophy type 8 (Chap. 439), the expanded intronic repeats generate expanded RNA repeats that form intranuclear foci and may confer toxicity by sequestering transcription factors or by undergoing noncanonical protein translation across all possible reading frames of the expanded RNA tracts. Importantly, the latter process generates lengthy dipeptides that are detected in the spinal fluid and are a unique biomarker for C9orf72 ALS. TDP43 and FUS are multifunctional proteins that bind RNA and DNA and shuttle between the nucleus and the cytoplasm, playing multiple roles in the control of cell proliferation, DNA repair and transcription,

and gene translation, both in the cytoplasm and locally in dendritic spines in response to electrical activity. How mutations in FUS/TLS provoke motor neuron cell death is not clear, although this may represent loss of function of FUS/TLS in the nucleus or an acquired, toxic function of the mutant proteins in the cytosol. In the third group of ALS genes, the primary problem is defective axonal cytoskeleton and transport (dynactin, profilin-1). It is striking that variants in other genes influence survival in ALS but not ALS susceptibility. Intermediate-length polyglutamine-coding expansions (-CAG-) in the gene *ataxin-2* confer increased ALS susceptibility; suppression of ataxin-2 expression extends survival in transgenic ALS mice and is the basis for clinical trials of ataxin-2 suppression. Beyond the upstream, primary defects, it is also evident that the ultimate neuronal cell death process is complex, involving multiple cellular processes acting in diverse components of the motor neuron (dendrites, cell body, axons, neuromuscular junction) to accelerate cell death. These include but are not limited to excitotoxicity, defective autophagy, impairment of axonal transport, oxidative stress, activation of endoplasmic reticulum stress and the unfolded protein response, and mitochondrial dysfunction. As well, the hexanucleotide expansions that cause C9orf72 ALS disrupt nucleocytoplasmic transport; the importance of this observation is underscored by the finding that mutations in the gene encoding GLE1, a protein that mediates mRNA export, cause an aggressive, infantile motor neuron disease.

Multiple studies have convincingly demonstrated that proliferating, activated nonneuronal cells such as microglia and astrocytes importantly influence the disease course, at least in ALS-transgenic mice. A striking additional finding in ALS and most neurodegenerative disorders is that miscreant proteins arising from gene defects in familial forms of these diseases are often implicated in sporadic forms of the same disorder. For example, some reports propose that nonheritable, posttranslational modifications in SOD1 are pathogenic in sporadic ALS; indeed, SOD1 aggregates are sometimes observed in spinal cord in sporadic ALS without SOD1 mutations. Germline mutations in the genes encoding β -amyloid and α -synuclein cause familial forms of Alzheimer's and Parkinson's diseases, and posttranslational, noninherited abnormalities in these proteins are also central to sporadic Alzheimer's and Parkinson's diseases.

TREATMENT

Amyotrophic Lateral Sclerosis

No treatment arrests the underlying pathologic process in ALS. The drug riluzole (100 mg/d) was approved for ALS because it produces a modest lengthening of survival. In one trial, the survival rate at 18 months with riluzole was similar to placebo at 15 months. The mechanism of this effect is not known with certainty; riluzole may reduce excitotoxicity by diminishing glutamate release. Riluzole is generally well tolerated; nausea, dizziness, weight loss, and elevated liver enzymes occur occasionally. A second drug, edaravone, has also been approved by the U.S. Food and Drug Administration based on a single 6-month study in a highly selected ALS population that demonstrated a modest reduction in the trajectory of worsening on an ALS disability scale; survival was not included as an endpoint. This drug, which is believed to act as an antioxidant, is administered via recurring monthly 10-day series of daily intravenous infusions. Recently the combined oral administration of phenylbutyrate and taurursodiol was reported to slow progression and prolong survival in ALS by improving function in mitochondria and the endoplasmic reticulum.

Interventions such as antisense oligonucleotides (ASO) and microRNAs that diminish expression of mutant SOD1 protein prolong survival in transgenic-ALS rodent models and are also now in clinical trials for SOD1-mediated ALS; initial pilot data from human trials document reductions in SOD1 levels but have not yet shown clear clinical benefit. Human trials are now also underway for promising ASOs that suppress expression of the C9orf72 gene. Pathophysiologic studies of mutant SOD1-related ALS in mice have disclosed diverse targets for therapy; consequently, multiple therapies are presently in clinical trials for ALS including experimental trials of small molecules, mesenchymal stem cells, and immunosuppression.

In the absence of a primary therapy for ALS, a variety of rehabilitative aids may substantially assist ALS patients. Foot-drop splints facilitate ambulation by obviating the need for excessive hip flexion and by preventing tripping on a floppy foot. Finger-extension splints can potentiate grip. Respiratory support may be life-sustaining. For patients electing against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (weeks to months) relief from hypercarbia and hypoxia. Also extremely beneficial for some patients is a respiratory device (cough assist machine) that produces an artificial cough. This is highly effective in clearing airways and preventing aspiration pneumonia. When bulbar disease prevents normal chewing and swallowing, gastrostomy is uniformly helpful, restoring normal nutrition and hydration. Fortunately, an increasing variety of speech synthesizers are now available to augment speech when there is advanced bulbar palsy. These facilitate oral communication and may be effective for telephone use.

In contrast to ALS, several of the disorders (Tables 437-1 and 437-3) that bear some clinical resemblance to ALS are treatable. For this reason, a careful search for causes of secondary motor neuron disease is warranted.

OTHER MOTOR NEURON DISEASES

■ SELECTED LOWER MOTOR NEURON DISORDERS

In these motor neuron diseases, the peripheral motor neurons are affected without evidence of involvement of the corticospinal motor system (Tables 437-1, 437-2, and 437-3).

X-Linked Spinobulbar Muscular Atrophy (Kennedy's Disease) This is an X-linked lower motor neuron disorder in which progressive weakness and wasting of limb and bulbar muscles begins in males in mid-adult life and is conjoined with androgen insensitivity manifested by gynecomastia and reduced fertility (Chap. 391). In addition to gynecomastia, which may be subtle, two findings distinguishing this

disorder from ALS are the absence of signs of pyramidal tract disease (spasticity) and the presence of a subtle sensory neuropathy in some patients. The underlying molecular defect is an expanded trinucleotide repeat (CAG) in the first exon of the androgen receptor gene on the X chromosome. An inverse correlation appears to exist between the number of CAG repeats and the age of onset of the disease.

Adult Tay-Sachs Disease Several reports have described adult-onset, predominantly lower motor neuropathies arising from deficiency of the enzyme β -hexosaminidase (hex A). These tend to be distinguishable from ALS because they are very slowly progressive and in some cases may have been symptomatic for years; dysarthria and radiographically evident cerebellar atrophy may be prominent. In rare cases, spasticity may also be present, although it is generally absent (Chap. 419).

Spinal Muscular Atrophy The SMAs are a family of selective lower motor neuron diseases of early onset. Despite some phenotypic variability (largely in age of onset), the defect in the majority of families with SMA is loss of a protein (SMN, for survival motor neuron) that is important in the formation and trafficking of RNA complexes across the nuclear membrane. Neuropathologically these disorders are characterized by extensive loss of large motor neurons; muscle biopsy reveals evidence of denervation atrophy. Several clinical forms exist.

Infantile SMA (SMA I, Werdnig-Hoffmann disease) has the earliest onset and most rapidly fatal course. In some instances, it is apparent even before birth, as indicated by decreased fetal movements late in the third trimester. Though alert, afflicted infants are weak and floppy (hypotonic) and lack muscle-stretch reflexes. Death generally ensues within the first year of life. **Chronic childhood SMA** (SMA II) begins later in childhood and evolves with a more slowly progressive course. **Juvenile SMA** (SMA III, Kugelberg-Welander disease) manifests during late childhood and runs a slow, indolent course. Unlike most denervating diseases, in this chronic disorder weakness is greatest in the proximal muscles; indeed, the pattern of clinical weakness can suggest a primary myopathy such as limb-girdle dystrophy. Electrophysiologic and muscle biopsy evidence of denervation distinguish SMA III from the myopathic syndromes. Remarkably, two treatments have shown dramatic benefit in infantile SMA. One, nusinersen, now an approved therapy, entails administering small oligonucleotides that alter mRNA splicing of one of the SMN genes, generating sufficient normal SMN protein to provide clinical benefit (including prolonged survival). The other treatment uses systemically administered adeno-associated virus (AAV) to deliver the missing SMN gene to motor neurons and other cells.

Multifocal Motor Neuropathy with Conduction Block In this disorder, lower motor neuron function is regionally and chronically disrupted by focal blocks in conduction. Many cases have elevated serum titers of mono- and polyclonal antibodies to ganglioside GM1; it is hypothesized that the antibodies produce selective, focal, paranodal demyelination of motor neurons. MMCB is not typically associated with corticospinal signs. In contrast with ALS, MMCB may respond dramatically to therapy such as IV immunoglobulin or chemotherapy; thus, it is imperative that MMCB be excluded when considering a diagnosis of ALS.

Other Forms of Lower Motor Neuron Disease In individual families, other syndromes characterized by selective lower motor neuron dysfunction in an SMA-like pattern have been described. There are rare X-linked and autosomal dominant forms of apparent SMA. There is an ALS variant of juvenile onset, the Fazio-Londe syndrome, that involves mainly the musculature innervated by the brainstem. A component of lower motor neuron dysfunction is also found in degenerative disorders such as Machado-Joseph disease and the related olivopontocerebellar degenerations (Chap. 439).

■ SELECTED DISORDERS OF THE UPPER MOTOR NEURON

Primary Lateral Sclerosis This rare disorder arises sporadically in adults in mid-to-late life. Clinically, PLS is characterized by progressive spastic weakness of the limbs, preceded or followed by spastic dysarthria and dysphagia, indicating combined involvement of the

corticospinal and corticobulbar tracts. Fasciculations, amyotrophy, and sensory changes are absent; neither electromyography nor muscle biopsy shows denervation. On neuropathologic examination, there is selective loss of the large pyramidal cells in the precentral gyrus and degeneration of the corticospinal and corticobulbar projections. The peripheral motor neurons and other neuronal systems are spared. The course of PLS is variable; although long-term survival is documented, the course may be as aggressive as in ALS, with ~3-year survival from onset to death. Early in its course, PLS raises the question of multiple sclerosis or other demyelinating diseases as diagnostic considerations (Chap. 444). A myopathy suggestive of PLS is infrequently seen with infection with the retrovirus human T-cell lymphotropic virus 1 (HTLV-1) (Chap. 442). The clinical course and laboratory testing will distinguish these possibilities.

Hereditary Spastic Paraparesis In its pure form, HSP is usually transmitted as an autosomal trait; most adult-onset cases are dominantly inherited. There are more than 80 genetic types of HSP for which causative mutations in more than 60 genes have been identified. Table 437-3 lists more commonly identified genetic types of HSP. Symptoms usually begin in the third or fourth decade of life, presenting as progressive spastic weakness beginning in the lower extremities; however, there are variants with onset so early that the differential diagnosis includes cerebral palsy. HSP typically has a long survival, presumably because respiratory function is spared. Late in the illness, there may be urinary urgency and incontinence and sometimes fecal incontinence; sexual function tends to be preserved.

In pure forms of HSP, the spastic leg weakness is often accompanied by posterior column (vibration and position) abnormalities and disturbance of bowel and bladder function. Some family members may have spasticity without clinical symptoms.

By contrast, particularly when recessively inherited, HSP may have complex or complicated forms in which altered corticospinal and dorsal column function is accompanied by significant involvement of other regions of the nervous system, including amyotrophy, mental retardation, optic atrophy, and sensory neuropathy.

Neuropathologically, in HSP there is degeneration of the corticospinal tracts, which appear nearly normal in the brainstem but show increasing atrophy at more caudal levels in the spinal cord; in effect, this pathologic picture is of a dying-back or distal axonopathy of long neuronal fibers within the CNS.

Defects at numerous loci underlie both dominantly and recessively inherited forms of HSP (Table 437-3). The gene most commonly implicated in dominantly inherited HSP is *spastin*, which encodes a microtubule interacting protein. The most common childhood-onset dominant form arises from mutations in the *atlastin* gene.

An infantile-onset form of X-linked, recessive HSP arises from mutations in the gene for myelin proteolipid protein. This is an example of rather striking allelic variation, as most other mutations in the same gene cause not HSP but Pelizaeus-Merzbacher disease, a widespread disorder of CNS myelin. Another recessive variant is caused by defects in the *paraplegin* gene. Paraplegin has homology to metalloproteases that are important in mitochondrial function in yeast. A slowly progressive, adult-onset X-linked progressive spastic paraparesis designated adrenomyeloneuropathy is caused by mutations in the ABCD1 gene; these cases are associated with elevated serum levels of very-long-chain fatty acids (Chap. 442).

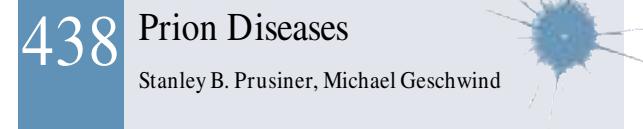
FURTHER READING

- B RH, A -C A: Review article: Amyotrophic lateral sclerosis. N Engl J Med 377:162, 2017.
- F RS et al: Treatment of infantile-onset spinal muscular atrophy with nusinersin: A phase 2, open-label, dose-escalation study. Lancet 388:3017, 2016.
- G TF et al: Poly(GP) proteins are a useful pharmacodynamic marker for C9ORF72-associated amyotrophic lateral sclerosis. Sci Transl Med 9:pii:eaai7866, 2017.
- M TM et al: Phase 1 trial of antisense oligonucleotide tofersen for *SOD1* ALS. N Engl J Med 383:109, 2020.

- M C et al: SOD1 suppression with adeno-associated virus and microRNA in familial ALS. N Engl J Med 383:151, 2020.
- R W, P T: The changing scene of amyotrophic lateral sclerosis. Nat Rev Neurosci 14:248, 2013.
- S R et al: Hereditary spastic paraparesia: Clinicogenetic lessons from 608 patients. Ann Neurol 79:646, 2016.
- T JP et al: Decoding ALS: From genes to mechanism. Nature 539:197, 2016.
- V D P, R W: STING-Induced Inflammation—A Novel Therapeutic Target in ALS? N Engl J Med 384:765, 2021.
- V AE et al: Multicentre, population-based, case-control study of particulates, combustion products and amyotrophic lateral sclerosis risk. J Neurol Neurosurg Psychiatry 90:854, 2019.
- T W G B E (MCI-186) ALS 19 STUDY GROUP: Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: A randomised, double-blind, placebo controlled trial. Lancet Neurol 16:505, 2017.

WEBSITES

Several websites provide valuable information on ALS including those offered by the Muscular Dystrophy Association (www.mdausa.org), the Amyotrophic Lateral Sclerosis Association (www.alsa.org), the World Federation of Neurology and the Neuromuscular Unit at Washington University in St. Louis (www.neuro.wustl.edu), and the Northeast Amyotrophic Lateral Sclerosis Consortium (www.neals.org).



Prions are proteins that adopt alternative conformations, which become self-propagating. Some prions cause degeneration of the central nervous system (CNS). Once relegated to causing a group of rare CNS disorders, such as Creutzfeldt-Jakob disease (CJD), increasing evidence argues that prions cause more common neurodegenerative diseases (NDs) including Alzheimer's disease (AD) and Parkinson's disease (PD). While CJD is caused by the accumulation of PrP^{Sc} prions, recent investigations demonstrate unequivocally that α -synuclein prions cause multiple system atrophy (MSA) (Chap. 440). Infectious MSA prions have been recovered from human brain samples stored in formalin for up to 20 years. Similar resistance to formalin was demonstrated for brain samples from sheep with scrapie. Increasingly, studies show that A β and tau prions together cause AD, α -synuclein prions cause both PD and MSA, and tau prions alone cause frontotemporal lobar degeneration (FTLD). In this chapter, we confine our discussion to CJD, which typically presents with a rapidly progressive dementia as well as motor and behavioral abnormalities. The illness is relentlessly progressive and generally causes death within 7 months of onset. Most patients with CJD are between 50 and 75 years of age; however, patients as young as 12 and as old as 96 have been recorded. The role of prions in the pathogenesis of NDs is reviewed in Chap. 424.

CJD is one malady in a group of disorders caused by prions composed of the prion protein (PrP). PrP prions reproduce by binding to the normal, cellular isoform of the prion protein (PrP^C) and stimulating conversion of PrP^C into the disease-causing isoform PrP^{Sc}. PrP^C is rich in α -helix and has little β -structure, whereas PrP^{Sc} has less α -helix and a high amount of β -structure. The α -to- β structural transition in PrP is the fundamental event underlying this group of prion diseases (Table 438-1).

Four new concepts have emerged from studies of PrP prions: (1) Prions are the only known transmissible pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of

TABLE 438-1 Glossary of PrP Prion Terminology

Prion	Proteinaceous infectious particle that lacks nucleic acid. Prions are composed entirely of alternatively folded proteins that undergo self-propagation. Distinct strains of prions exhibit different biologic properties, which are epigenetically heritable. PrP prions cause scrapie in sheep and goats, mad cow disease, and related neurodegenerative diseases of humans such as Creutzfeldt-Jakob disease (CJD).
PrP^{Sc}	Disease-causing Scrapie isoform of the prion protein. This protein is the only identifiable macromolecule in purified preparations of scrapie prions.
PrP^C	Cellular isoform of the prion protein. PrP ^C is the precursor of PrP ^{Sc} .
PrP 27-30	A fragment of PrP ^{Sc} , generated by truncation of the NH ₂ -terminus by limited digestion with proteinase K. PrP 27-30 retains prion infectivity and polymerizes into amyloid.
PRNP	PrP gene located on human chromosome 20.
Prion rod	An aggregate of prions composed largely of PrP 27-30 molecules. Created by detergent extraction and limited proteolysis of PrP ^{Sc} . Morphologically and histochemically indistinguishable from many amyloids.
PrP amyloid	Amyloid containing PrP in the brains of animals or humans with prion disease; often accumulates as plaques.

either RNA or DNA that direct the synthesis of their progeny. (2) Prion diseases may manifest as infectious, genetic, or sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations. (3) Prion diseases result from the accumulation of PrP^{Sc}, the conformation of which differs substantially from that of its precursor, PrP^C. (4) Distinct strains of prions exhibit different biologic properties, which are epigenetically inherited. In other words, PrP^{Sc} can exist in a variety of different conformations, many of which seem to specify particular disease phenotypes.

How a specific conformation of a PrP^{Sc} molecule is imparted to PrP^C during prion replication to produce nascent PrP^{Sc} with the same conformation is not well understood. Additionally, it is unclear what factors determine where in the CNS a particular PrP^{Sc} molecule will be created.

SPECTRUM OF PRP PRION DISEASES

The sporadic form of CJD is the most common PrP prion disorder in humans. Sporadic CJD (sCJD) accounts for ~85% of all cases of human PrP prion disease, and genetic prion diseases account for 10–15% of all cases (Table 438-2). Genetic prion diseases were historically divided into three forms: familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, and fatal familial insomnia (FFI). All dominantly inherited PrP prion diseases are caused by mutations in the PrP gene.

Although infectious PrP prion diseases account for <1% of all cases and infection does not seem to play an important role in the natural history of these illnesses, the transmissibility of PrP prions is an important biologic feature. Kuru of the Fore people of Papua New Guinea is well established to have resulted from the consumption of brains from dead relatives during ritualistic cannibalism. After the cessation of ritualistic cannibalism in the late 1950s, kuru nearly disappeared, with the exception of a few recent patients exhibiting incubation periods of >40 years. Iatrogenic CJD (iCJD) seems to be the result of the accidental inoculation of patients with prions. Variant CJD (vCJD) in teenagers and young adults in Europe is the result of exposure to tainted beef from cattle with bovine spongiform encephalopathy (BSE). Although occasional cases of iCJD still occur, this form of CJD is currently on the decline due to public health measures aimed at preventing the spread of PrP prions.

More than seven diseases of animals are caused by prions (Table 438-2). Scrapie of sheep and goats is the prototypic PrP prion disease. Mink encephalopathy, BSE, feline spongiform encephalopathy, and exotic ungulate encephalopathy are all thought to occur after the consumption of prion-infected foodstuffs. The BSE epidemic emerged in Britain in the late 1980s and was shown to be due to industrial

TABLE 438-2 The PrP Prion Diseases

DISEASE	HOST	MECHANISM OF PATHOGENESIS
Human		
Kuru	Fore people	Infection through ritualistic cannibalism
iCJD	Humans	Infection from prion-contaminated hGH, dura mater grafts, etc.
vCJD	Humans	Infection from bovine prions
fCJD	Humans	Germline mutations in <i>PRNP</i>
GSS	Humans	Germline mutations in <i>PRNP</i>
FFI	Humans	Germline mutation in <i>PRNP</i> (D178N, M129)
sCJD	Humans	Somatic mutation or spontaneous conversion of PrP ^C into PrP ^{Sc} ?
sFI	Humans	Somatic mutation or spontaneous conversion of PrP ^C into PrP ^{Sc} ?
Animal		
Scrapie	Sheep, goats	Infection in genetically susceptible sheep and goats
BSE	Cattle	Infection with prion-contaminated MBM
TME	Mink	Infection with prions from sheep or cattle
CWD	Mule deer, elk	Unknown
FSE	Cats	Infection with prion-contaminated beef
Exotic ungulate encephalopathy	Greater kudu, nyala, or oryx	Infection with prion-contaminated MBM

Abbreviations: BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; CWD, chronic wasting disease; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FSE, feline spongiform encephalopathy; GSS, Gerstmann-Sträussler-Scheinker disease; hGH, human growth hormone; iCJD, iatrogenic Creutzfeldt-Jakob disease; MBM, meat and bone meal; sCJD, sporadic Creutzfeldt-Jakob disease; sFI, sporadic fatal insomnia; TME, transmissible mink encephalopathy; vCJD, variant Creutzfeldt-Jakob disease.

cannibalism. Whether BSE began as a sporadic case of BSE in a cow or started with scrapie in sheep is unknown. The origin of chronic wasting disease (CWD), a prion disease endemic in deer and elk in regions of North America, and more recently identified in isolated populations in Scandinavia and Korea, is uncertain. In contrast to other prion diseases, CWD is highly communicable among cervids. Bodily excretions, such as feces, urine, and saliva, from asymptomatic, infected cervids contain prions that are likely to be responsible for the spread of CWD.

■ EPIDEMIOLOGY

CJD is found throughout the world. The incidence of sCJD is ~1 case per million population, although a person's lifetime risk of dying from CJD is ~1 in 5000 deaths. Because sCJD is an age-dependent ND, its incidence is expected to increase steadily as older segments of populations in developed and developing countries continue to expand. Although many geographic clusters of CJD have been reported, each has been shown to segregate with a PrP gene mutation and/or included misdiagnoses. Attempts to identify common exposure to some etiologic agent have been unsuccessful for both the sporadic and familial cases. Ingestion of scrapie-infected sheep or goats as a cause of CJD in humans has not been demonstrated by epidemiologic studies, although speculation about this potential route of infection continues. Of particular interest are deer hunters who develop CJD, because up to 90% of culled deer in some game herds have been shown to harbor CWD prions. Whether PrP prion disease in deer, elk, or moose has passed to cows, sheep, or directly to humans remains unknown. Studies with rodents demonstrate that oral infection with prions can occur, but the process is inefficient compared to intracerebral inoculation.

■ PATHOGENESIS

The human PrP prion diseases were initially classified as NDs of unknown etiology on the basis of pathologic changes being confined to the CNS. Even though the familial nature of GSS and a subset of CJD

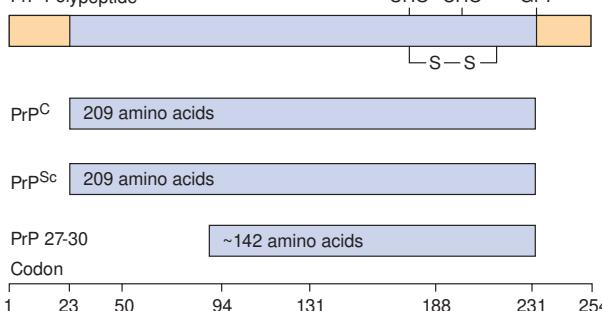


FIGURE 438-1 PrP prion protein isoforms. Bar diagram of Syrian hamster PrP, which consists of 254 amino acids. After processing of the NH₂ and COOH termini, both PrP^C and PrP^{Sc} consist of 209 residues. After limited proteolysis, the NH₂ terminus of PrP^{Sc} is truncated to form PrP 27-30 composed of ~142 amino acids. CHO, N-linked sugars; GPI, glycosylphosphatidylinositol anchor attachment site; S-S, disulfide bond.

cases was well described, the significance of this observation became more obscure with the transmission of GSS and CJD to animals. With the transmission of kuru and CJD to nonhuman primates, investigators began to view these diseases as infectious CNS illnesses caused by slow viruses. Eventually, the familial nature of GSS and a minority of CJD cases became clear with the discovery in 1989 of mutations in the PrP gene (*PRNP*) of these patients. The prion concept explains how a single disease can manifest as sporadic, heritable, and infectious. Moreover, the hallmark of all PrP prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant folding of the PrP protein.

A major feature that distinguishes PrP prions from viruses is the finding that both PrP isoforms are encoded by a chromosomal gene. In humans, the PrP gene is designated *PRNP* and is located on the short arm of chromosome 20. Limited proteolysis of PrP^{Sc} produces a smaller, protease-resistant molecule of ~142 amino acids designated PrP 27-30; PrP^C is completely hydrolyzed under the same conditions (Fig. 438-1). PrP 27-30 polymerizes into prion rods that are morphologically indistinguishable from the filaments that aggregate to form PrP amyloid plaques in the CNS. This discovery raised the possibility that many other NDs might be caused by different proteins, all of which can fold into prions.

Prion Strains Distinct strains of PrP prions exhibit different biologic properties, which are epigenetically heritable. The existence of prion strains raised the question of how heritable biologic information can be enciphered in a molecule other than nucleic acid. Various strains of PrP prions have been defined by incubation times, distribution of neuronal vacuolation on neuropathology, and stabilities of PrP^{Sc} to denaturation. Subsequently, the patterns of PrP^{Sc} deposition were found to correlate with vacuolation profiles, and these patterns were also used to characterize prion strains.

Persuasive evidence that strain-specific information is enciphered in the tertiary structure of PrP^{Sc} comes from transmission of two different

inherited human prion diseases to mice expressing a chimeric human–mouse PrP transgene. In most forms of fCJD and the majority of sCJD cases, the protease-resistant fragment of PrP^{Sc} after deglycosylation has a molecular mass of 21 kDa (i.e., type 1 prions), whereas in FFI, and a minority of sCJD cases, it is 19 kDa (type 2 prions) (Table 438-3). This difference in molecular mass was shown to be due to different sites of proteolytic cleavage at the NH₂ termini of the two human PrP^{Sc} molecules, reflecting different tertiary structures. These distinct conformations were not unexpected because the amino acid sequences of the PrP fragments differ. Extracts from the brains of patients with FFI transmitted disease to the mice expressing the chimeric human–mouse PrP transgene and resulted in the formation of 19-kDa PrP^{Sc}, whereas brain extracts from fCJD and sCJD patients harboring 21-kDa PrP^{Sc} resulted in 21-kDa PrP^{Sc} in mice expressing the same transgene. On second passage, these differences were maintained, demonstrating that chimeric PrP^{Sc} can exist in two different conformations as demonstrated by the sizes of the protease-resistant fragments, even though the amino acid sequence of PrP^{Sc} is invariant.

This analysis was extended when patients with sporadic fatal insomnia (sFI) were identified. Although they did not carry a *PRNP* mutation, the patients demonstrated a clinical and pathologic phenotype that was indistinguishable from that of patients with FFI. Furthermore, 19-kDa PrP^{Sc} was found in their brains, and on passage of sFI prion disease to mice expressing the chimeric human–mouse PrP transgene, 19-kDa PrP^{Sc} was also found. These findings indicate that the disease phenotype is dictated by the conformation of PrP^{Sc} and not the amino acid sequence. PrP^{Sc} acts as a template for the conversion of PrP^C into nascent PrP^{Sc}. On the passage of prions into mice expressing a chimeric hamster–mouse PrP transgene, a change in the conformation of PrP^{Sc} was accompanied by the emergence of a new strain of prions.

Many new strains of prions were generated using recombinant (rec) PrP produced in bacteria; recPrP was polymerized into amyloid fibrils to make “synthetic prions,” which were inoculated into transgenic mice over-expressing high levels of wild-type mouse PrP^C. Approximately 500 days later, the mice died of prion disease. The incubation times of the “synthetic prions” in mice were dependent on the conditions used for polymerization of the amyloid fibrils, which affected the stability of those amyloid fibrils. Highly stable amyloids gave rise to stable prions with long incubation times; low-stability amyloids led to prions with short incubation times. Amyloids of intermediate stability gave rise to prions with intermediate stabilities and intermediate incubation times. Such findings are consistent with earlier studies showing that the incubation times of synthetic and naturally occurring prions are directly proportional to the stability of the prion.

Species Barrier Studies on the role of the primary and tertiary structures of PrP in the transmission of prion disease have provided new insights into the pathogenesis of these maladies. The amino acid sequence of PrP encodes the species of the prion, and the prion derives its PrP^{Sc} sequence from the last mammal in which it was passaged. While the primary structure of PrP is likely to be the most important or even the sole determinant of the tertiary structure of PrP^C, PrP^{Sc} seems to function as a template in determining the tertiary structure of nascent PrP^{Sc} molecules as they are formed from PrP^C. In turn, prion

TABLE 438-3 Distinct Prion Strains Generated in Humans with Inherited Prion Diseases and Transmitted to Transgenic Mice*

INOCULUM	HOST SPECIES	HOST PrP GENOTYPE	INCUBATION TIME [DAYS ± SEM] (n/n)	PrP ^{Sc} (kDa)
None	Human	fCJD(E200K)		19
FFI	Mouse	Tg(MHu2M)	206 ± 7 (7/7)	19
FFI → Tg(MHu2M)	Mouse	Tg(MHu2M)	136 ± 1 (6/6)	19
None	Human	fCJD(E200K)		21
fCJD	Mouse	Tg(MHu2M)	170 ± 2 (10/10)	21
fCJD → Tg(MHu2M)	Mouse	Tg(MHu2M)	167 ± 3 (15/15)	21

*Tg(MHu2M) mice express a chimeric mouse-human PrP gene.

Notes: Clinicopathologic phenotype is determined by the conformation of PrP^{Sc} in accord with the results of the transmission of human prions from patients with FFI to transgenic mice.

Abbreviations: fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; SEM, standard error of the mean.

diversity appears to be enciphered in the conformation of PrP^{Sc}, and thus prion strains seem to represent different conformers of PrP^{Sc}.

In general, transmission of PrP prion disease from one species to another is inefficient, in that not all intracerebrally inoculated animals develop disease, and those that fall ill do so only after long incubation times that can approach the natural life span of the animal. This “species barrier” to transmission is correlated with the degree of similarity between the amino acid sequences of PrP^C in the inoculated host and of PrP^{Sc} in the inoculum. The importance of sequence similarity between the host and donor PrP argues that PrP^C directly interacts with PrP^{Sc} in the prion conversion process.

SPORADIC AND INHERITED P P PRION DISEASES

Several different scenarios might explain the initiation of sporadic prion disease: (1) A somatic mutation may be the cause and thus follow a path similar to that for germline mutations in inherited disease. In this situation, the mutant PrP^{Sc} must be capable of targeting wild-type PrP^C, a process known to be possible for some mutations but less likely for others. (2) The activation energy barrier separating wild-type PrP^C from PrP^{Sc} could be crossed on rare occasions when viewed in the context of a population. Most individuals would be spared, but presentations in older persons, with an incidence of ~1 per million, would be seen. (3) PrP^{Sc} may be present at low levels in some normal cells, where it performs an important, but as yet unknown, function. The level of PrP^{Sc} in such cells is hypothesized to be sufficiently low as not to be detected by routine bioassay. In some altered metabolic states, the cellular mechanisms for clearing PrP^{Sc} might become compromised, and the rate of PrP^{Sc} formation would then begin to exceed the capacity of the cell to clear it. The third possible mechanism is attractive because it suggests that PrP^{Sc} is not simply a misfolded protein, as proposed for the first and second mechanisms, but that it is an alternatively folded molecule with a function. Moreover, the multitude of conformational states that PrP^{Sc} can adopt, as described above, raises the possibility that PrP^{Sc} or another protein might function in a process such as short-term memory where information storage is thought to occur in the absence of new protein synthesis.

More than 40 different mutations resulting in nonconservative substitutions in the human *PRNP* gene have been found to segregate with inherited human prion diseases. Missense mutations, a deletion, and expansions in the octapeptide repeat region of the gene, called octapeptide repeat insertions (OPRIs), are responsible for genetic forms of prion disease.

Although phenotypes may vary dramatically, even within families, specific phenotypes observed with certain mutations appear to cause sCJD. More than 20 missense variants—including substitutions at codons 102, 105, 117, 198, and 217, and mid to longer OPRIs—cause the GSS form of PrP prion disease with prominent parkinsonian and cerebellar features. Regarding OPRI mutations, the normal human PrP sequence contains an unstable section in the N-terminal region comprised of five repeats—a nine-amino-acid sequence or nonapeptide (R1) followed by four octapeptide repeats. Insertions from 2 to 12 extra octapeptide repeats frequently cause variable phenotypes including conditions indistinguishable from sCJD, GSS-like presentations, and even a slowly progressive dementing illness of many years in duration to an early-age-of-onset disorder that is similar to AD. A mutation at codon 178 that results in substitution of asparagine for aspartic acid generally causes FFI if methionine is encoded at codon 129 on the same allele. In contrast, a typical dementing CJD phenotype has been generally found with a valine encoded at codon 129 of the same allele. Stop codon (nonsense) mutations are rare and cause a range of phenotypes, including some with a prolonged course of years to decades, GSS- or AD-like presentations, autonomic and sensory peripheral nervous system involvement, chronic gastrointestinal upset, and extensive PrP^{Sc} amyloid deposits.

HUMAN *PRNP* GENE POLYMORPHISMS

Polymorphisms influence the susceptibility to sporadic, genetic, and acquired forms of PrP prion disease. The methionine/valine

polymorphism at codon 129 of *PRNP* not only modulates the age of onset of some genetic prion diseases but also can affect the clinical phenotype. The findings that homozygosity at codon 129 (both alleles being either methionine [M] or valine [V]) predisposes an individual to sCJD and that codon 129 MM predisposes a person to vCJD support a model of prion production that favors PrP interactions between homologous proteins.

Substitution of the basic residue lysine at position 218 in mouse PrP produced dominant-negative inhibition of prion replication in transgenic mice. This same lysine at position 219 in human PrP has been found in 12% of the Japanese population, a group that appears to be resistant to prion disease. Dominant-negative inhibition of prion replication was also found with substitution of the basic residue arginine at position 171; sheep with arginine were resistant to scrapie prions but were susceptible to BSE prions that were inoculated intracerebrally. A very interesting polymorphism at codon 127 in *PRNP* was identified among longtime survivors of the kuru epidemic in the Fore ethnic group of Papua New Guinea, which when expressed in transgenic mice with humanized *PRNP* prevented the animals from acquiring prion disease.

ACQUIRED P P PRION DISEASES

IATROGENIC CJD

Accidental transmission of CJD to humans appears to have occurred with corneal transplantation, contaminated electroencephalogram (EEG) electrode implantation, and surgical procedures. Corneas from donors with unsuspected CJD have been transplanted to apparently healthy recipients who developed CJD after variable incubation periods. The same improperly decontaminated EEG electrodes that caused CJD in two young patients with intractable epilepsy caused CJD in a chimpanzee 18 months after their experimental implantation.

Surgical procedures may have resulted in accidental inoculation of patients with prions, presumably because some instrument or apparatus in the operating theater became contaminated when a CJD patient underwent surgery. Although the epidemiology of these studies is highly suggestive, no proof for such episodes exists.

Dura Mater Grafts More than 160 cases of CJD after implantation of dura mater grafts have been recorded. All of the grafts appear to have been acquired from a single manufacturer whose preparative procedures were inadequate to inactivate human prions. One case of CJD occurred after repair of an eardrum perforation with a pericardium graft.

Human Growth Hormone and Pituitary Gonadotropin Therapy The transmission of CJD prions from contaminated human growth hormone (hGH) preparations derived from human pituitaries has been responsible for fatal cerebellar disorders with dementia in >180 patients ranging in age from 10 to 41 years. These patients received injections of hGH every 2–4 days for 4–12 years. If it is thought that these patients developed CJD from injections of prion-contaminated hGH preparations, the possible incubation periods range from 4 to 30 years. Only recombinant hGH is now used therapeutically so that possible contamination with prions is no longer an issue.

Notably, evidence has accumulated in deceased patients with hGH CJD that some also carry A β prions. This finding demonstrated the iatrogenic propagation of A β prions in the human CNS.

Four cases of CJD have occurred in women receiving human pituitary gonadotropin.

VARIANT CJD

The restricted geographic occurrence and chronology of vCJD raised the possibility that BSE prions had been transmitted to humans through the consumption of tainted beef. More than 190 cases of vCJD have occurred, with >90% of these in Britain. Variant CJD has also been reported in people either living in or originating from France, Ireland, Italy, the Netherlands, Portugal, Spain, Saudi Arabia, the United States, Canada, and Japan.

The steady decline in the number of vCJD cases over the past decade argues either that there will not be a prion disease epidemic in

3420 Europe, similar to those seen for BSE and kuru. What is certain is that PrP-prion-tainted meat should be prevented from entering the human food supply.

The most compelling evidence that vCJD is caused by BSE prions was obtained from experiments in mice expressing the bovine PrP transgene. Both BSE and vCJD prions were efficiently transmitted to these transgenic mice and with similar incubation periods. In contrast to sCJD prions, vCJD prions did not transmit disease efficiently to mice expressing a chimeric human–mouse PrP transgene. Earlier studies with nontransgenic mice suggested that vCJD and BSE might be derived from the same source because both inocula transmitted disease with similar but very long incubation periods.

Attempts to determine the origin of BSE and vCJD prions have relied on passaging studies in mice, some of which are described above, as well as studies of the conformation and glycosylation of PrP^{Sc}. One scenario suggests that a particular conformation of bovine PrP^{Sc} was selected for heat resistance during the rendering process and was then reselected multiple times as cattle infected by ingesting prion-contaminated meat and bone meal (MBM) were slaughtered and their offal rendered into more MBM. Variant CJD cases have virtually disappeared with protection of the beef supply in Europe. Interestingly, almost all of the approximately 238 cases of vCJD reported as of 2021 have been homozygous for methionine (MM) at codon 129 in *PRNP*, except two of the more recent cases were codon 129 MV, which is the most common codon 129 polymorphism.

■ NEUROPATHOLOGY

Frequently, the brains of patients with CJD have no recognizable abnormalities on gross examination. Patients who survive for several years have variable degrees of cerebral atrophy.

On light microscopy, the pathologic hallmarks of CJD are spongiform degeneration (vacuolation), neuronal loss, and astrocytic gliosis. The lack of an inflammatory response in CJD and other prion diseases is an important pathologic feature of these degenerative disorders. Spongiform degeneration is characterized by many 1- to 5-µm vacuoles in the neuropil between nerve cell bodies. Generally, the spongiform changes occur in the cerebral cortex, putamen, caudate nucleus, thalamus, and molecular layer of the cerebellum. Astrocytic gliosis is a constant but nonspecific feature of PrP prion diseases. Widespread proliferation of fibrous astrocytes is found throughout the gray matter of brains infected with CJD prions. Astrocytic processes filled with glial filaments form extensive networks.

Amyloid plaques have been found in ~10% of CJD cases. Purified CJD prions from humans and animals exhibit the ultrastructural and histochemical characteristics of amyloid when treated with detergents during limited proteolysis. On first passage of samples from some human Japanese CJD cases into mice, amyloid plaques were found. These plaques stain with antibodies raised against PrP, demonstrating that the amyloid is composed of PrP.

The amyloid plaques of GSS disease are morphologically distinct from those seen in kuru or scrapie. GSS plaques consist of a central dense core of amyloid surrounded by smaller globules of amyloid. Ultrastructurally, they consist of a radiating fibrillar network of amyloid fibrils, with scant or no neuritic degeneration. The plaques can be distributed throughout the brain but are most frequently found in the cerebellum. They are often located adjacent to blood vessels. Congoophilic angiopathy has been noted in some cases of GSS disease.

In vCJD, a characteristic feature is the presence of “florid plaques.” These are composed of a central core of PrP amyloid, surrounded by vacuoles in a pattern suggesting petals on a flower.

■ CLINICAL FEATURES

Nonspecific prodromal symptoms occur in approximately a third of patients with CJD and may include fatigue, sleep disturbance, weight loss, headache, anxiety, vertigo, malaise, and ill-defined pain. Most patients with CJD present with deficits in higher cortical function. Behavioral and psychiatric symptoms, such as depression, apathy, insomnia, appetite changes, psychosis, and visual hallucinations, are

very common and often the defining features of the illness. These deficits almost always progress over weeks or months to a state of profound dementia characterized by memory loss, impaired judgment, and a decline in virtually all aspects of intellectual function. A few patients present early with either isolated visual impairment or cerebellar gait and coordination deficits, referred to as the Heidenhain and Brownell-Oppenheim variants, respectively. Frequently, the cerebellar deficits are rapidly followed by progressive dementia. Visual problems often begin with blurred vision and diminished acuity, rapidly followed by dementia. Patients with early visual deficits appear to have a faster decline overall.

Other symptoms and signs include extrapyramidal dysfunction manifested as rigidity, masklike facies, dystonia, myoclonus, or less commonly choreoathetoid movements and pyramidal signs (usually mild and not actual weakness). Some uncommon features include seizures (usually major motor), hypoesthesia, supranuclear gaze palsy, motor neuron disease, optic atrophy, and vegetative signs such as changes in weight, temperature, sweating, or menstruation.

Myoclonus A majority of patients with CJD eventually develop myoclonus that appears at various times throughout the illness. Unlike other involuntary movements, myoclonus persists during sleep. Startle myoclonus elicited by loud sounds or bright lights is frequent. It is important to stress that myoclonus is neither specific nor confined to CJD and tends to occur later in the course of CJD. Dementia with myoclonus can also be due to AD (Chap. 431), dementia with Lewy bodies (Chap. 434), corticobasal degeneration (Chap. 432), cryptococcal encephalitis (Chap. 215), or the myoclonic epilepsy disorder Unverricht-Lundborg disease (Chap. 425).

Clinical Course In documented cases of accidental transmission of CJD to humans, an incubation period of 1.5–2 years preceded the development of clinical disease. In other cases, incubation periods >40 years have been suggested. Most patients with CJD live 6–12 months after the onset of clinical signs and symptoms, whereas some live for up to a few years. Some mutations causing genetic prion disease can have durations of a decade or longer.

■ DIAGNOSIS

The constellation of dementia, myoclonus, and periodic electrical bursts in an afebrile 60-year-old patient generally indicates CJD. Clinical abnormalities in CJD are confined to the CNS. Fever, elevated sedimentation rate, leukocytosis in blood, or a pleocytosis in cerebrospinal fluid (CSF) should alert the physician to another etiology to explain the patient's CNS dysfunction, although there are rare cases of CJD in which mild CSF pleocytosis is observed.

Variations in the typical course appear in inherited and transmitted forms of the disease. Most mutations causing fCJD have a slightly earlier mean age of onset, although usually an otherwise similar clinical and radiologic presentation to sCJD. In GSS, ataxia is usually a prominent and presenting feature, with dementia occurring late in the disease course. GSS presents earlier than sCJD (mean age 43 years) and is typically more slowly progressive than sCJD; death usually occurs within 5 years of onset. FFI is characterized by insomnia and dysautonomia; dementia occurs only in the terminal phase of the illness. Rare sporadic cases have been identified. Variant CJD has an unusual clinical course, with a prominent psychiatric prodrome that may include visual hallucinations and early ataxia, whereas frank dementia is usually a late sign of vCJD.

■ DIFFERENTIAL DIAGNOSIS

Many conditions mimic CJD. Dementia with Lewy bodies (Chap. 434) is the most common disorder to be mistaken for CJD. It can present in a subacute fashion with delirium, myoclonus, and extrapyramidal features. Other neurodegenerative disorders to consider include AD, FTD, corticobasal degeneration, progressive supranuclear palsy, ceroid lipofuscinosis, and myoclonic epilepsy with Lafora bodies. The absence of abnormalities on diffusion-weighted and fluid-attenuated inversion

recovery (FLAIR) MRI will almost always distinguish these dementing conditions from CJD.

Hashimoto's encephalopathy, which presents as a subacute progressive encephalopathy with myoclonus and periodic triphasic complexes on the EEG, should be excluded in every case of suspected CJD. It is diagnosed by the finding of high titers of antithyroglobulin or antithyroid peroxidase (antimicrosomal) antibodies in the blood and improves with glucocorticoid therapy. Unlike CJD, fluctuations in severity typically occur in Hashimoto's encephalopathy.

Intracranial vasculitides (Chap. 363) may produce nearly all of the symptoms and signs associated with CJD, sometimes without systemic abnormalities. Myoclonus is exceptional with cerebral vasculitis, but focal seizures may confuse the picture. Prominent headache, absence of myoclonus, stepwise change in deficits, abnormal CSF, and focal white matter change on MRI or angiographic abnormalities all favor vasculitis.

Autoimmune and paraneoplastic conditions (Chap. 94), particularly limbic encephalitis and cortical encephalitis, can also mimic CJD. In many of these patients, dementia appears prior to the diagnosis of a tumor, and in some, no tumor is ever found. Detection of the paraneoplastic antibodies is often the only way to distinguish these cases from CJD.

Other diseases that can simulate CJD include neurosyphilis (Chap. 182), AIDS dementia complex (Chap. 202), progressive multifocal leukoencephalopathy (Chap. 137), subacute sclerosing panencephalitis, progressive rubella panencephalitis, herpes simplex encephalitis (Chap. 137), diffuse intracranial tumor (gliomatosis cerebri; Chap. 90), anoxic encephalopathy, dialysis dementia, uremia, hepatic encephalopathy, and lithium or bismuth intoxication.

■ LABORATORY TESTS

The only specific diagnostic tests for CJD and other human PrP prion diseases measure PrP^{Sc}. The most widely used method involves limited proteolysis that generates PrP 27-30, which is detected by immunoassay after denaturation. The conformation-dependent immunoassay (CDI) is based on immunoreactive epitopes that are exposed in PrP^C but buried in PrP^{Sc}. In humans, the diagnosis of CJD can be established by brain biopsy if PrP^{Sc} is detected although biopsy is rarely indicated. If no attempt is made to measure PrP^{Sc}, but the constellation of pathologic changes frequently found in CJD is seen in a brain biopsy, then the diagnosis is reasonably secure (see "Neuropathology," above). The high sensitivity and specificity of cortical ribboning and basal ganglia hyperintensity on FLAIR and diffusion-weighted MRI for the diagnosis of CJD have greatly diminished the need for brain biopsy in patients with suspected CJD. Because PrP^{Sc} is not uniformly distributed throughout the CNS, the apparent absence of PrP^{Sc} in a limited sample such as a biopsy does not rule out prion disease. At autopsy, sufficient brain samples should be taken for both PrP^{Sc} immunoassay, preferably by CDI, and immunohistochemistry of tissue sections.

To establish the diagnosis of either sCJD or familial prion disease, sequencing the *PRNP* gene must be performed. Finding the wild-type *PRNP* gene sequence permits the diagnosis of sCJD if there is no history to suggest infection from an exogenous source of prions. The identification of a mutation in the *PRNP* gene sequence that encodes a nonconservative amino acid substitution argues for familial prion disease.

MRI is valuable for distinguishing sCJD from most other conditions. On FLAIR sequences and diffusion-weighted imaging, ~90% of patients show increased intensity in the basal ganglia and cortical ribboning (Fig. 438-2). This pattern is not seen with other neurodegenerative disorders but has been seen infrequently with viral encephalitis, paraneoplastic syndromes, or seizures. When the typical MRI pattern is present, in the proper clinical setting, diagnosis is facilitated. However, some cases of sCJD do not show this typical pattern, and other early diagnostic approaches are still needed. CT findings are generally nonspecific; they may be normal or show cortical atrophy.

CSF is nearly always normal but may show protein elevation and, rarely, mild pleocytosis. Although the stress protein 14-3-3 is elevated in the CSF of some patients with CJD, similar elevations of 14-3-3 are

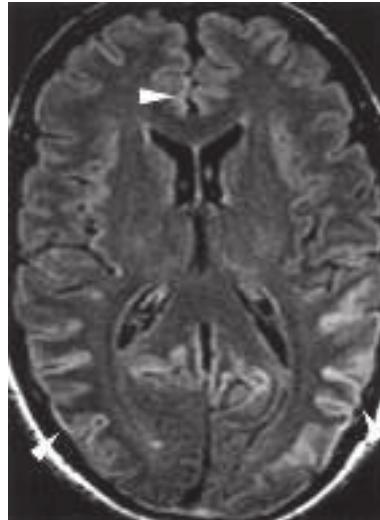


FIGURE 438-2 T2-weighted FLAIR MRI showing hyperintensity in the cortex in a patient with sCJD. This so-called cortical ribboning along with increased intensity in the basal ganglia on T2- or diffusion-weighted imaging can aid in the diagnosis of CJD.

found in patients with other disorders; thus, this elevation is not specific. Similarly, elevations of CSF neuron-specific enolase and tau occur in CJD but lack specificity for diagnosis.

The EEG is often useful in the diagnosis of CJD, although only ~60% of individuals show the typical pattern, which appears quite late in the clinical course. During the early phase of CJD, the EEG is usually normal or shows only scattered theta activity. In most advanced cases, repetitive, high-voltage, triphasic, and polyphasic sharp discharges are seen, but in many cases, their presence is transient. The presence of these stereotyped periodic bursts of <200 ms in duration, occurring every 1–2 s, makes the diagnosis of CJD very likely. These discharges are frequently but not always symmetric; there may be a one-sided predominance in amplitude. As CJD progresses, normal background rhythms become fragmentary and slower.

■ CARE OF CJD PATIENTS

Although CJD is communicable, the likelihood of transmission from one patient to another is remote. The risk of accidental inoculation by aerosols is small; nonetheless, procedures producing aerosols should be performed in certified biosafety cabinets. Biosafety level 2 practices, containment equipment, and facilities are recommended by the Centers for Disease Control and Prevention and the National Institutes of Health. The primary worry in caring for patients with CJD is the inadvertent infection of health care workers by needle and stab wounds, although with the possible exception of vCJD even blood transfusions appear to carry minimal risk for transmission. Electroencephalographic and electromyographic needles should not be reused after studies on patients with CJD have been performed.

Autopsies on patients whose clinical diagnosis is CJD can be performed with minimal risk to pathologists or other morgue employees. Standard microbiologic practices outlined here, along with specific recommendations for decontamination, are generally adequate precautions for the care of patients with CJD and the handling of infected specimens.

■ DECONTAMINATION OF CJD PRIONS

Prions are generally resistant to commonly used inactivation procedures, and there is some disagreement about the optimal conditions for sterilization. Some investigators recommend treating CJD-contaminated materials once with 1 N NaOH at room temperature,

but we believe this procedure may be inadequate for sterilization. Autoclaving at 134°C for 5 h or treatment with 2 N NaOH for several hours is recommended for sterilization of prions. The term *sterilization* implies complete destruction of prions; any residual infectivity can be hazardous. Transgenic mouse studies show that sCJD prions bound to stainless-steel surfaces are resistant to inactivation by autoclaving at 134°C for 2 h; exposure of bound prions to an acidic detergent solution prior to autoclaving rendered prions susceptible to inactivation. Recent studies show that α -synuclein prions in brain homogenates prepared from MSA patients bind to stainless-steel wires and that the bound prions can be transmitted to transgenic mice expressing mutant human α -synuclein.

■ PREVENTION AND THERAPEUTICS

There is no known effective therapy for preventing or treating CJD. The finding that phenothiazines and acridines inhibit PrP^{Sc} formation in cultured cells led to clinical studies of quinacrine in CJD patients. Unfortunately, quinacrine failed to slow the rate of cognitive decline in CJD, possibly because therapeutic concentrations of quinacrine were not achieved in the brain. Although inhibition of the P-glycoprotein (Pgp) transport system resulted in substantially increased quinacrine levels in the brains of mice, the prion incubation times were not extended by treatment with the drug. Whether such an approach can be used to treat CJD remains to be established.

Like the acridines, anti-PrP antibodies have been shown to eliminate PrP^{Sc} from cultured cells. Additionally, such antibodies in mice, either administered by injection or produced from a transgene, have been shown to prevent prion disease when prions are introduced by a peripheral route, such as intraperitoneal inoculation. Unfortunately, the antibodies were ineffective in mice inoculated intracerebrally with prions. Several drugs, including pentosan polysulfate as well as porphyrin and phenylhydrazine derivatives, delay the onset of disease in animals inoculated intracerebrally with prions if the drugs are given intracerebrally beginning soon after inoculation.

DIFFERENT PRIONS CAUSING OTHER NEURODEGENERATIVE DISEASES

There is a rapidly expanding body of literature demonstrating that besides PrP, other proteins including amyloid beta (A β), tau, α -synuclein, and huntingtin can all refold into prions (Chap. 424). Experimental and postmortem studies have shown that mutant transgenes in cultured cells or mice expressing the amyloid precursor protein (APP), tau, or α -synuclein produce prions. Both cultured cells and Tg mice, either spontaneously or after inoculation with prions from autopsy specimens, support prion propagation. For example, transgenic mice expressing mutant APP produce A β amyloid plaques containing fibrils composed of the A β peptide that can be transmitted serially to Tg mice and cultured cells. Similarly, tau aggregates in transgenic mice and cultured cells can initiate the aggregation of tau into fibrils that resemble those found in neurofibrillary tangles and Pick bodies. Such tangles have been found in AD, FTDs, Pick's disease, as well as posttraumatic brain injury (chronic traumatic encephalopathy) (Chap. 443), all of which are thought to be caused by the prion isoforms of A β and/or tau.

In patients with advanced PD who received grafts of fetal substantia nigral neurons, Lewy bodies containing β -sheet-rich α -synuclein were identified in grafted cells ~10 years after transplantation, arguing for the axonal transport of misfolded α -synuclein crossing into grafted neurons, where it initiated aggregation of nascent α -synuclein into fibrils that coalesced into Lewy bodies. These findings combined with MSA studies argue that the synucleinopathies are caused by prions. Brain homogenates from MSA patients injected into transgenic mice transmitted lethal neurodegeneration in ~3 months; moreover, recombinant synuclein injected into wild-type mice initiated the deposition of synuclein fibrils. Similar to the Tg mouse studies with A β and tau, cultured cells expressing mutant α -synuclein also support prion formation.

In summary, a wealth of evidence continues to accumulate arguing that proteins causing AD, PD, FTDs, amyotrophic lateral sclerosis

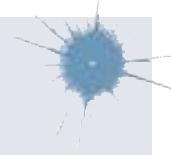
(ALS), and even Huntington's disease (HD) acquire alternative conformations that become self-propagating. Each of these NDs is thought to be caused by the aberrant folding of a different protein that undergoes a self-replicating conformational change to become a prion. Prions explain many of the features that NDs have in common: (1) incidence increases with age, (2) steady progression over years, (3) spread from one region of the CNS to another, (4) protein deposits often but not always consisting of amyloid fibrils, and (5) late onset of inherited forms. Notably, amyloid plaques containing PrP^{Sc} are a nonobligatory feature of PrP prion disease in humans and animals. Furthermore, amyloid plaques in AD do not correlate with the level of dementia; however, the level of soluble (oligomeric) A β peptide does correlate with memory loss and other intellectual deficits.

■ FURTHER READING

- A A et al: A β and tau prion-like activities decline with longevity in the Alzheimer's disease human brain. *Sci Transl Med* 11:eaat8462, 2019.
- C J: Mammalian prions and their wider relevance in neurodegenerative diseases. *Nature* 539:217, 2016.
- K A et al: Structure of an infectious mammalian prion. *bioRxiv* preprint, 2021.
- P SB (ed): *Prion Biology*. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 2017.
- P SB (ed): *Prion Diseases*. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 2017.
- P SB et al: Evidence for α -synuclein prions causing multiple system atrophy in humans with parkinsonism. *Proc Natl Acad Sci USA* 112:E5308, 2015.

439 Ataxic Disorders

Roger N. Rosenberg



APPROACH TO THE PATIENT

Ataxic Disorders

Symptoms and signs of ataxia consist of gait impairment, unclear ("scanning") speech, visual blurring due to nystagmus, hand incoordination, and tremor with movement. These result from the involvement of the cerebellum and its afferent and efferent pathways, including the spinocerebellar pathways, and the frontopontocerebellar pathway originating in the rostral frontal lobe. True cerebellar ataxia must be distinguished from ataxia associated with vestibular nerve or labyrinthine disease, as the latter results in a disorder of gait associated with a significant degree of dizziness, light-headedness, or the perception of movement (Chap. 19). True cerebellar ataxia is devoid of these vertiginous complaints and is clearly an unsteady gait due to imbalance. Sensory disturbances can also on occasion simulate the imbalance of cerebellar disease; with sensory ataxia, imbalance dramatically worsens when visual input is removed (Romberg sign). Rarely, weakness of proximal leg muscles mimics cerebellar disease. In the patient who presents with ataxia, the rate and pattern of the development of cerebellar symptoms help to narrow the diagnostic possibilities (Table 439-1). A gradual and progressive increase in symptoms with bilateral and symmetric involvement suggests a genetic, metabolic, immune, or toxic etiology. Conversely, focal, unilateral symptoms with headache and impaired level of consciousness accompanied by ipsilateral cranial nerve palsies and contralateral weakness imply a space-occupying cerebellar lesion.

TABLE 439-1 Etiology of Cerebellar Ataxia

SYMMETRIC AND PROGRESSIVE SIGNS			FOCAL AND IPSILATERAL CEREBELLAR SIGNS		
ACUTE (HOURS TO DAYS)	SUBACUTE (DAYS TO WEEKS)	CHRONIC (MONTHS TO YEARS)	ACUTE (HOURS TO DAYS)	SUBACUTE (DAYS TO WEEKS)	CHRONIC (MONTHS TO YEARS)
Intoxication: alcohol, lithium, phenytoin, barbiturates (positive history and toxicology screen)	Intoxication: mercury, solvents, gasoline, glue	Paraneoplastic syndrome	Vascular: cerebellar infarction, hemorrhage, or subdural hematoma	Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT)	Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months)
Acute viral cerebellitis (CSF supportive of acute viral infection)	Cytotoxic chemotherapeutic drugs	Antigliadin antibody syndrome	Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion)	Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent)	Congenital lesion: Chiari or Dandy-Walker malformations (malformation noted on MRI/CT)
Postinfection syndrome	Alcoholic-nutritional (vitamin B ₁ and B ₁₂ deficiency)	Hypothyroidism		AIDS-related multifocal leukoencephalopathy (positive HIV test and CD4+ cell count for AIDS)	
	Lyme disease	Inherited diseases			
		Tabes dorsalis (tertiary syphilis)			
		Phenytoin toxicity			
		Amiodarone			

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

SYMMETRIC ATAXIA

Progressive and symmetric ataxia can be classified with respect to onset as acute (over hours or days), subacute (weeks or months), or chronic (months to years). Acute and reversible ataxias include those caused by intoxication with alcohol, phenytoin, lithium, barbiturates, and other drugs. Intoxication caused by toluene exposure, gasoline sniffing, glue sniffing, spray painting, or exposure to methyl mercury or bismuth are additional causes of acute or subacute ataxia, as is treatment with cytotoxic chemotherapeutic drugs such as fluorouracil and paclitaxel. Patients with a postinfectious syndrome (especially after varicella) may develop gait ataxia and mild dysarthria, both of which are reversible (Chap. 444). Rare infectious causes of acquired ataxia include poliovirus, coxsackievirus, echovirus, Epstein-Barr virus, toxoplasmosis, *Legionella*, and Lyme disease.

The subacute development of ataxia of gait over weeks to months (degeneration of the cerebellar vermis) may be due to the combined effects of alcoholism and malnutrition, particularly with deficiencies of vitamins B₁ and B₁₂. Hyponatremia has also been associated with ataxia. Paraneoplastic cerebellar ataxia is associated with a number of different tumors (and autoantibodies) such as breast and ovarian cancers (anti-Yo), small-cell lung cancer (anti-PQ-type voltage-gated calcium channel), and Hodgkin's disease (anti-Tr) (Chap. 94). Another paraneoplastic syndrome associated with myoclonus and opsoclonus occurs with breast (anti-Ri) and lung cancers and neuroblastoma. Elevated serum anti-glutamic acid decarboxylase (GAD) antibodies have been associated with a progressive ataxic syndrome affecting speech and gait. For all of these paraneoplastic ataxias, the neurologic syndrome may be the presenting symptom of the cancer. Another immune-mediated progressive ataxia is associated with antigliadin (and antiendomysium) antibodies and the human leukocyte antigen (HLA) DQB1*0201 haplotype; in some affected patients, biopsy of the small intestine reveals villus atrophy consistent with gluten-sensitive enteropathy (Chap. 325). Finally, subacute progressive ataxia may be caused by a prion disorder, especially when an infectious etiology, such as transmission from contaminated human growth hormone, is responsible (Chap. 438).

Chronic symmetric gait ataxia suggests an inherited ataxia (discussed below), a metabolic disorder, or a chronic infection. Hypothyroidism must always be considered as a readily treatable and reversible form of gait ataxia. Infectious diseases that can present with ataxia are meningovascular syphilis and tabes dorsalis due to degeneration of the posterior columns and spinocerebellar pathways in the spinal cord.

FOCAL ATAXIA

Acute focal ataxia commonly results from cerebrovascular disease, usually ischemic infarction or cerebellar hemorrhage. These lesions typically produce cerebellar symptoms ipsilateral to the

injured cerebellum and may be associated with an impaired level of consciousness due to brainstem compression and increased intracranial pressure; ipsilateral pontine signs, including sixth and seventh nerve palsies, may be present. Focal and worsening signs of acute ataxia should also prompt consideration of a posterior fossa subdural hematoma, bacterial abscess, or primary or metastatic cerebellar tumor. CT or MRI studies will reveal clinically significant processes of this type. Many of these lesions represent true neurologic emergencies, as sudden herniation, either rostrally through the tentorium or caudal herniation of cerebellar tonsils through the foramen magnum, can occur and is usually devastating. Acute surgical decompression may be required (Chap. 301). Lymphoma or progressive multifocal leukoencephalopathy (PML) in a patient with AIDS may present with an acute or subacute focal cerebellar syndrome. Chronic etiologies of progressive ataxia include multiple sclerosis (Chap. 444) and congenital lesions such as a Chiari malformation (Chap. 442) or a congenital cyst of the posterior fossa (Dandy-Walker syndrome).

THE INHERITED ATAXIAS

Inherited ataxias may show autosomal dominant, autosomal recessive, or maternal (mitochondrial) modes of inheritance. A genomic classification (Table 439-2)¹ has now largely superseded previous ones based on clinical expression alone.

Although the clinical manifestations and neuropathologic findings of cerebellar disease dominate the clinical picture, there may also be characteristic changes in the basal ganglia, brainstem, spinal cord, optic nerves, retina, and peripheral nerves. In large families with dominantly inherited ataxias, many gradations are observed from purely cerebellar manifestations to mixed cerebellar and brainstem disorders, cerebellar and basal ganglia syndromes, and spinal cord or peripheral nerve disease. Rarely, dementia is present as well. The clinical picture may be homogeneous within a family with dominantly inherited ataxia, but sometimes most affected family members show one characteristic syndrome, while one or several members have an entirely different phenotype.

■ AUTOSOMAL DOMINANT ATAXIAS

The autosomal spinocerebellar ataxias (SCAs) include SCA types 1 through 43, dentatorubropallidolysian atrophy (DRPLA), and episodic ataxia (EA) types 1 to 7 (Table 439-2). SCA1, SCA2, SCA3 (Machado-Joseph disease [MJD]), SCA6, SCA7, and SCA17 are caused by CAG triplet repeat expansions in different genes. SCA8 is due to an untranslated CTG repeat expansion, SCA12 is linked to an untranslated CAG repeat, and SCA10 is caused by an untranslated pentanucleotide repeat. The clinical phenotypes of these SCAs overlap. The genotype

¹Table 439-2 can be found online at www.accessmedicine.com.

has become the gold standard for diagnosis and classification. CAG encodes glutamine, and these expanded CAG triplet repeat expansions result in expanded polyglutamine proteins, termed *ataxins*, that produce a toxic gain of function with autosomal dominant inheritance. Although the phenotype is variable for any given disease gene, a pattern of neuronal loss with gliosis is produced that is relatively unique for each ataxia. Immunohistochemical and biochemical studies have shown cytoplasmic (SCA2), neuronal (SCA1, MJD, SCA7), and nucleolar (SCA7) accumulation of the specific mutant polyglutamine-containing ataxin proteins. Expanded polyglutamine ataxins with more than ~40 glutamines are potentially toxic to neurons for a variety of reasons including: high levels of gene expression for the mutant polyglutamine ataxin in affected neurons; conformational change of the aggregated protein to a β-pleated structure; abnormal transport of the ataxin into the nucleus (SCA1, MJD, SCA7); binding to other polyglutamine proteins, including the TATA-binding transcription protein and the CREB-binding protein, impairing their functions; altering the efficiency of the ubiquitin-proteasome system of protein turnover; and inducing neuronal apoptosis. An earlier age of onset (anticipation) and more aggressive disease in subsequent generations are due to further expansion of the CAG triplet repeat and increased polyglutamine number in the mutant ataxin. The most common disorders are discussed below.

■ SCA1

SCA1 was previously referred to as *olivopontocerebellar atrophy*, but genomic data have shown that that entity represents several different genotypes with overlapping clinical features.

Symptoms and Signs SCA1 is characterized by the development in early- or middle-adult life of progressive cerebellar ataxia of the trunk and limbs, impairment of equilibrium and gait, slowness of voluntary movements, scanning speech, nystagmoid eye movements, and oscillatory tremor of the head and trunk. Dysarthria, dysphagia, and oculomotor and facial palsies may also occur. Extrapyramidal symptoms include rigidity, an immobile face, and parkinsonian tremor. The reflexes are usually normal, but knee and ankle jerks may be lost, and extensor plantar responses may occur. Dementia may be noted but is usually mild. Impairment of sphincter function is common, with urinary and sometimes fecal incontinence. Cerebellar and brainstem atrophy are evident on MRI (Fig. 439-1).

Marked shrinkage of the ventral half of the pons, disappearance of the olfactory eminence on the ventral surface of the medulla, and atrophy of the cerebellum are evident on gross postmortem inspection of the

brain. Variable loss of Purkinje cells, reduced numbers of cells in the molecular and granular layer, demyelination of the middle cerebellar peduncle and the cerebellar hemispheres, and severe loss of cells in the pontine nuclei and olives are found on histologic examination. Degenerative changes in the striatum, especially the putamen, and loss of the pigmented cells of the substantia nigra may be found in cases with extrapyramidal features. More widespread degeneration in the central nervous system (CNS), including involvement of the posterior columns and the spinocerebellar fibers, is often present.

■ GENETIC CONSIDERATIONS

 SCA1 encodes a gene product, called *ataxin-1* that regulates transcriptional repression with various nuclear factors. As a protein that can bind RNA, ataxin 1 may also regulate gene transcription posttranslationally. The mutant allele has 40 CAG repeats located within the coding region, whereas alleles from unaffected individuals have ≤36 repeats. A few patients with 38–40 CAG repeats have been described. There is a direct correlation between a larger number of repeats and a younger age of onset for SCA1. Juvenile patients have higher numbers of repeats, and anticipation is present in subsequent generations. Transgenic mice carrying SCA1 developed ataxia and Purkinje cell pathology. Leucine-rich acidic nuclear protein localization, but not aggregation, of ataxin-1 appears to be required for cell death initiated by the mutant protein.

■ SCA2

Symptoms and Signs Another clinical phenotype, SCA2, has been described in patients from Cuba and India. Cuban patients probably are descendants of a common ancestor, and the population may be the largest homogeneous group of patients with ataxia described. The age of onset ranges from 2 to 65 years, and there is considerable clinical variability within families. Although neuropathologic and clinical findings are compatible with a diagnosis of SCA1, including slow saccadic eye movements, ataxia, dysarthria, parkinsonian rigidity, optic disc pallor, mild spasticity, and retinal degeneration, SCA2 is a unique form of cerebellar degenerative disease.

■ GENETIC CONSIDERATIONS

 The gene in SCA2 families also contains CAG repeat expansions coding for a polyglutamine-containing protein, ataxin-2. Normal alleles contain 15–32 repeats; mutant alleles have 35–77 repeats. Ataxin-2 has recently been shown to assemble with polyribosomes. Ataxin-2 is also an important risk factor for sporadic amyotrophic lateral sclerosis (ALS).

■ MACHADO JOSEPH DISEASE/ SCA3

MJD was first described among the Portuguese and their descendants in New England and California. Subsequently, MJD has been found in families from Portugal, Australia, Brazil, Canada, China, England, France, India, Israel, Italy, Japan, Spain, Taiwan, and the United States. In most populations, it is the most common autosomal dominant ataxia.

Symptoms and Signs MJD has been classified into three clinical types. In type I MJD (ALS-parkinsonism-dystonia type), neurologic deficits appear in the first two decades and involve weakness and spasticity of extremities, especially the legs, often with dystonia of the face, neck, trunk, and extremities. Patellar and ankle clonus are common, as are extensor plantar responses. The gait is slow and stiff, with a slightly broadened base and lurching from side to side; this gait results from spasticity, not true ataxia. There is no truncal titubation. Pharyngeal weakness and spasticity cause difficulty with speech and swallowing. Of note is the prominence of horizontal and vertical nystagmus, loss of fast saccadic eye movements, hypermetric and hypometric saccades, and impairment of upward vertical gaze. Facial fasciculations, facial myokymia, lingual fasciculations without atrophy, ophthalmoparesis, and ocular prominence are common early manifestations.

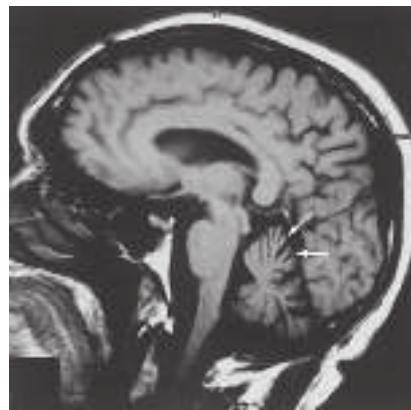


FIGURE 439-1 Sagittal magnetic resonance imaging (MRI) of the brain of a 60-year-old man with gait ataxia and dysarthria due to spinocerebellar atrophy type 1 (SCA1), illustrating cerebellar atrophy (arrows). (Reproduced with permission from RN Rosenberg, P Khemani, in RN Rosenberg, JM Pascual [eds]: Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th ed. London, Elsevier, 2015.)

In type II MJD (ataxic type), true cerebellar deficits of dysarthria and gait and extremity ataxia begin in the second to fourth decades along with corticospinal and extrapyramidal deficits of spasticity, rigidity, and dystonia. Type II is the most common form of MJD. Ophthalmoparesis, upward vertical gaze deficits, and facial and lingual fasciculations are also present. Type II MJD can be distinguished from the clinically similar disorders SCA1 and SCA2.

Type III MJD (ataxic-amyotrophic type) presents in the fifth to seventh decades with a pancerebellar disorder that includes dysarthria and gait and extremity ataxia. Distal sensory loss involving pain, touch, vibration, and position senses and distal atrophy are prominent, indicating the presence of peripheral neuropathy. The deep tendon reflexes are depressed to absent, and there are no corticospinal or extrapyramidal findings.

The mean age of onset of symptoms in MJD is 25 years. Neurologic deficits invariably progress and lead to death from debilitation within 15 years of onset, especially in patients with types I and II disease. Usually, patients retain full intellectual function.

The major pathologic findings are variable loss of neurons and glial replacement in the corpus striatum and severe loss of neurons in the pars compacta of the substantia nigra. A moderate loss of neurons occurs in the dentate nucleus of the cerebellum and in the red nucleus. Purkinje cell loss and granule cell loss occur in the cerebellar cortex. Cell loss also occurs in the dentate nucleus and in the cranial nerve motor nuclei. Sparing of the inferior olives distinguishes MJD from other dominantly inherited ataxias.

■ GENETIC CONSIDERATIONS

 The gene for MJD maps to 14q24.3-q32. Unstable CAG repeat expansions are present in the MJD gene coding for a polyglutamine-containing protein named ataxin-3, or MJD-ataxin. An earlier age of onset is associated with longer repeats. Alleles from normal individuals have between 12 and 37 CAG repeats, whereas MJD alleles have 60–84 CAG repeats. Polyglutamine-containing aggregates of ataxin-3 (MJD-ataxin) have been described in neuronal nuclei undergoing degeneration. MJD-ataxin codes for a ubiquitin protease, which is inactive due to expanded polyglutamines. Proteasome function is impaired, resulting in altered clearance of proteins and cerebellar neuronal loss.

■ SCA6

Genomic screening for CAG repeats in other families with autosomal dominant ataxia and vibratory and proprioceptive sensory loss have yielded another locus. Of interest is that different mutations in the same gene for the α_{1A} voltage-dependent calcium channel subunit (CACNLIA4; also referred to as the CACNA1A gene) at 19p13 result in different clinical disorders. CAG repeat expansions (21–27 in patients; 4–16 triplets in normal individuals) result in late-onset progressive ataxia with cerebellar degeneration. Missense mutations in this gene result in familial hemiplegic migraine. Nonsense mutations resulting in termination of protein synthesis of the gene product yield hereditary paroxysmal cerebellar ataxia or EA. Some patients with familial hemiplegic migraine develop progressive ataxia and also have cerebellar atrophy.

■ SCA7

This disorder is distinguished from all other SCAs by the presence of retinal pigmentary degeneration. The visual abnormalities first appear as blue-yellow color blindness and proceed to frank visual loss with macular degeneration. In almost all other respects, SCA7 resembles several other SCAs in which ataxia is accompanied by various noncerebellar findings, including ophthalmoparesis and extensor plantar responses. The genetic defect is an expanded CAG repeat in the SCA7 gene at 3p14-p21.1. The expanded repeat size in SCA7 is highly variable. Consistent with this, the severity of clinical findings varies from essentially asymptomatic to mild late-onset symptoms to severe, aggressive disease in childhood with rapid progression. Marked anticipation has been recorded, especially with paternal transmission. The disease protein, ataxin-7, forms aggregates in nuclei of affected

neurons, as has also been described for SCA1 and SCA3/MJD. Ataxin 7 is a subunit of GCN5, a histone acetyltransferase-containing complex.

■ SCA8

This form of ataxia is caused by a CTG repeat expansion in an untranslated region of a gene on chromosome 13q21. There is marked maternal bias in transmission, perhaps reflecting contractions of the repeat during spermatogenesis. The mutation is not fully penetrant. Symptoms include slowly progressive dysarthria and gait ataxia beginning at ~40 years of age with a range between 20 and 65 years. Other features include nystagmus, leg spasticity, and reduced vibratory sensation. Severely affected individuals are nonambulatory by the fourth to sixth decades. MRI shows cerebellar atrophy. The mechanism of disease may involve a dominant “toxic” effect occurring at the RNA level, as occurs in myotonic dystrophy.

■ DENTATORUBROPALLIDOLUYSIAN ATROPHY

DRPLA has a variable presentation that may include progressive ataxia, choreoathetosis, dystonia, seizures, myoclonus, and dementia. DRPLA is due to unstable CAG triplet repeats in the open reading frame of a gene named *atrophin* located on chromosome 12p12-ter. Larger expansions are found in patients with earlier onset. The number of repeats is 49 in patients with DRPLA and ~26 in normal individuals. Anticipation occurs in successive generations, with earlier onset of disease in association with an increasing CAG repeat number in children who inherit the disease from their father. One well-characterized family in North Carolina has a phenotypic variant known as the *Haw River syndrome*, now recognized to be due to the DRPLA mutation.

■ EPISODIC ATAXIA

EA types 1 and 2 are two rare dominantly inherited disorders that have been mapped to chromosomes 12p (a potassium channel gene, KCNA1, Phe249Leu mutation) for type 1 and 19p for type 2. Patients with EA-1 have brief episodes of ataxia with myokymia and nystagmus that last only minutes. Startle, sudden change in posture, and exercise can induce episodes. Acetazolamide or anticonvulsants may be therapeutic. Patients with EA-2 have episodes of ataxia with nystagmus that can last for hours or days. Stress, exercise, or excessive fatigue may be precipitants. Acetazolamide may be therapeutic and can reverse the relative intracellular alkalosis detected by magnetic resonance spectroscopy. Stop codon, nonsense mutations causing EA-2 have been found in the CACNA1A gene, encoding the α_{1A} voltage-dependent calcium channel subunit (see “SCA6,” above).

■ AUTOSOMAL RECESSIVE ATAXIAS

Friedreich's Ataxia This is the most common form of inherited ataxia, comprising one-half of all hereditary ataxias. It can occur in a classic form or in association with a genetically determined vitamin E deficiency syndrome; the two forms are clinically indistinguishable.

SYMPTOMS AND SIGNS Friedreich's ataxia presents before 25 years of age with progressive staggering gait, frequent falling, and titubation. The lower extremities are more severely involved than the upper ones. Dysarthria occasionally is the presenting symptom; rarely, progressive scoliosis, foot deformity, nystagmus, or cardiopathy is the initial sign.

The neurologic examination reveals nystagmus, loss of fast saccadic eye movements, truncal titubation, dysarthria, dysmetria, and ataxia of trunk and limb movements. Extensor plantar responses (with normal tone in trunk and extremities), absence of deep tendon reflexes, and weakness (greater distally than proximally) are usually found. Loss of vibratory and proprioceptive sensation occurs. The median age of death is 35 years. Women have a significantly better prognosis than men.

Cardiac involvement occurs in 90% of patients. Cardiomegaly, symmetric hypertrophy, murmurs, and conduction defects are reported. Moderate mental retardation or psychiatric syndromes are present in a small percentage of patients. A high incidence (20%) of diabetes mellitus is found and is associated with insulin resistance and pancreatic β -cell dysfunction. Musculoskeletal deformities are common and



FIGURE 439-2 Sagittal magnetic resonance imaging (MRI) of the brain and spinal cord of a patient with Friedreich's ataxia, demonstrating spinal cord atrophy. (Reproduced with permission from RN Rosenberg, P Khemani, in RN Rosenberg, JM Pascual [eds]: Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th ed. London, Elsevier, 2015.)

include pes cavus, pes equinovarus, and scoliosis. MRI of the spinal cord shows atrophy (Fig. 439-2).

The primary sites of pathology are the spinal cord, dorsal root ganglion cells, and the peripheral nerves. Slight atrophy of the cerebellum and cerebral gyri may occur. Sclerosis and degeneration occur predominantly in the spinocerebellar tracts, lateral corticospinal tracts, and posterior columns. Degeneration of the glossopharyngeal, vagus, hypoglossal, and deep cerebellar nuclei is described. The cerebral cortex is histologically normal except for loss of Betz cells in the precentral gyrus. The peripheral nerves are extensively involved, with a loss of large myelinated fibers. Cardiac pathology consists of myocytic hypertrophy and fibrosis, focal vascular fibromuscular dysplasia with subintimal or medial deposition of periodic acid-Schiff (PAS)-positive material, myopathy with unusual pleomorphic nuclei, and focal degeneration of nerves and cardiac ganglia.

■ GENETIC CONSIDERATIONS

 The classic form of Friedreich's ataxia has been mapped to 9q13-q21.1, and the mutant gene, *frataxin*, contains expanded GAA triplet repeats in the first intron. There is homozygosity for expanded GAA repeats in >95% of patients. Normal persons have 7–22 GAA repeats, and patients have 200–900 GAA repeats. A more varied clinical syndrome has been described in compound heterozygotes who have one copy of the GAA expansion and the other copy a point mutation in the *frataxin* gene. When the point mutation is located in the region of the gene that encodes the amino-terminal half of frataxin, the phenotype is milder, often consisting of a spastic gait, retained or exaggerated reflexes, no dysarthria, and mild or absent ataxia.

Patients with Friedreich's ataxia have undetectable or extremely low levels of *frataxin* mRNA, as compared with carriers and unrelated individuals; thus, disease appears to be caused by a loss of expression of the *frataxin* protein. Frataxin is a mitochondrial protein involved in iron homeostasis. Mitochondrial iron accumulation due to loss of the iron transporter coded by the mutant *frataxin* gene results in a deficiency in iron/sulfur clusters containing mitochondrial enzymes, decreased ATP production, and accumulation of iron in the heart. Excess oxidized iron results in turn in the oxidation of cellular components and irreversible cell injury.

Two forms of hereditary ataxia associated with abnormalities in the interactions of vitamin E (α -tocopherol) with very-low-density lipoprotein (VLDL) have been delineated. These are abetalipoproteinemia (Bassen-Kornzweig syndrome) and ataxia with vitamin E deficiency (AVED). Abetalipoproteinemia is caused by mutations in the gene coding for the larger subunit of the microsomal triglyceride transfer protein (MTP). Defects in MTP result in impairment of formation and

secretion of VLDL in liver. This defect results in a deficiency of delivery of vitamin E to tissues, including the central and peripheral nervous system, as VLDL is the transport molecule for vitamin E and other fat-soluble substitutes. AVED is due to mutations in the gene for α -tocopherol transfer protein (α -TTP). These patients have an impaired ability to bind vitamin E into the VLDL produced and secreted by the liver, resulting in a deficiency of vitamin E in peripheral tissues. Hence, either absence of VLDL (abetalipoproteinemia) or impaired binding of vitamin E to VLDL (AVED) causes an ataxic syndrome. Once again, a genotype classification has proved to be essential in sorting out the various forms of the Friedreich's disease syndrome, which may be clinically indistinguishable.

Ataxia Telangiectasia • SYMPTOMS AND SIGNS Patients with ataxia telangiectasia (AT) present in the first decade of life with progressive telangiectatic lesions associated with deficits in cerebellar function and nystagmus. The neurologic manifestations correspond to those in Friedreich's disease, which should be included in the differential diagnosis. Truncal and limb ataxia, dysarthria, extensor plantar responses, myoclonic jerks, areflexia, and distal sensory deficits may develop. There is a high incidence of recurrent pulmonary infections and neoplasms of the lymphatic and reticuloendothelial system in patients with AT. Thymic hypoplasia with cellular and humoral (IgA and IgG2) immunodeficiencies, premature aging, and endocrine disorders such as type 1 diabetes mellitus are described. There is an increased incidence of lymphomas, Hodgkin's disease, acute T-cell leukemias, and breast cancer.

The most striking neuropathologic changes include loss of Purkinje, granule, and basket cells in the cerebellar cortex as well as of neurons in the deep cerebellar nuclei. The inferior olives of the medulla may also have neuronal loss. There is a loss of anterior horn neurons in the spinal cord and of dorsal root ganglion cells associated with posterior column spinal cord demyelination. A poorly developed or absent thymus gland is the most consistent defect of the lymphoid system.

■ GENETIC CONSIDERATIONS

The gene for AT (the *ATM* gene) at 11q22-23 encodes a protein that is similar to several yeast and mammalian phosphatidylinositol-3' kinases involved in mitogenic signal transduction, meiotic recombination, and cell cycle control. Defective DNA repair in AT fibroblasts exposed to ultraviolet light has been demonstrated. The discovery of *ATM* permits early diagnosis and identification of heterozygotes who are at risk for cancer (e.g., breast cancer). Elevated serum alpha-fetoprotein and immunoglobulin deficiency are noted.

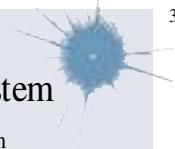
■ MITOCHONDRIAL ATAXIAS

Spinocerebellar syndromes have been identified with mutations in mitochondrial DNA (mtDNA). Thirty pathogenic mtDNA point mutations and 60 different types of mtDNA deletions are known, several of which cause or are associated with ataxia (Chap. 449).

TREATMENT

Ataxic Disorders

The most important goal in management of patients with ataxia is to identify treatable disease entities. Mass lesions must be recognized promptly and treated appropriately. Autoimmune paraneoplastic disorders can often be identified by the clinical patterns of disease that they produce, measurement of specific autoantibodies, and uncovering the primary cancer; these disorders are often refractory to therapy, but some patients improve following removal of the tumor or immunotherapy (Chap. 94). Ataxia with antigliadin antibodies and gluten-sensitive enteropathy may improve with a gluten-free diet. Malabsorption syndromes leading to vitamin E deficiency may lead to ataxia. The vitamin E deficiency form of Friedreich's ataxia must be considered, and serum vitamin E levels measured. Vitamin E therapy is indicated for these rare patients. Vitamin B₁ and B₁₂ levels in serum should be measured, and the



vitamins administered to patients having deficient levels. Hypothyroidism is easily treated. The cerebrospinal fluid should be tested for a syphilitic infection in patients with progressive ataxia and other features of tabes dorsalis. Similarly, antibody titers for Lyme disease and *Legionella* should be measured and appropriate antibiotic therapy should be instituted in antibody-positive patients. Aminoacidopathies, leukodystrophies, urea-cycle abnormalities, and mitochondrial encephalomyopathies may produce ataxia, and some dietary or metabolic therapies are available for these disorders. The deleterious effects of phenytoin and alcohol on the cerebellum are well known, and these exposures should be avoided in patients with ataxia of any cause.

There is no proven therapy for any of the autosomal dominant ataxias (SCA1 to SCA43). There is preliminary evidence that idebenone, a free-radical scavenger, can improve myocardial hypertrophy in patients with classic Friedreich's ataxia; there is no current evidence, however, that it improves neurologic function. A small preliminary study in a mixed population of patients with different inherited ataxias raised the possibility that the glutamate antagonist riluzole may offer modest benefit. Iron chelators and antioxidant drugs are potentially harmful in Friedreich's patients because they may increase heart muscle injury. Acetazolamide can reduce the duration of symptoms of EA. At present, identification of an at-risk person's genotype, together with appropriate family and genetic counseling, can reduce the incidence of these cerebellar syndromes in future generations (Chap. 467).

■ GENETIC DIAGNOSTIC LABORATORIES

1. Baylor College of Medicine; Houston, Texas, 1-713-798-6522
<http://www.bcm.edu/genetics/index.cfm?pmid=21387>
2. GeneDx
<http://www.genedx.com>
3. Transgenomic, 1-877-274-9432
<http://www.transgenomic.com/labs/neurology>

■ GLOBAL FEATURES

Ataxias with autosomal dominant, autosomal recessive, X-linked, or mitochondrial forms of inheritance are present on a worldwide basis. Machado-Joseph disease (SCA3) (autosomal dominant) and Friedreich's ataxia (autosomal recessive) are the most common types in most populations. Genetic markers are now commercially available to precisely identify the genetic mutation for correct diagnosis and also for family planning. Early detection of asymptomatic preclinical disease can reduce or eliminate the inherited form of ataxia in some families on a global, worldwide basis.

■ FURTHER READING

- A M et al: The autosomal recessive cerebellar ataxias. *N Engl J Med* 366:636, 2012.
- J H et al: Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: A longitudinal cohort study. *Lancet Neurol* 14:1101, 2015.
- M D, H M: Role of repeats in protein clearance. *Nature* 545:33, 2017.
- P HL et al: Polyglutamine spinocerebellar ataxias—from genes to potential therapy. *Nat Rev Neurosci* 18:613, 2017.
- R S et al: Riluzole in patients with hereditary cerebellar ataxia: A randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 14:985, 2015.

The autonomic nervous system (ANS) innervates the entire neuraxis and influences all organ systems. It regulates blood pressure (BP); heart rate; sleep; and glandular, pupillary, bladder, and bowel function. It maintains organ homeostasis and operates automatically; its full importance becomes recognized only when ANS function is compromised, resulting in dysautonomia. Dysautonomia can result from a primary disorder of the central or peripheral nervous system, or from a nonneurogenic cause. Not infrequently more than one contributor may be present, for example the additive effects of a medication in a patient with diabetes mellitus, cardiovascular insufficiency, or normal aging may be responsible. It is helpful to characterize dysautonomia by its time course (acute, subacute, or chronic; progressive or static), severity, and whether manifestations are continuous or intermittent. *Hypothalamic disorders that cause disturbances in homeostasis are discussed in Chaps. 18 and 378.*

ANATOMIC ORGANIZATION

The activity of the ANS is regulated by central neurons responsive to diverse afferent inputs. After central integration of afferent information, autonomic outflow is adjusted to permit the functioning of the major organ systems in accordance with the needs of the whole organism. Connections between the cerebral cortex and the autonomic centers in the brainstem coordinate autonomic outflow with higher mental functions.

The preganglionic neurons of the parasympathetic nervous system leave the central nervous system (CNS) in the third, seventh, ninth, and tenth cranial nerves as well as the second and third sacral nerves, whereas the preganglionic neurons of the sympathetic nervous system exit the spinal cord between the first thoracic and the second lumbar segments (Fig. 440-1). The autonomic preganglionic fibers are thinly myelinated. The postganglionic neurons, located in ganglia outside the CNS, give rise to the postganglionic unmyelinated autonomic nerves that innervate organs and tissues throughout the body. Responses to sympathetic and parasympathetic stimulation are frequently antagonistic (Table 440-1), reflecting highly coordinated interactions within the CNS; the resultant changes in parasympathetic and sympathetic activity provide more precise control of autonomic responses than could be achieved by the modulation of a single system. In general, the “fight or flight” response is a consequence of increased sympathetic activity while the “rest and digest” reflects increased parasympathetic activity.

Acetylcholine (ACh) is the preganglionic neurotransmitter for both the sympathetic and parasympathetic divisions of the ANS as well as the postganglionic neurotransmitter of the parasympathetic neurons; the preganglionic receptors are nicotinic, and the postganglionic are muscarinic in type. Norepinephrine (NE) is the neurotransmitter of the postganglionic sympathetic neurons, except for cholinergic neurons innervating the eccrine sweat glands.

The gastrointestinal (GI) tract has long been described as part of the sympathetic and parasympathetic nervous systems. However, it has many unique characteristics such that it is now considered separately as the enteric nervous system. Parasympathetic control of the GI system is through the craniospinal nerves (vagus and S2-S4 nerves) while sympathetic efferent control is through the thoracolumbar region. The enteric nervous system itself is made up of a series of ganglia that form a network of plexuses with several hundred million cells (the equivalent of the number of cells in the spinal cord). Meissner's (submucosal) plexus, Auerbach's (myenteric), Cajal's (deep muscular), mucosal,

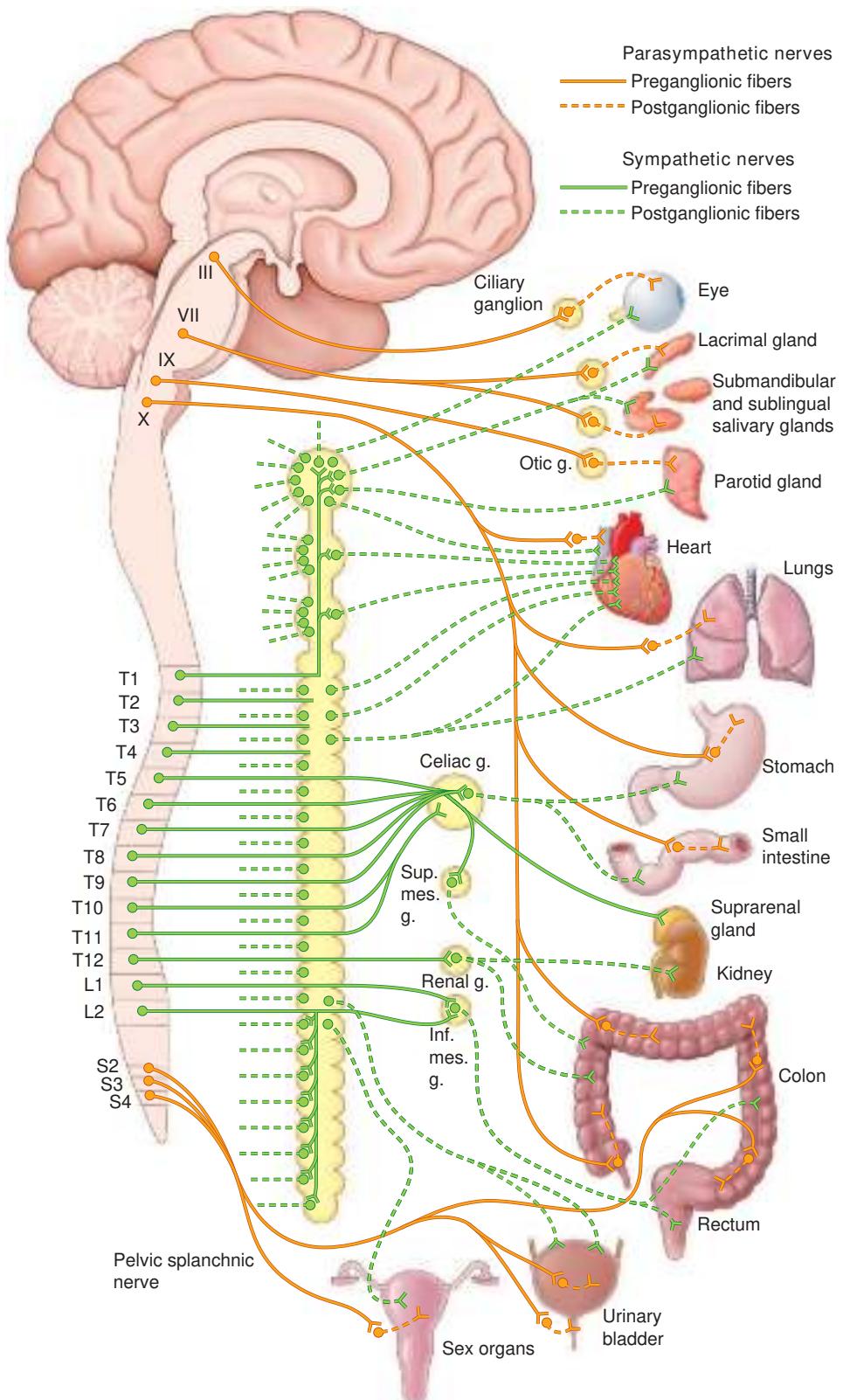


FIGURE 440-1 Schematic representation of the autonomic nervous system. (Adapted with permission from R Snell: Clinical Neuroanatomy, 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2009.)

TABLE 440-1 Effects of Sympathetic and Parasympathetic Systems on Various Effector Organs

	SYMPATHETIC	PARASYMPATHETIC
Pupil	Pupillodilation (alpha)	Pupilloconstriction
Accommodation	Decreased	Increased
Heart	Positive chronotropic effect (beta)	Negative chronotropic effect
	Positive inotropic effect (beta)	Negative inotropic effect
Arteries	Vasoconstriction (alpha) Vasodilation (beta)	Vasodilation
Veins	Vasoconstriction (alpha) Vasoconstriction (beta)	
Tracheobronchial tree	Bronchodilation (beta)	Bronchoconstriction Increased bronchial gland secretions
Gastrointestinal tract	Decreased motility (beta) Contraction of sphincters (alpha)	Increased motility Relaxation of sphincter
Bladder	Detrusor relaxation (beta) Contraction of sphincter (alpha)	Detrusor contraction Relaxation of sphincter
Salivary glands	Scant, thick, viscid saliva (alpha)	Copious, thin, watery saliva
Skin	Piloerection (cutis anserina)	No piloerection
Sweat glands	Increased secretion (cholinergic)	Decreased secretion
Genitalia	Ejaculation	Ejaculation/Erection
Adrenal medulla	Catecholamine release	
Glycogen	Glycogenolysis (alpha and beta) Lipolysis (alpha and beta)	Glycogen synthesis

Source: Reproduced with permission from WW Campbell: The autonomic nervous system, in DeJong's The Neurologic Examination, 8th ed. Wolters Kluwer, 2020.

and submucosal plexuses comprise the majority of nerves within the enteric nervous system. Numerous neurotransmitters have now been identified within the enteric nervous system, with many neurons containing both primary and co-transmitter neurotransmitters.

CLINICAL EVALUATION

■ CLASSIFICATION

Disorders of the ANS may result from pathology of either the CNS or the peripheral nervous system (PNS) (Table 440-2). Signs and symptoms may result from interruption of the afferent limb, CNS processing centers, or efferent limb of reflex arcs controlling autonomic responses. For example, a lesion of the medulla produced by a posterior fossa tumor can impair BP responses to postural changes and result in orthostatic hypotension (OH). OH can also be caused by lesions of the afferent limb of the baroreflex arc (e.g., radiation or congenital disease), spinal cord, or peripheral vasomotor nerve fibers (e.g., diabetic and other neuropathies). Lesions of the efferent limb cause the most consistent and severe OH. The site of reflex interruption is usually established by the clinical context in which the dysautonomia arises, combined with judicious use of ANS testing and neuroimaging studies. The presence or absence of CNS signs, association with sensory or motor polyneuropathy, medical illnesses, medication use, and family history are important considerations. Some syndromes do not fit easily into any classification scheme.

■ SYMPTOMS OF AUTONOMIC DYSFUNCTION

Clinical manifestations can result from loss of function, overactivity, or dysregulation of autonomic circuits. Disorders of autonomic function

should be considered in patients with unexplained OH, syncope, sleep dysfunction, altered sweating (hyperhidrosis or hypohidrosis), impotence, constipation, or other GI symptoms (bloating, nausea, vomiting of old food, diarrhea), or bladder disorders (urinary frequency, hesitancy, or incontinence). Symptoms may be widespread or regional in distribution. An autonomic history focuses on systemic functions (orthostatic symptoms, BP, heart rate, sleep, fever, hypothermia, sweating) and involvement of individual organ systems (pupils, bowel, bladder, sexual function). Specific symptoms of orthostatic intolerance are diverse (Table 440-3).

Early autonomic symptoms may be overlooked. Impotence, although not specific for autonomic failure, often heralds autonomic failure in men and may precede other symptoms by years (Chap. 397). A decrease in the frequency of spontaneous early-morning erections may occur months before loss of nocturnal penile tumescence and development of total impotence. Bladder dysfunction may appear early in men and women, particularly in those with a CNS etiology. Cold feet may indicate increased peripheral vasomotor constriction, although this symptom is a very common complaint among healthy individuals as well. Brain and spinal cord disease above the level of the lumbar spine results first in urinary frequency and small bladder volumes and eventually in urinary incontinence (upper motor neuron or spastic bladder). By contrast, PNS disease of autonomic nerve fibers results in large bladder volumes, urinary frequency, and overflow incontinence (lower motor neuron or flaccid bladder). Measurements of bladder volume (postvoid residual), or urodynamic studies, are useful tests for distinguishing between upper and lower motor neuron bladder dysfunction in the early stages of dysautonomia. GI autonomic dysfunction typically presents as progressively severe constipation. Diarrhea may develop (typically in diabetes mellitus) due to many reasons including rapid transit of contents, uncoordinated small-bowel motor activity, an osmotic basis from bacterial overgrowth associated with small-bowel stasis, or anorectal dysfunction with diminished sphincter control and increased intestinal secretion. Impaired glandular secretory function may cause difficulty with food intake due to decreased salivation or eye irritation due to decreased lacrimation. Loss of sweat function (anhidrosis), a critical element of thermoregulation, may result in hyperthermia. Patients with a length-dependent neuropathy may present with distal anhidrosis but the primary symptom may be proximal hyperhidrosis that occurs to maintain thermoregulation (Chap. 18). Lack of sweating after a hot bath, during exercise, or on a hot day can suggest sudomotor failure.

OH (also called *postural hypotension*) is perhaps the most common and disabling feature of autonomic dysfunction. There are numerous causes of OH (e.g., medications, anemia, dehydration, or volume depletion), but when the OH is specifically due to dysfunction of the ANS it is referred to as neurogenic OH. The prevalence of OH is relatively high, especially when OH associated with aging and diabetes mellitus is included (Table 440-4). OH can cause a variety of symptoms, including dimming or loss of vision, light-headedness, diaphoresis, diminished hearing, pallor, weakness, and shortness of breath. Syncope results when the drop in BP impairs cerebral perfusion. Other manifestations of impaired baroreflexes are supine hypertension, a heart rate that is fixed regardless of posture, postprandial hypotension, and an excessively high nocturnal BP. Many patients with OH have a preexisting diagnosis of hypertension or have concomitant supine hypertension, reflecting the great importance of baroreflexes in maintaining postural and supine normotension. The appearance of OH in patients receiving antihypertensive treatment may indicate overtreatment or the onset of an autonomic disorder. The most common causes of OH are not neurologic in origin (Table 440-5); these must be distinguished from the neurogenic causes. The mortality rates of nonneurogenic OH are similar to that of the general population while neurogenic OH carries a three- to sevenfold higher mortality rate. *Neurocardiogenic and cardiac causes of syncope* are considered in Chap. 21.

TABLE 440-2 Classification of Clinical Autonomic Disorders

I. Autonomic Disorders with Brain Involvement

A. Associated with multisystem degeneration	3. Disorders of the hypothalamus
1. Multisystem degeneration: autonomic failure clinically prominent	a. Thiamine deficiency (Wernicke-Korsakoff syndrome)
a. Multiple-system atrophy (MSA)	b. Diencephalic syndrome
b. Parkinson's disease with autonomic failure	c. Neuroleptic malignant syndrome
c. Diffuse Lewy body disease with autonomic failure	d. Serotonin syndrome
2. Multisystem degeneration: autonomic failure clinically not usually prominent	e. Fatal familial insomnia
a. Parkinson's disease without autonomic failure	f. Antidiuretic hormone (ADH) syndromes (diabetes insipidus, inappropriate ADH secretion)
b. Other extrapyramidal disorders (inherited spinocerebellar atrophies, progressive supranuclear palsy, corticobasal degeneration, Machado-Joseph disease, fragile X syndrome [FXTAS])	g. Disturbances of temperature regulation (hyperthermia, hypothermia)
B. Unassociated with multisystem degeneration (focal CNS disorders)	h. Disturbances of sexual function
1. Disorders mainly due to cerebral cortex involvement	i. Disturbances of appetite
a. Frontal cortex lesions causing urinary/bowel incontinence	j. Disturbances of BP/HR and gastric function
b. Focal seizures (temporal lobe or anterior cingulate)	k. Horner's syndrome
c. Cerebral infarction of the insula	4. Disorders of the brainstem and cerebellum
2. Disorders of the limbic and paralimbic circuits	a. Posterior fossa tumors
a. Shapiro's syndrome (agenesis of corpus callosum, hyperhidrosis, hypothermia)	b. Syringobulbia and Arnold-Chiari malformation
b. Autonomic seizures	c. Disorders of BP control (hypertension, hypotension)
c. Limbic encephalitis	d. Cardiac arrhythmias
	e. Central sleep apnea
	f. Baroreflex failure
	g. Horner's syndrome
	h. Vertebrobasilar and lateral medullary (Wallenberg's) syndromes
	i. Brainstem encephalitis

II. Autonomic Disorders with Spinal Cord Involvement

A. Traumatic quadriplegia	E. Amyotrophic lateral sclerosis
B. Syringomyelia	F. Tetanus
C. Subacute combined degeneration	G. Stiff-person syndrome
D. Multiple sclerosis and neuromyelitis optica	H. Spinal cord tumors

III. Autonomic Neuropathies

A. Acute/subacute autonomic neuropathies	B. Chronic peripheral autonomic neuropathies
a. Subacute autoimmune autonomic ganglionopathy (AAG)	1. Distal small fiber neuropathy—cryptogenic sensory polyneuropathy (CSPN)
b. Subacute paraneoplastic autonomic neuropathy	2. Combined sympathetic and parasympathetic failure
c. Guillain-Barré syndrome	a. Amyloid
d. Botulism	b. Diabetic autonomic neuropathy
e. Porphyria	c. AAG (paraneoplastic and idiopathic)
f. Drug-induced autonomic neuropathies—stimulants, drug withdrawal, vasoconstrictor, vasodilators, beta-receptor antagonists, beta-agonists	d. Sensory neuronopathy with autonomic failure
g. Toxin-induced autonomic neuropathies	e. Familial dysautonomia (Riley-Day syndrome)
h. Subacute cholinergic neuropathy	f. Diabetic, uremic, or nutritional deficiency
	g. Geriatric dysautonomia (age >80 years)
	h. Hereditary sensory and autonomic neuropathy
	i. HIV-related autonomic neuropathy
	3. Disorders of orthostatic intolerance: reflex syncope; POTS; prolonged bed rest; space flight; chronic fatigue

Abbreviations: BP, blood pressure; CNS, central nervous system; HR, heart rate; POTS, postural orthostatic tachycardia syndrome.

TABLE 440-3 Symptoms of Orthostatic Intolerance

Light-headedness (dizziness)	88%
Weakness or tiredness	72%
Cognitive difficulty (thinking/concentrating)	47%
Blurred vision	47%
Tremulousness	38%
Vertigo	37%
Pallor	31%
Anxiety	29%
Palpitations	26%
Clammy feeling	19%
Nausea	18%

Source: Reproduced with permission from PA Low et al: Prospective evaluation of clinical characteristics of orthostatic hypotension. Mayo Clinic Proceedings 70:617, 1995.

TABLE 440-4 Prevalence of Orthostatic Hypotension in Different Situations

DISORDER	PREVALENCE
Aging	14–20%
Diabetic neuropathy	10%
Other autonomic neuropathies	>60%
Multiple-system atrophy	>90%
Pure autonomic failure	>95%

TABLE 440-5 Nonneurogenic Causes of Orthostatic Hypotension

Cardiac Pump Failure
• Myocardial infarction
• Myocarditis
• Constrictive pericarditis
• Aortic stenosis
• Tachyarrhythmias
• Bradyarrhythmias
• Venous obstruction
Reduced Intravascular Volume
• Straining or heavy lifting, urination, defecation
• Dehydration
• Diarrhea, emesis
• Hemorrhage
• Burns
• Salt-losing nephropathy
• Adrenal insufficiency
• Diabetes insipidus
Metabolic
• Adrenocortical insufficiency
• Hypoaldosteronism
• Pheochromocytoma
• Severe potassium depletion
Venous Pooling
• Alcohol
• Postprandial dilation of splanchnic vessel beds
• Vigorous exercise with dilation of skeletal vessel beds
• Heat: hot environment, hot showers and baths, fever
• Prolonged recumbency or standing
• Sepsis
Medications
• Antihypertensives
• Diuretics
• Vasodilators: nitrates, hydralazine
• Alpha- and beta-blocking agents
• Central nervous system sedatives: barbiturates, opiates
• Tricyclic antidepressants
• Phenothiazines

APPROACH TO THE PATIENT

Orthostatic Hypotension and Other ANS Disorders

The first step in the evaluation of symptomatic OH is the exclusion of treatable causes. The history should include a review of medications that may affect the ANS (**Table 440-6**). The main classes of drugs that may cause OH are diuretics, antihypertensive agents (preload reducers, vasodilators, negative inotropic or chronotropic agents), antidepressants (tricyclic antidepressants and SSRIs), ethanol, opioids, insulin, dopamine agonists, and barbiturates. However, the precipitation of OH by medications may also be the first sign of an underlying autonomic disorder. The history may reveal an underlying cause for symptoms (e.g., diabetes, Parkinson's disease) or specific underlying mechanisms (e.g., cardiac pump failure, reduced intravascular volume). The relationship of symptoms to meals (splanchnic pooling), standing on awakening in the morning (intravascular volume depletion), ambient warming (vasodilatation), or exercise (muscle arteriolar vasodilatation) should be sought. Standing time to first symptom and to presyncope (**Chap. 21**) should be followed for management.

Physical examination includes measurement of supine and standing pulse and BP. OH is defined as a sustained drop in systolic (≥ 20 mmHg) or diastolic (≥ 10 mmHg) BP after 3 min of standing. In nonneurogenic causes of OH (such as hypovolemia), the BP

TABLE 440-6 Some Drugs That Affect Autonomic Function

SYMPMOM	DRUG CLASS	SPECIFIC EXAMPLES
Impotence	Opioids	Tylenol #3
	Anabolic steroids	—
	Some antiarrhythmics	Prazosin
	Some antihypertensives	Clonidine
	Some diuretics	Benzazepril
	Some SSRIs	Venlafaxine
Urinary retention	Opioids	Fentanyl
	Decongestants	Brompheniramine Diphenhydramine
Diaphoresis	Some antihypertensives	Amlodipine
	Some SSRIs	Citalopram
	Opioids	Morphine

Abbreviations: CCBs, calcium channel blockers; HCTZ, hydrochlorothiazide; SSRIs, selective serotonin reuptake inhibitors.

drop is accompanied by a compensatory increase in heart rate of >15 beats/min. In neurogenic OH, the pulse fails to rise despite the drop in blood pressure. A clue that the patient has neurogenic OH is the aggravation or precipitation of OH by autonomic stressors (a meal, hot bath, or exercise). Neurologic examination should include mental status (neurodegenerative disorders such as Lewy body dementia can be accompanied by significant dysautonomia), cranial nerves (abnormal pupils with Horner's or Adie's syndrome), motor tone (parkinsonian syndromes), and motor strength and sensation (polyneuropathies). In patients without a clear diagnosis initially, follow-up evaluations every few months or whenever symptoms worsen may reveal the underlying cause.

AUTONOMIC TESTING

Autonomic function tests are helpful to document and localize abnormalities when findings on history and examination are inconclusive; to detect subclinical involvement; or to follow the course of an autonomic disorder.

Heart Rate Variation With Deep Breathing This tests the parasympathetic component of cardiovascular reflexes via the vagus nerve. Results are influenced by multiple factors including the subject's position (recumbent, sitting, or standing), rate and depth of respiration (6 breaths per minute and a forced vital capacity [FVC] >1.5 L are optimal), age, medications, weight, and degree of hypoxia. Interpretation of results requires comparison of test data with results from age-matched controls collected under identical test conditions. For example, the lower limit of normal heart rate variation with deep breathing in persons <20 years of age is $>15\text{--}20$ beats/min, but for persons aged >60 it is 5–8 beats/min. Heart rate variation with deep breathing (respiratory sinus arrhythmia) is abolished by the muscarinic ACh receptor antagonist atropine but is unaffected by sympathetic postganglionic blockade (e.g., propranolol).

Valsalva Response This response (**Table 440-7**) assesses the integrity of the baroreflex control of heart rate (parasympathetic) and BP (sympathetic adrenergic). Under normal conditions, increases in BP at the carotid bulb trigger a reduction in heart rate (increased vagal tone), and decreases in BP trigger an increase in heart rate (reduced vagal tone). The Valsalva response is tested in the supine position. The subject exhales against a closed glottis (or into a manometer maintaining a constant expiratory pressure of 40 mmHg) for 15 s while measuring changes in heart rate and beat-to-beat BP. Without directly measuring expiratory pressure, heart rate, and beat-to-beat blood pressure, the Valsalva maneuver cannot be interpreted correctly. There are four phases of the BP and heart rate response to the Valsalva maneuver. Phases I and III are mechanical and related to changes in intrathoracic and intraabdominal pressure. In early phase II, reduced venous return results in a

TABLE 440-7 Normal Blood Pressure and Heart Rate Changes During the Valsalva Maneuver

PHASE	MANEUVER	BLOOD PRESSURE	HEART RATE	COMMENTS
I	Forced expiration against a partially closed glottis	Rises; aortic compression from raised intrathoracic pressure	Decreases	Mechanical
II early	Continued expiration	Falls; decreased venous return to the heart	Increases (reflex tachycardia)	Reduced vagal tone
II late	Continued expiration	Rises; reflex increase in peripheral vascular resistance	Increases at slower rate	Requires intact efferent sympathetic response
III	End of expiration	Falls; increased capacitance of pulmonary bed	Increases further	Mechanical
IV	Recovery	Rises; persistent vasoconstriction and increased cardiac output	Compensatory bradycardia	Requires intact efferent sympathetic response

fall in stroke volume and BP, counteracted by a combination of reflex tachycardia and increased total peripheral resistance. Increased total peripheral resistance arrests the BP drop ~5–8 s after the onset of the maneuver. Late phase II begins with a progressive rise in BP toward or above baseline. Venous return and cardiac output return to normal in phase IV. Persistent peripheral arteriolar vasoconstriction and increased cardiac adrenergic tone result in a temporary BP overshoot and phase IV bradycardia (mediated by the baroreceptor reflex). Abnormalities in BP during phase II recovery or phase IV overshoot suggest sympathetic adrenergic dysfunction.

Autonomic parasympathetic function during the Valsalva maneuver is measured using heart rate changes. The *Valsalva ratio* is defined as the maximum phase II tachycardia divided by the minimum phase IV bradycardia (Table 440-8) and is predominantly a measure of parasympathetic function.

Sudomotor Function Sweating is induced by release of ACh from sympathetic postganglionic fibers. The quantitative sudomotor axon reflex test (QSART) is a measure of regional autonomic function mediated by ACh-induced sweating. A reduced or absent response indicates a lesion of the postganglionic sudomotor axon. For example, sweating may be reduced in the feet as a result of distal polyneuropathy (e.g., diabetes). The thermoregulatory sweat test (TST) is a qualitative measure of global sweat production in response to an elevation of body temperature under controlled conditions. An indicator powder placed on the anterior surface of the body changes color with sweat production during temperature elevation. The pattern of color change measures the integrity of both the preganglionic and postganglionic sudomotor function. A postganglionic lesion is present if both QSART and TST show absent sweating. In a preganglionic lesion, the QSART is normal but TST shows anhidrosis.

TABLE 440-8 Neural Pathways Underlying Some Standardized Autonomic Tests

TEST EVALUATED	PROCEDURE	AUTONOMIC FUNCTION
HRDB	6 deep breaths/min	Cardiovagal (parasympathetic) function
Valsalva ratio	Expiratory pressure, 40 mmHg for 10–15 s	Cardiovagal (parasympathetic) function
QSART	Axon-reflex test 4 limb sites	Preganglionic (sympathetic cholinergic) sudomotor function
BP _{BB} to VM	BP _{BB} response to VM	Sympathetic adrenergic function: baroreflex adrenergic control of vagal and vasomotor function
HUT	BP _{BB} and heart rate response to HUT	Sympathetic adrenergic and cardiovagal (parasympathetic) responses to HUT

Abbreviations: BP_{BB}, beat-to-beat blood pressure; HRDB, heart rate response to deep breathing; HUT, head-up tilt; QSART, quantitative sudomotor axon reflex test; VM, Valsalva maneuver.

Orthostatic BP Recordings Beat-to-beat BP measurements determined in supine, 70° tilt, and tilt-back positions are useful to quantitate orthostatic failure of BP control. Allow a 20-min period of rest in the supine position before assessing changes in BP during tilting. The BP change combined with heart rate monitoring is useful for the evaluation of patients with suspected OH or unexplained syncope.

Tilt Table Testing For Syncope The great majority of patients with syncope do not have autonomic failure. Tilt table testing can be used to make the diagnosis of vasovagal syncope with sensitivity, specificity, and reproducibility. A standardized protocol is used that specifies the tilt apparatus, tilt angle, and duration of tilt. A passive phase for 30–40 min with a tilt angle at 60°–70° can identify reflex syncope, psychogenic syncope, or be nondiagnostic. Pharmacologic provocation of syncope (with intravenous, sublingual, or spray nitroglycerin) is controversial because it increases sensitivity at the cost of specificity. Recommendations for the performance of tilt studies for syncope have been incorporated in consensus guidelines.

SPECIFIC SYNDROMES OF ANS DYSFUNCTION

MULTIPLE SYSTEM ATROPHY

Multiple-system atrophy (MSA) is an entity that comprises autonomic failure (OH or a neurogenic bladder) and either parkinsonism (MSA-p) or a cerebellar syndrome (MSA-c). MSA-p is the more common form; the parkinsonism is atypical in that there is more symmetric motor involvement than in Parkinson's disease (PD; Chap. 435), tremor is not as prominent, and there is a poor or only transient response to levodopa. Symptomatic OH within 1 year of onset of parkinsonism is suggestive of MSA-p. There is a very high frequency of impotence in men. Although autonomic abnormalities are common in advanced PD, the severity and distribution of autonomic failure are more severe and generalized in MSA. Brain MRI is a useful diagnostic adjunct: in MSA-p, iron deposition in the striatum may be evident as T2 hypointensity, and in MSA-c, cerebellar atrophy is present with a characteristic T2 hyperintense signal ("hot cross bun" sign) in the pons (Fig. 440-2). However, these MRI findings are typically present only with advanced disease. Cardiac postganglionic adrenergic innervation, measured by uptake of fluorodopamine on positron emission tomography, is markedly impaired in the dysautonomia of PD but is usually normal in MSA. Neuropathologic changes include neuronal loss and gliosis in many CNS regions, including the brainstem, cerebellum, striatum, and intermediolateral cell column of the thoracolumbar spinal cord. Glial cytoplasmic inclusions that stain positively (for Lewy bodies) are present primarily in oligodendrocytes in MSA, in contrast to neuronal inclusions in PD. Furthermore, transfer of brain extracts from MSA patients into susceptible mice resulted in widespread α -synuclein aggregate formation and neurodegeneration, consistent with a prion mechanism.

MSA is uncommon, with a prevalence estimated at 2–5 per 100,000 individuals. Onset is typically in the mid-fifties, men are slightly more often affected than women, and most cases are sporadic. The diagnosis should be considered in adults aged >30 years who present with

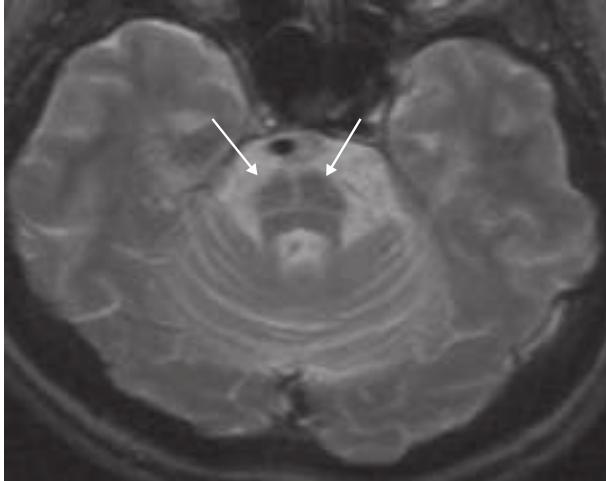


FIGURE 440-2 Multiple-system atrophy, cerebellar type (MSA-c). Axial T2-weighted magnetic resonance image at the level of the pons shows a characteristic hyperintense signal, the “hot cross bun” sign (arrows). This appearance can also be seen in some spinocerebellar atrophies, as well as other neurodegenerative conditions affecting the brainstem.

OH or urinary incontinence and either parkinsonism that is poorly responsive to dopamine replacement or a cerebellar syndrome. MSA generally progresses relentlessly to death 7–10 years after onset, but survival beyond 15 years has been reported. MSA-p is more prevalent in Western countries, while MSA-c is more common in Japan. Factors that predict a worse prognosis include early autonomic dysfunction, rapid progression of disability, bladder dysfunction, female gender, the MSA-p subtype, and an older age at onset. Management is symptomatic for neurogenic OH (see below), sleep disorders including laryngeal stridor, GI, and urinary dysfunction. GI management includes frequent small meals, soft diet, stool softeners, and bulk agents. Gastroparesis is difficult to treat; metoclopramide stimulates gastric emptying but worsens parkinsonism by blocking central dopamine receptors. The peripheral dopamine (D_1 and D_2) receptor antagonist domperidone has been used in patients with various GI conditions in many countries, and although not available in the United States, it can be obtained through the U.S. Food and Drug Administration’s (FDA) Expanded Access to Investigational Drugs program.

Autonomic dysfunction is also a common feature in dementia with Lewy bodies (Chap. 434), with the severity usually intermediate between that found in MSA and PD. In multiple sclerosis (MS; Chap. 444), autonomic complications reflect the CNS location of MS involvement and generally worsen with disease duration and disability, but are generally a secondary complaint and not of the severity seen in the synucleinopathies.

■ SPINAL CORD

Spinal cord lesions from any cause can result in focal autonomic deficits or autonomic hyperreflexia (e.g., spinal cord transection or hemisection) affecting bowel, bladder, sexual, temperature-regulation, or cardiovascular functions. Quadriparetic patients exhibit both supine hypertension and OH after upward tilting. *Autonomic dysreflexia* describes a dramatic increase in BP in patients with traumatic spinal cord lesions above the T6 level, often in response to irritation of the bladder, skin, or muscles. Cord injury below T6 allows for compensatory splanchnic vasodilation and prevents autonomic dysreflexia. The triggers may be clinically silent because perception of painful sensations arising from structures innervated below the level of a spinal cord lesion is often blunted or absent. A distended bladder, often from an obstructed Foley catheter or a urinary infection, is a common trigger of dysreflexia. Associated symptoms can include facial flushing, headache, hypertension, or piloerection. Potential complications include intracranial vasospasm or hemorrhage, cardiac arrhythmia, and death. Awareness of the syndrome, identifying the trigger, and

careful monitoring of BP during procedures in patients with acute or chronic spinal cord injury are essential. In patients with supine hypertension, BP can be lowered by tilting the head upward or sitting the patient up. Vasodilator drugs may be used to treat acute elevations in BP. Clonidine can be used prophylactically to reduce the hypertension resulting from bladder stimulation. Dangerous increases or decreases in body temperature may result from an inability to sense heat or cold exposure or control peripheral vasoconstriction or sweating below the level of the spinal cord injury.

■ PERIPHERAL NERVE AND NEUROMUSCULAR JUNCTION DISORDERS

Peripheral neuropathies (Chap. 446) are the most common cause of chronic autonomic insufficiency. Polyneuropathies that affect small myelinated and unmyelinated fibers of the sympathetic and parasympathetic nerves commonly occur in diabetes mellitus, amyloidosis, chronic alcoholism, porphyria, idiopathic small-fiber polyneuropathy, and Guillain-Barré syndrome. Neuromuscular junction disorders with autonomic involvement include botulism and Lambert-Eaton syndrome (Chap. 448).

Diabetes Mellitus The presence of autonomic neuropathy in patients with diabetes increases the mortality rate 1.5- to 3-fold, even after adjusting for other cardiovascular risk factors. Estimates of 5-year mortality risk among these patients are 15–53%. Although many deaths are due to secondary vascular disease, there are patients who specifically suffer cardiac arrest due to autonomic neuropathy. The autonomic involvement is also predictive of other complications including renal disease, stroke, and sleep apnea. Tight glycemic control with insulin significantly reduces the long-term risk of autonomic cardiovascular neuropathy. *Diabetes mellitus* is discussed in Chaps. 403–405.

Amyloidosis Autonomic neuropathy occurs in both sporadic and familial forms of amyloidosis. The AL (immunoglobulin light chain) type is associated with primary amyloidosis or amyloidosis secondary to multiple myeloma. The amyloid transthyretin (TTR) type, with transthyretin as the primary protein component, is responsible for the most common form of inherited amyloidosis. Although patients usually present with a distal sensorimotor polyneuropathy accompanied by autonomic insufficiency that can precede the development of the polyneuropathy or occur in isolation. The diagnosis can be made by protein electrophoresis of blood and urine, tissue biopsy (abdominal fat pad, rectal mucosa, or sural nerve) to search for amyloid deposits, and genetic testing for transthyretin mutations in familial cases. Recently two gene-modulating therapies have been shown to be effective in hereditary amyloidosis from TTR mutations. Death is usually due to cardiac or renal involvement. Postmortem studies reveal amyloid deposition in many organs, including two sites that contribute to autonomic failure: intraneuronal blood vessels and autonomic ganglia. Pathologic examination reveals a loss of both unmyelinated and myelinated nerve fibers. *Amyloidosis* is discussed in Chap. 112.

Alcoholic Neuropathy Abnormalities in parasympathetic vagal and efferent sympathetic function are usually mild in alcoholic polyneuropathy. OH is usually due to brainstem involvement, rather than injury to the PNS. Impotence is a major problem, but concurrent gonadal hormone abnormalities may play a role in this symptom. Clinical symptoms of autonomic failure generally appear only when the stocking-glove polyneuropathy is severe, and there is usually coexisting Wernicke’s encephalopathy (Chap. 307). Autonomic involvement may contribute to the high mortality rates associated with alcoholism. *Alcoholism* is discussed in Chap. 453.

Porphyria Autonomic dysfunction is most extensively documented in acute intermittent porphyria but can also occur with variegate porphyria and hereditary coproporphyria. Autonomic symptoms include tachycardia, sweating, urinary retention, abdominal pain, nausea and vomiting, insomnia, hypertension, and (less commonly) hypotension. Another prominent symptom is anxiety. Abnormal autonomic

3434 function can occur both during acute attacks and during remissions. Elevated catecholamine levels during acute attacks correlate with the degree of tachycardia and hypertension that is present. *Porphyria is discussed in Chap. 416.*

Guillain-Barré Syndrome BP fluctuations and arrhythmias from autonomic instability can be severe. It is estimated that 2–10% of patients with severe Guillain-Barré syndrome suffer fatal cardiovascular collapse. GI autonomic involvement, sphincter disturbances, abnormal sweating, and pupillary dysfunction can also occur. Demyelination has been described in the vagus and glossopharyngeal nerves, the sympathetic chain, and the white rami communicantes. Interestingly, the degree of autonomic involvement appears to be independent of the severity of motor or sensory neuropathy. Acute autonomic and sensory neuropathy is a variant that spares the motor system and presents with neurogenic OH and varying degrees of sensory loss. It is treated similarly to Guillain-Barré syndrome, but prognosis is less favorable, with persistent severe sensory deficits and variable degrees of OH in many patients. *Guillain-Barré Syndrome is discussed in Chap. 447.*

Autoimmune Autonomic Ganglionopathy (AAG) and Seronegative Autoimmune Autonomic Neuropathy (SAAN) These conditions present with the subacute development of autonomic disturbances including OH, enteric neuropathy (gastroparesis, ileus, constipation/diarrhea), flaccid bladder, and cholinergic failure (e.g., loss of sweating, sicca complex, and a tonic pupil). A chronic form of AAG resembles pure autonomic failure (PAF) (see below). Autoantibodies against the $\alpha 3$ subunit of the ganglionic Ach receptor are considered diagnostic of AAG. When these antibodies are not detected, the cases may be labeled SAAN, but it is unclear if these can be clearly divided into different categories. Pathology shows preferential involvement of small unmyelinated nerve fibers, with sparing of larger myelinated ones. Onset of the neuropathy follows a viral infection in approximately half of cases. Up to one-third of untreated patients experience significant functional improvement over time. Immunotherapies that have been reported to be helpful include plasmapheresis, intravenous immune globulin, glucocorticoids, azathioprine, rituximab, and mycophenolate mofetil. OH, gastroparesis, and sicca symptoms can be managed symptomatically.

AAG can also occur on a paraneoplastic basis, with adenocarcinoma or small-cell carcinoma of the lung, lymphoma, or thymoma being the most common (Chap. 94). Cerebellar involvement or dementia may coexist (see Tables 94-1–94-3), and the neoplasm can be occult.

Botulism Botulinum toxin binds presynaptically to cholinergic nerve terminals and, after uptake into the cytosol, blocks ACh release. This acute cholinergic neuropathy presents as motor paralysis and autonomic disturbances that include blurred vision, dry mouth, nausea, unreactive or sluggishly reactive pupils, constipation, and urinary retention (Chap. 153).

PURE AUTONOMIC FAILURE PAF

This sporadic syndrome consists of postural hypotension, impotence, bladder dysfunction, and impaired sweating. The disorder begins in midlife and occurs in women more often than men. The symptoms can be disabling, but life span is unaffected. The clinical and pharmacologic characteristics suggest primary involvement of postganglionic autonomic neurons. A severe reduction in the density of neurons within sympathetic ganglia results in low supine plasma NE levels and noradrenergic supersensitivity. Some patients who are initially labeled with this diagnosis subsequently go on to develop AAG, but more often a neurodegenerative disease supervenes, typically Lewy body dementia, PD, or MSA. In one recent series, more than one-third of patients initially diagnosed with PAF developed a CNS synucleinopathy within 4 years, and the presence of rapid eye movement sleep behavior disorder (RBD; Chap. 31) was predictive of subsequent CNS disease. Skin biopsies and autopsy studies demonstrate phosphorylated α -synuclein inclusions in postganglionic sympathetic adrenergic and cholinergic nerve fibers, distinguishing PAF from AAG and indicating that PAF is

a synucleinopathy; notably, patients with PD also have alpha synuclein inclusions in sympathetic nerve biopsies.

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME POTS

This syndrome is characterized by symptomatic orthostatic intolerance without OH, accompanied by either an increase in heart rate to >120 beats/min or an increase of 30 beats/min with standing that subsides on sitting or lying down. Women are affected approximately five times more often than men, and most develop the syndrome between the ages of 15 and 50. Presyncopal symptoms (light-headedness, weakness, blurred vision) combined with symptoms of autonomic overactivity (palpitations, tremulousness, nausea) are common. The pathogenesis is typically multifactorial, which frequently confounds the clinical picture. A number of potential causes have been reported, including sympathetic denervation distally in the legs with preserved cardiovascular function or reduced cardiac function due to deconditioning. Hypovolemia, venous pooling, impaired brainstem baroreceptor regulation, or increased sympathetic activity may also play a role. No standardized approach to diagnosis has been established, and therapy typically has included symptomatic relief with a focus on cardiovascular rehabilitation, including a sustained exercise program. Expansion of fluid volume with water, salt, and fludrocortisone can be helpful as an initial intervention. In some patients, low-dose propranolol (20 mg) provides a modest improvement in heart rate control and exercise capacity. If these approaches are inadequate, then midodrine, pyridostigmine, or clonidine can be considered.

INHERITED DISORDERS

Eight hereditary sensory and autonomic neuropathies (HSANs) exist, designated HSAN I–VIII. The most important autonomic variants are HSAN I and HSAN III. HSAN I is dominantly inherited and often presents as a distal small-fiber neuropathy (burning feet syndrome) associated with sensory loss and foot ulcers. The most common responsible gene, on chromosome 9q, is *SPTLC1*. SPTLC is a key enzyme in the regulation of ceramide. Cells from HSAN I patients with the mutation produce higher-than-normal levels of glucosyl ceramide, perhaps triggering apoptosis. HSAN III (Riley-Day syndrome; familial dysautonomia) is an autosomal recessive disorder of Ashkenazi Jewish children and adults and is much less prevalent than HSAN I. Decreased tearing, hyperhidrosis, reduced sensitivity to pain, areflexia, absent fungiform papillae on the tongue, and labile BP may be present. Individuals with HSAN III have afferent, but not efferent, baroreflex failure that causes the classic episodic abdominal crises and blood pressure surges in response to emotional stimuli. Pathologic examination of nerves reveals a loss of sympathetic, parasympathetic, and sensory neurons. The defective gene, *IKBKAP*, prevents normal transcription of important molecules in neural development.

PRIMARY FOCAL HYPERHIDROSIS

This syndrome presents with excess sweating of the palms and soles or excess sweating of the axilla beginning in childhood or early adulthood. The condition tends to improve with age. The disorder affects 0.6–1.0% of the population. The etiology is unclear, but there may be a genetic component because 25% of patients have a positive family history. The condition can be socially embarrassing (e.g., shaking hands) or even disabling (e.g., inability to write without soiling the paper). Topical antiperspirants are occasionally helpful. More useful are potent anticholinergic drugs such as glycopyrrolate 1–2 mg PO tid or oxybutynin 5 mg po bid. T2 ganglionectomy or sympathectomy is successful in >90% of patients with palmar hyperhidrosis. The advent of endoscopic transaxillary T2 sympathectomy has lowered the complication rate of the procedure. The most common postoperative complication is compensatory hyperhidrosis, which improves spontaneously over months. Other potential complications include recurrent hyperhidrosis (16%), Horner's syndrome (<2%), gustatory sweating, wound infection, hemothorax, and intercostal neuralgia. Local injection of botulinum toxin has also been used to block cholinergic, postganglionic sympathetic fibers to sweat glands. This

approach is effective but limited by the need for repetitive injections (the effect usually lasts 4 months before waning).

■ ACUTE SYMPATHETIC OVERACTIVITY SYNDROMES

An *autonomic storm* is an acute state of sustained sympathetic surge that results in variable combinations of alterations in BP and heart rate, body temperature, respiration, and sweating. Causes of autonomic storm include brain and spinal cord injury, toxins and drugs, autonomic neuropathy, and chemodectomas (e.g., pheochromocytoma). Brain injury is the most common cause of autonomic storm and typically follows severe head trauma and postresuscitation anoxic-ischemic brain injury. Autonomic storm can also occur with other acute intracranial lesions such as hemorrhage, cerebral infarction, rapidly expanding tumors, subarachnoid hemorrhage, hydrocephalus, or (less commonly) an acute spinal cord lesion. The most consistent setting is that of an acute intracranial catastrophe of sufficient size and rapidity to produce a massive catecholaminergic surge. The surge can cause seizures, neurogenic pulmonary edema, and myocardial injury. Manifestations include fever, tachycardia, hypertension, tachypnea, hyperhidrosis, pupillary dilatation, and flushing. Lesions of the afferent limb of the baroreflex can result in milder recurrent autonomic storms; these can be associated with tumors or follow neck irradiation or surgery that damages the vagus and glossopharyngeal nerves.

Drugs and toxins may also be responsible, including sympathomimetics such as phenylpropanolamine, cocaine, amphetamines, and tricyclic antidepressants; tetanus; and, less often, botulinum toxin. The serotonin syndrome can occur from polypharmaceutical use of drugs that inhibit serotonin uptake and metabolism (particularly selective serotonin reuptake inhibitors and mixed norepinephrine/serotonin reuptake inhibitors; see Chap. 452) or an antidepressant monoamine oxidase inhibitor can produce a dramatic autonomic syndrome with hypertension, sweating, tachycardia, dilated pupils, and mental status changes. Cocaine, including “crack,” can cause a hypertensive state with flushing, hypertension, tachycardia, fever, mydriasis, anhidrosis, and a toxic psychosis. The hyperadrenergic state associated with Guillain-Barré syndrome can produce a moderate autonomic storm. Pheochromocytoma (Chap. 387) presents with a paroxysmal or sustained hyperadrenergic state, headache, hyperhidrosis, palpitations, anxiety, tremulousness, and hypertension.

Neuroleptic malignant syndrome refers to a syndrome of muscle rigidity, hyperthermia, and hypertension in patients treated with neuroleptic agents (including lower potency and atypical antipsychotic agents, and even antiemetic drugs such as metoclopramide and promethazine) (Chap. 436). Management of autonomic storm includes ruling out other causes of autonomic instability, including malignant hyperthermia, porphyria, and seizures. Sepsis and encephalitis need to be excluded with appropriate studies. An electroencephalogram (EEG) should be done to search for seizure activity; MRI of the brain and spine is often necessary. The patient should be managed in an intensive care unit and the causal agent discontinued. Management with lorazepam, dantrolene, bromocriptine, or apomorphine is based upon clinical experience and not clinical trials. Supportive treatment may need to be maintained for several weeks. For chronic and milder autonomic storm, propranolol and/or clonidine can be effective.

■ MISCELLANEOUS AND CONTROVERSIAL AUTONOMIC SYNDROMES

Other conditions associated with autonomic failure include infections, malignancy, and poisoning (organophosphates). Disorders of the hypothalamus can affect autonomic function and produce abnormalities in temperature control, satiety, sexual function, and circadian rhythms (Chap. 380).

■ COMPLEX REGIONAL PAIN SYNDROMES CRPS

The failure to identify a primary role of the ANS in the pathogenesis of these disorders has resulted in a change of nomenclature. The terms *CRPS types I and II* are now used in place of reflex sympathetic dystrophy (RSD) and causalgia.

CRPS type I is a regional pain syndrome that often develops after tissue injury and most commonly affects one limb. Examples of associated injury include minor shoulder or limb trauma, fractures, myocardial infarction, or stroke. *Allodynia* (the perception of a nonpainful stimulus as painful), *hyperpathia* (an exaggerated pain response to a painful stimulus), and spontaneous pain occur. The symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve. CRPS type II is a regional pain syndrome that develops after injury to a specific peripheral nerve, often a major nerve trunk. Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution. Although CRPS type I (RSD) has been classically divided into three clinical phases, there is little evidence that CRPS “progresses” from one stage to another. Currently, the Budapest consensus criteria for clinical diagnosis of CRPS delete staging and require at least three symptoms and two signs in the following four categories: (1) sensory, (2) vasomotor, (3) sudomotor/edema, and (4) motor/trophic. Pain (usually burning or electrical in quality) is the primary clinical feature of CRPS. Limb pain syndromes that do not meet these criteria are best classified as “limb pain—not otherwise specified.” In CRPS, localized sweating (increased resting sweat output) and changes in blood flow may produce temperature differences between affected and unaffected limbs.

The natural history of typical CRPS may be more benign and more variable than previously recognized. A variety of surgical and medical treatments have been developed, with conflicting reports of efficacy. Clinical trials suggest that early mobilization with physical therapy or a brief course of glucocorticoids may be helpful for early CRPS type I or II. Chronic glucocorticoid treatment is not recommended. Medications to treat neuropathic pain can be helpful. Current treatment paradigms are multidisciplinary with a focus on early mobilization, physical therapy, pain management, patient education, and psychological support.

TREATMENT

Autonomic Failure

Management of autonomic failure is aimed at specific treatment of the cause and alleviation of symptoms. Of particular importance is the removal of drugs or amelioration of underlying conditions that cause or aggravate the autonomic symptoms, especially in the elderly. For example, OH can be caused or aggravated by antihypertensive agents, antidepressants, levodopa or dopaminergic agonists, ethanol, opioids, insulin, and barbiturates. A summary of drugs that can cause impotence, urinary retention, or diaphoresis by class and putative mechanism is shown in Table 440-6.

PATIENT EDUCATION

Only a minority of patients with OH require drug treatment. All patients should be taught the mechanisms of postural normotension (volume status, resistance and capacitance bed, autoregulation) and the nature of orthostatic stressors (time of day and the influence of meals, heat, standing, and exercise). Patients should learn to recognize orthostatic symptoms early (especially subtle cognitive symptoms, weakness, and fatigue) and to modify or avoid activities that provoke episodes. Other measures may include keeping a BP log and dietary education (salt/fluids). Learning physical countermeasures that reduce standing OH and practicing postural and resistance training and cardiovascular reconditioning are frequently helpful.

SYMPTOMATIC TREATMENT

Nonpharmacologic approaches are summarized in Table 440-9. Adequate intake of salt and fluids to produce a voiding volume of 1.5–2.5 L of urine (containing >170 meq/L of Na^+) each 24 h is essential. Sleeping with the head of the bed elevated will minimize the effects of supine nocturnal hypertension. Prolonged recumbency should be avoided when possible. Patients are advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand in the morning; other postural stressors

TABLE 440-9 Initial Treatment of Orthostatic Hypotension (OH)

- Patient education: mechanisms and stressors of OH
- High-salt diet (10–20 g/d)
- High-fluid intake (2 L/d)
- Elevate head of bed 10 cm (4 in.) to minimize supine hypertension
- Maintain postural stimuli
- Learn physical counter-maneuvers
- Compression garments
- Correct anemia

should be similarly approached in a gradual manner. One maneuver that can reduce OH is leg-crossing with maintained contraction of leg muscles for 30 seconds; this compresses leg veins and increases systemic resistance. Compressive garments, such as compression stockings or abdominal binders, are helpful on occasion but are uncomfortable for many patients. For transient worsening of OH, drinking two 250-mL (8-oz) glasses of water within 5 min can raise standing BP 20–30 mmHg for about 2 h, beginning ~5 min after the fluid load. The patient can increase intake of salt and fluids (bouillon treatment), increase use of physical counter-maneuvers (elevate the legs when supine), or temporarily resort to a full-body stocking (compression pressure 30–40 mmHg).

Anemia can be corrected with erythropoietin, administered subcutaneously at doses of 25–75 U/kg three times per week. The hematocrit increases after 2–6 weeks. A weekly maintenance dose is usually necessary. However, the increased intravascular volume that accompanies the rise in hematocrit can exacerbate supine hypertension and requires monitoring.

If these measures are not sufficient, additional pharmacologic treatment may be necessary. Midodrine, a directly acting α_1 -agonist that does not cross the blood-brain barrier, is effective. It has a duration of action of 2–4 h. The usual dose is 5–10 mg orally tid, but some patients respond best to a decremental dose (e.g., 15 mg on awakening, 10 mg at noon, and 5 mg in the afternoon). Midodrine should not be taken after 6:00 . Side effects include pruritus, uncomfortable piloerection, and supine hypertension, especially at higher doses. Droxidopa (Northera) for treatment of neurogenic OH associated with PAF, PD, or MSA is effective in decreasing symptoms of OH. Pyridostigmine appears to improve OH without aggravating supine hypertension by enhancing ganglionic transmission (maximal when orthostatic, minimal when supine), but with only modest clinical effects on BP. Fludrocortisone will reduce OH but aggravates supine hypertension. At doses between 0.1 mg/d and 0.3 mg bid orally, it enhances renal sodium conservation and increases the sensitivity of arterioles to NE. Susceptible patients may develop fluid overload, congestive heart failure, supine hypertension, or hypokalemia. Potassium supplements are often necessary with chronic administration of fludrocortisone. Sustained elevations of supine BP >180/110 mmHg should be avoided. Supine hypertension (>180/110 mmHg) can be self-treated by avoiding the supine position (e.g., sleeping in a recumbent chair or elevating the head of the bed) and reducing fludrocortisone. If these simple measures are not adequate, drugs to be considered include oral hydralazine (25 mg qhs), oral nifedipine (Procardia; 10 mg qhs), or a nitroglycerin patch.

A promising drug combination (atomoxetine and yohimbine) has been studied for use in human subjects with severe OH not responsive to other agents, as can occur in some patients with diabetes and severe autonomic neuropathy not responsive to other medications. The atomoxetine blocks the NE reuptake transporter, and yohimbine blocks α_2 receptors that mediate the sympathetic feedback loop for downregulation of BP in response to atomoxetine. The result is a dramatic increase in BP and standing tolerance. Yohimbine is no longer produced commercially and must be obtained from a compounding pharmacy. This combination is not FDA approved for this purpose.

Postprandial OH may respond to several measures. Frequent, small, low-carbohydrate meals may diminish splanchnic shunting of blood after meals and reduce postprandial OH. Prostaglandin inhibitors (ibuprofen or indomethacin) taken with meals or midodrine (10 mg with the meal) can be helpful. The somatostatin analogue octreotide can be useful in the treatment of postprandial syncope by inhibiting the release of GI peptides that have vasodilator and hypotensive effects. The subcutaneous dose ranges from 25 µg bid to 200 µg tid.

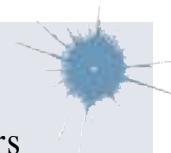
FURTHER READING

- C WW, B RJ: The Autonomic Nervous System, in *Dekong's The Neurologic Examination*, 8th ed. WW Campbell, RJ Barohn (eds). Philadelphia, Wolters Kluwer, 2020.
- F J et al: The serotonin syndrome: From molecular mechanisms to clinical practice. *Int J Mol Sci* 20:2288, 2019.
- G CH et al: The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. *J Neurol* 264:1587, 2017.
- G EP et al: Seronegative autoimmune autonomic neuropathy: A distinct clinical entity. *Clin Auto Res* 28:115; 2018.
- K H et al: Natural history of pure autonomic failure: A United States prospective cohort. *Ann Neurol* 81:287, 2017.
- M D S et al: Longitudinal follow-up of biopsy-proven small fiber neuropathy. *Muscle Nerve* 60:376, 2019.
- N P: Autonomic disorders. *Am J Med* 132:420, 2018.
- W AL et al: Kinetics of α -synuclein prions preceding neuropathological inclusions in multiple system atrophy. *PLoS Pathol* 16:e1008222, 2020.

441

Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders

Vanja C. Douglas, Stephen L. Hauser



The cranial nerves consist of 12 paired nerves that mediate variable combinations of motor, sensory, and autonomic functions. They are considered as a group because of their close anatomic relationship to the brainstem (Fig. 441-1) and to one another, and tendency to be involved together in a variety of disease states. Nine cranial nerves connect directly with brainstem nuclei; the exceptions are cranial nerves 1 (olfactory) and 2 (optic) that are more accurately considered fiber tracts of the brain, and cranial nerve 11 (spinal accessory) whose motor neurons reside largely in the upper cervical cord. Analogous to spinal nerves (Chap. 442), motor fibers of the cranial nerves have their origin in the brainstem or upper cervical cord, while sensory nerves are pseudounipolar, with ganglia outside the central nervous system and a synapse with second-order fibers in the brainstem.

Symptoms and signs of cranial nerve pathology are common in internal medicine. They often develop in the context of a widespread neurologic disturbance, and in such situations, cranial nerve involvement may represent the initial manifestation of the illness. In other disorders, involvement is largely restricted to one or several cranial nerves; these distinctive disorders are reviewed in this chapter. Disorders of olfaction are discussed in Chap. 33, vision and ocular movement in Chap. 32, hearing in Chap. 34, and vestibular function in Chap. 22.

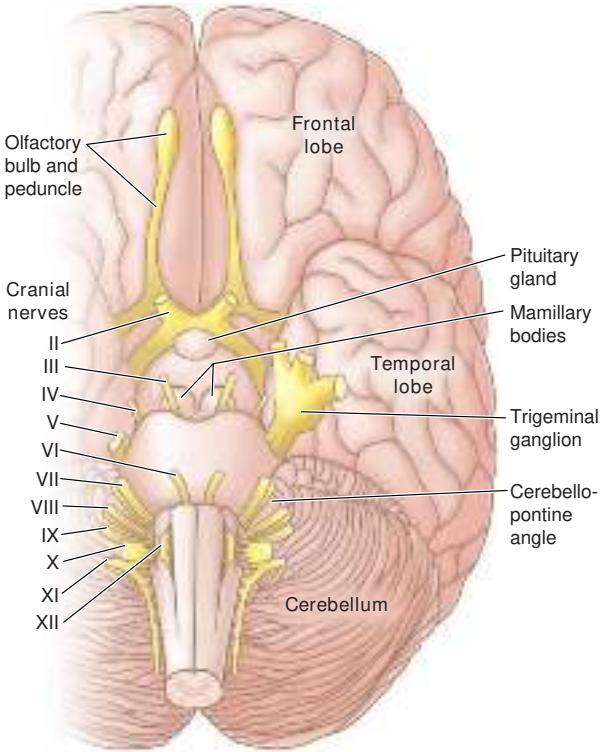


FIGURE 441-1 Ventral view of the brain, illustrating relationships between the 12 pairs of cranial nerves and the brainstem. (Adapted from SG Waxman: *Clinical Neuroanatomy*, 29th ed. <http://www.accessmedicine.com>)

FACIAL PAIN OR NUMBNESS

■ ANATOMIC CONSIDERATIONS

The trigeminal (fifth cranial) nerve supplies sensation to the skin of the face, anterior half of the head, and the nasal and oral mucosa (Fig. 441-2). The motor part innervates the muscles involved in chewing (including masseters and pterygoids) as well as the anterior belly of the digastric, mylohyoid, tensor veli palatini, and the tensor tympani (hearing especially for high-pitched tones). It is the largest of the cranial nerves. It exits in the lateral midpons and traverses the middle cranial fossa to the semilunar (gasserian, trigeminal) ganglion in Meckel's cave, where the nerve splits into three divisions (ophthalmic [V1], maxillary [V2], and mandibular [V3]). V1 and V2 traverse the cavernous sinus to exit in the superior orbital fissure and foramen rotundum; V3 exits through the foramen ovale. The trigeminal nerve is predominantly sensory, and motor innervation is exclusively carried in V3. The cornea is primarily innervated by V1, although an inferior crescent may be V2. Upon entering the pons, pain and temperature fibers descend ipsilaterally to the upper cervical spinal cord as the spinal tract of V, before synapsing with the spinal nucleus of V; this accounts for the facial numbness that can occur with spinal cord lesions above C2. In the brainstem, the spinal tract of V is also located adjacent to crossed ascending fibers of the spinothalamic tract, producing a “crossed” sensory loss for pain and temperature (ipsilateral face, contralateral arm/trunk/leg) with lesions of the lateral lower brainstem. CN V is also ensheathed by oligodendrocyte-derived, rather than Schwann cell-derived, myelin for up to 7 mm after it leaves the brainstem, unlike just a few millimeters for other cranial and spinal nerves; this may explain the high frequency of trigeminal neuralgia in multiple sclerosis (MS) (Chap. 444), a disorder of oligodendrocyte myelin.

■ TRIGEMINAL NEURALGIA TIC DOULOUREUX

Clinical Manifestations Trigeminal neuralgia is characterized by excruciating paroxysms of pain in the lips, gums, cheek, or chin and,

very rarely, in the distribution of the ophthalmic division of the fifth nerve. The pain seldom lasts more than a few seconds or a minute or two but may be so intense that the patient winces, hence the term tic. The paroxysms, experienced as single jabs or clusters, tend to recur frequently, both day and night, for several weeks at a time. They may occur spontaneously or be brought on with movements of affected areas by speaking, chewing, or smiling. Another characteristic feature is the presence of trigger zones, typically on the face, lips, or tongue, that provoke attacks; patients may report that tactile stimuli—e.g., washing the face, brushing the teeth, or exposure to a draft of air—generate excruciating pain. An essential feature of trigeminal neuralgia is that objective signs of sensory loss cannot be demonstrated on examination.

Trigeminal neuralgia is relatively common, with an estimated annual incidence of 4–8 per 100,000 individuals. Middle-aged and elderly persons are affected primarily, and ~60% of cases occur in women. Onset is typically sudden, and bouts tend to persist for weeks or months before remitting spontaneously. Remissions may be long-lasting, but in most patients, the disorder ultimately recurs.

Pathophysiology Symptoms result from ectopic generation of action potentials in pain-sensitive afferent fibers of the fifth cranial nerve root just before it enters the lateral surface of the pons. Compression or other pathology in the nerve leads to demyelination of large myelinated fibers that do not themselves carry pain sensation but become hyperexcitable and electrically coupled with smaller unmyelinated or poorly myelinated pain fibers in close proximity; this may explain why tactile stimuli, conveyed via the large myelinated fibers, can stimulate paroxysms of pain. Compression of the trigeminal nerve root by a blood vessel, most often the superior cerebellar artery or on occasion a tortuous vein, is believed to be the source of trigeminal neuralgia in most patients. In cases of vascular compression, age-related brain sagging and increased vascular thickness and tortuosity may explain the prevalence of trigeminal neuralgia in later life.

Differential Diagnosis Trigeminal neuralgia must be distinguished from other causes of face and head pain (Chap. 16) and from pain arising from diseases of the jaw, teeth, or sinuses. Pain from migraine or cluster headache tends to be deep-seated and steady, unlike the superficial stabbing quality of trigeminal neuralgia; rarely, cluster headache is associated with trigeminal neuralgia, a syndrome known as *cluster-tic*. Other rare headaches include short-lasting unilateral headache attacks with conjunctival injection and tearing (SUNCT; Chap. 430). In temporal arteritis, superficial facial pain is present but is not typically shocklike, the patient frequently complains of myalgias and other systemic symptoms, and an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) is usually present (Chap. 363). When trigeminal neuralgia develops in a young adult or is bilateral, MS is a key consideration, and in such cases, the cause is a demyelinating plaque near the root entry zone of the fifth nerve in the pons; often, evidence of facial sensory loss can be found on careful examination. Cases that are secondary to mass lesions—such as aneurysms, neurofibromas, acoustic schwannomas, or meningiomas—usually produce objective signs of sensory loss in the trigeminal nerve distribution (trigeminal neuropathy, see below).

Laboratory Evaluation An ESR or CRP is indicated if temporal arteritis is suspected. In typical cases of trigeminal neuralgia, neuroimaging studies are usually unnecessary but may be valuable in patients younger than 40 years or when symptoms are bilateral and MS is a consideration or in assessing overlying vascular lesions in order to plan for decompression surgery.

TREATMENT

Trigeminal Neuralgia

Drug therapy with carbamazepine is effective in ~50–75% of patients. Carbamazepine should be started as a single daily dose of 100 mg taken with food and increased gradually (by 100 mg daily in divided doses every 1–2 days) until substantial (>50%) pain relief

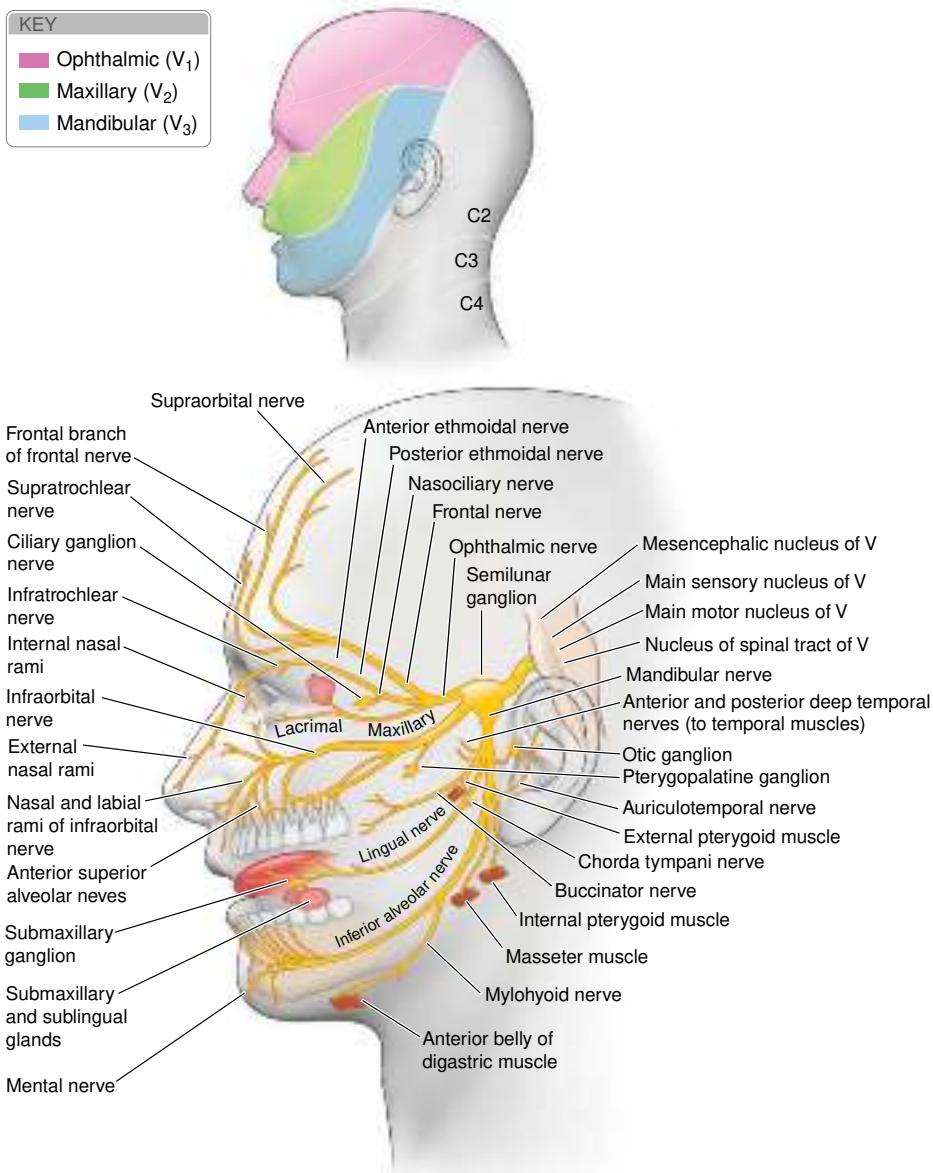


FIGURE 441-2 The trigeminal nerve and its branches and sensory distribution on the face. The three major sensory divisions of the trigeminal nerve consist of the ophthalmic, maxillary, and mandibular nerves. (Reproduced with permission from Waxman SG: Clinical Neuroanatomy, 26th ed. New York, McGraw-Hill, 2009.)

is achieved. Most patients require a maintenance dose of 200 mg four times daily. Doses >1200 mg daily provide no additional benefit. Dizziness, imbalance, sedation, and rare cases of agranulocytosis are the most important side effects of carbamazepine. If treatment is effective, it is usually continued for 1 month and then tapered as tolerated. Oxcarbazepine (300–1200 mg bid) is an alternative to carbamazepine that has less bone marrow toxicity and probably is equally efficacious. If these agents are not well tolerated or are ineffective, phenytoin (300–400 mg daily) is another option. Lamotrigine (400 mg daily), baclofen (10–20 mg tid), or topiramate (50 mg bid) may also be tried. Gabapentin, up to 3600 mg daily in divided doses, may occasionally provide relief.

If drug treatment fails, surgical therapy should be offered. The most widely used method is currently microvascular decompression to relieve pressure on the trigeminal nerve as it exits the pons. This procedure requires a suboccipital craniotomy. This

procedure appears to have a >70% efficacy rate and a low rate of pain recurrence in responders; the response is better for classic ticlike symptoms than for nonlancingating facial pains. High-resolution magnetic resonance angiography is useful preoperatively to visualize the relationships between the fifth cranial nerve root and nearby blood vessels.

Gamma knife radiosurgery of the trigeminal nerve root is also used for treatment and results in complete pain relief, sometimes delayed in onset, in approximately one-half of patients and a low risk of persistent facial numbness; the response is sometimes long-lasting, but recurrent pain develops over 2–3 years in one-third of patients. Compared with surgical decompression, gamma knife surgery appears to be somewhat less effective but has few serious complications.

Another procedure, radiofrequency thermal rhizotomy, creates a heat lesion of the trigeminal ganglion or nerve. Short-term relief

is experienced by >95% of patients; long-term studies indicate that pain recurs in up to one-third of treated patients. Postoperatively, partial numbness of the face is common, masseter (jaw) weakness may occur especially following bilateral procedures, and corneal denervation with secondary keratitis can follow rhizotomy for first-division trigeminal neuralgia. Percutaneous balloon compression of the trigeminal ganglion is an alternative approach performed under general anesthesia that results in similar rates of short- and long-term pain relief and is also commonly complicated by ipsilateral facial numbness.

■ TRIGEMINAL NEUROPATHY

A variety of diseases can affect the trigeminal nerve (Table 441-1). Most present with sensory loss on the face or with weakness of the jaw muscles. Deviation of the jaw on opening indicates weakness of the pterygoids on the side to which the jaw deviates. Some cases are due to Sjögren's syndrome or a collagen-vascular disease such as systemic lupus erythematosus, scleroderma, or mixed connective tissue disease. Among infectious causes, herpes zoster (acute or postherpetic) and leprosy should be considered. Tumors of the middle cranial fossa (meningiomas), of the trigeminal nerve (schwannomas), or of the base of the skull (metastatic tumors) may cause a combination of motor and sensory signs. Lesions in the cavernous sinus can affect the first and second divisions of the trigeminal nerve, and lesions of the superior orbital fissure can affect the first (ophthalmic) division; the accompanying corneal anesthesia increases the risk of ulceration (neurokeratitis).

Isolated sensory loss over the chin (mental neuropathy) can be the only manifestation of systemic malignancy. Rarely, an idiopathic form of trigeminal neuropathy is observed. It is characterized by numbness and paresthesias, sometimes bilaterally, with loss of sensation in the territory of the trigeminal nerve but without weakness of the jaw. Gradual recovery is the rule. Tonic spasm of the masticatory muscles, known as trismus, is symptomatic of tetanus (Chap. 152) or may occur in patients treated with phenothiazines.

TABLE 441-1 Trigeminal Nerve Disorders

Nuclear (Brainstem) Lesions

Multiple sclerosis

Stroke

Syringobulbia

Glioma

Lymphoma

Preganglionic Lesions

Acoustic neuroma

Meningioma

Metastasis

Chronic meningitis

Cavernous carotid aneurysm

Semilunar Ganglion Lesions

Trigeminal neuroma

Herpes zoster

Infection (spread from otitis media or mastoiditis)

Cavernous Sinus Lesions (see Table 441-2)

Peripheral Nerve Lesions

Tumor (e.g., nasopharyngeal carcinoma, squamous cell carcinoma, lymphoma)

Trauma

Guillain-Barré syndrome

Sjögren's syndrome

Collagen-vascular diseases

Sarcoidosis

Leprosy

Drugs (stilbamidine, trichloroethylene)

Idiopathic trigeminal neuropathy

FACIAL WEAKNESS

■ ANATOMIC CONSIDERATIONS

(Fig. 441-3) The seventh cranial nerve supplies all the muscles concerned with facial expression, as well as the stapedius, stylohyoid, and posterior belly of the digastric. The sensory and parasympathetic components (the nervus intermedius) convey taste sensation from the anterior two-thirds of the tongue, cutaneous impulses from the anterior wall of the external auditory canal, and preganglionic parasympathetic signals to the pterygopalatine and submaxillary ganglia, stimulating lacrimation, rhinorrhea and salivation. The motor nucleus of the seventh nerve lies anterior and lateral to the abducens nucleus. After leaving the pons, the seventh nerve enters the internal auditory meatus with the acoustic nerve. The nerve continues its course in its own bony channel, the facial canal, and exits from the skull via the stylomastoid foramen. It then passes through the parotid gland and subdivides to supply the facial muscles.

A complete interruption of the facial nerve at the stylomastoid foramen paralyzes all muscles of facial expression. The corner of the mouth droops, the creases and skinfolds are effaced, the forehead is unfurrowed, and the eyelids will not close. Upon attempted closure of the lids, the eye on the paralyzed side rolls upward (Bell's phenomenon). The lower lid sags and falls away from the conjunctiva, permitting tears to spill over the cheek. Food collects between the teeth and lips, and saliva may dribble from the corner of the mouth. The patient complains of a heaviness or numbness in the face, but sensory loss is rarely demonstrable and taste is intact.

If the lesion is in the middle-ear portion, taste is lost over the anterior two-thirds of the tongue on the same side. If the nerve to the stapedius is interrupted, there is hyperacusis (sensitivity to loud sounds). Lesions in the internal auditory meatus may affect the adjacent auditory and vestibular nerves, causing deafness, tinnitus, or dizziness. Intrapontine lesions that paralyze the face usually affect the abducens nucleus as well, and often the corticospinal and sensory tracts.

If the peripheral facial paralysis has existed for some time and recovery of motor function is incomplete, a continuous diffuse contraction of facial muscles may appear. The palpebral fissure becomes narrowed, and the nasolabial fold deepens. Facial spasms, initiated by movements of the face, may develop (hemifacial spasm). Anomalous regeneration of seventh nerve fibers may result in other troublesome phenomena. If fibers originally connected with the orbicularis oculi come to innervate the orbicularis oris, closure of the lids may cause a retraction of the mouth (synkinesis), or if parasympathetic fibers originally connected with salivary glands later innervate the lacrimal gland, anomalous tearing ("crocodile tears") may occur with eating. Another facial synkinesis is triggered by jaw opening, causing closure of the eyelids on the side of the facial palsy (jaw-winking).

■ BELL'S PALSY

The most common form of facial paralysis is Bell's palsy. The annual incidence of this idiopathic disorder is ~25 per 100,000 annually, or about 1 in 60 persons in a lifetime. Risk factors include pregnancy and diabetes mellitus.

Clinical Manifestations The onset of Bell's palsy is fairly abrupt, with maximal weakness being attained by 48 h as a general rule. Pain behind the ear may precede the paralysis for a day or two. Taste sensation may be lost unilaterally, and hyperacusis may be present. In some cases, there is mild cerebrospinal fluid lymphocytosis. MRI may reveal swelling and uniform enhancement of the geniculate ganglion and facial nerve and, in some cases, entrapment of the swollen nerve in the temporal bone. Approximately 80% of patients recover within a few weeks or months. Electromyography may be of some prognostic value; evidence of denervation after 10 days indicates there has been axonal degeneration, that there will be a long delay (3 months as a rule) before regeneration occurs, and that it may be incomplete. The presence of incomplete paralysis in the first week is the most favorable prognostic sign. Recurrences are reported in ~7% of cases.

Pathophysiology In acute Bell's palsy, there is inflammation of the facial nerve with mononuclear cells, consistent with an infectious

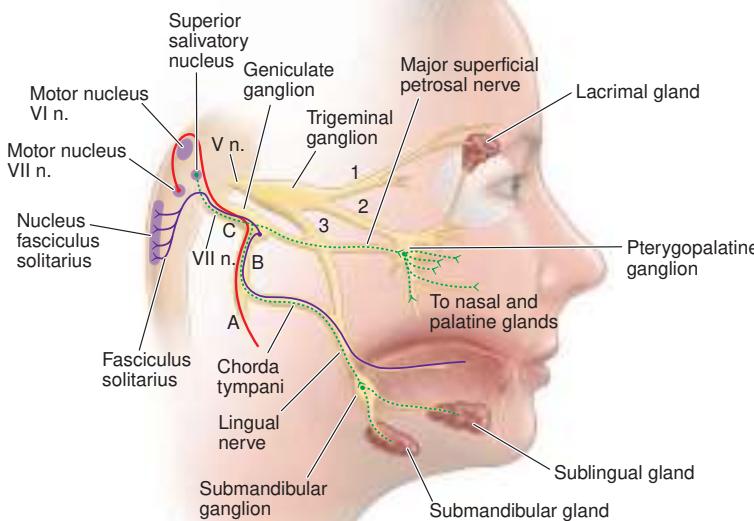


FIGURE 441-3 The facial nerve. A, B, and C denote lesions of the facial nerve at the stylomastoid foramen, distal and proximal to the geniculate ganglion, respectively. Green lines indicate the parasympathetic fibers, red line indicates motor fibers, and purple lines indicate visceral afferent fibers (taste). (Reproduced with permission from MB Carpenter: *Core Text of Neuroanatomy*, 2nd ed. Williams & Wilkins, 1978.)

or immune cause. Herpes simplex virus (HSV) type 1 DNA was frequently detected in endoneurial fluid and posterior auricular muscle, suggesting that a reactivation of this virus in the geniculate ganglion may be responsible for most cases. Reactivation of varicella-zoster virus is associated with Bell's palsy in up to one-third of cases and may represent the second most frequent cause. A variety of other viruses have also been implicated less commonly, and Bell's palsy can be observed in the setting of human immunodeficiency virus (HIV) seroconversion.

Differential Diagnosis There are many other causes of acute facial palsy that must be considered in the differential diagnosis of Bell's palsy. Lyme disease can cause unilateral or bilateral facial palsies; in endemic areas, $\geq 10\%$ of cases of facial palsy are likely due to infection with *Borrelia burgdorferi* (Chap. 186). Ramsay Hunt syndrome, caused by reactivation of herpes zoster in the geniculate ganglion, consists of a severe facial palsy associated with a vesicular eruption in the external auditory canal and sometimes in the pharynx and other parts of the cranial integument; often the eighth cranial nerve is affected as well. Facial palsy that is often bilateral occurs in sarcoidosis (Chap. 367) and in Guillain-Barré syndrome (Chap. 447). Leprosy frequently involves the facial nerve, and facial neuropathy may also occur in diabetes mellitus, connective tissue diseases including Sjögren's syndrome, and amyloidosis. The rare Melkersson-Rosenthal syndrome consists of recurrent facial paralysis; recurrent—and eventually permanent—facial (particularly labial) edema; and, less constantly, plication of the tongue. Its cause is unknown. Acoustic neuromas frequently involve the facial nerve by local compression. Infarcts, demyelinating lesions of MS, and tumors are the common pontine lesions that interrupt the facial nerve fibers; other signs of brainstem involvement are usually present. Tumors that invade the temporal bone (carotid body, cholesteatoma, dermoid) may produce a facial palsy, but the onset is insidious and the course progressive. Facial palsy after temporal bone fracture can present acutely or after a delay of several days; blunt head injury without temporal bone fracture may also trigger facial palsy.

All these forms of nuclear or peripheral facial palsy must be distinguished from the supranuclear type. In the latter, the frontalis and orbicularis oculi muscles of the forehead are involved less than those of the lower part of the face, since the upper facial muscles are innervated by corticobulbar pathways from both motor cortices, whereas the lower facial muscles are innervated only by the opposite hemisphere. In supranuclear lesions, there may be a dissociation of emotional and voluntary facial movements, and often some degree of paralysis of the arm and leg or an aphasia (in dominant-hemisphere lesions) is present.

Laboratory Evaluation The diagnosis of Bell's palsy can usually be made clinically in patients with (1) a typical presentation, (2) no risk factors or preexisting symptoms for other causes of facial paralysis, (3) absence of cutaneous lesions of herpes zoster in the external ear canal, and (4) a normal neurologic examination with the exception of the facial nerve. Particular attention to the eighth cranial nerve, which courses near to the facial nerve in the pontomedullary junction and in the temporal bone, and to other cranial nerves is essential. In atypical or uncertain cases, an ESR or CRP, testing for diabetes mellitus, a Lyme titer, HIV serologies, angiotensin-converting enzyme and chest imaging studies for possible sarcoidosis, a lumbar puncture for possible Guillain-Barré syndrome, or MRI scanning may be indicated. MRI often shows swelling and enhancement of the facial nerve in idiopathic Bell's palsy (Fig. 441-4).

TREATMENT

Bell's Palsy

Symptomatic measures include (1) the use of paper tape to depress the upper eyelid during sleep and prevent corneal drying, (2) artificial tears; and (3) massage of the weakened muscles. A course of glucocorticoids, given as prednisone 60–80 mg daily during the first 5 days and then tapered over the next 5 days, modestly shortens the recovery period and improves the functional outcome. Although large and well-controlled randomized trials found no added benefit

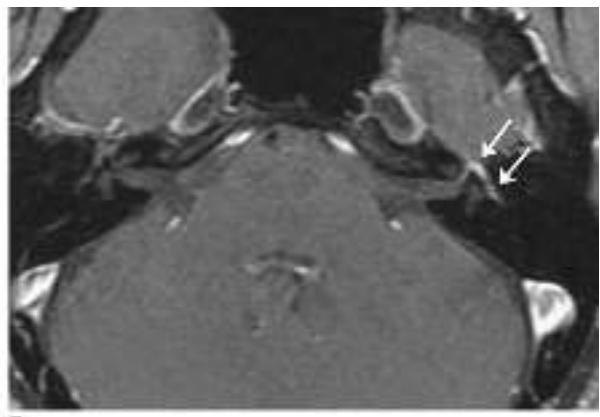
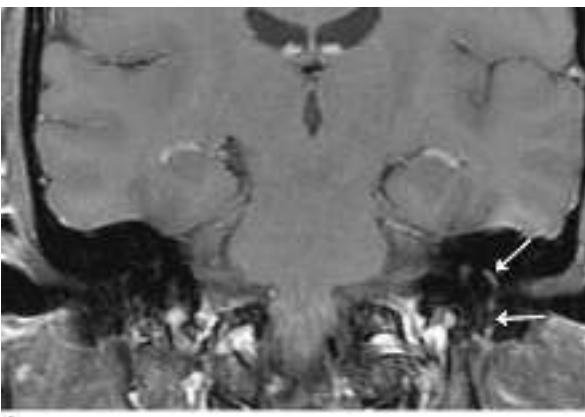


FIGURE 441-4 Axial and coronal T1-weighted images after gadolinium with fat suppression demonstrate diffuse smooth linear enhancement of the left facial nerve, involving the genu, tympanic, and mastoid segments within the temporal bone (arrows), without evidence of mass lesion. Although highly suggestive of Bell's palsy, similar findings may be seen with other etiologies such as Lyme disease, sarcoidosis, and perineural malignant spread.

of the antiviral agents valacyclovir (1000 mg daily for 5–7 days) or acyclovir (400 mg five times daily for 10 days) compared to glucocorticoids alone, either of these agents should be used if vesicular lesions are observed in the palate or external auditor canal. For patients with permanent paralysis from Bell's palsy, a number of cosmetic surgical procedures have been used to restore a relatively symmetric appearance to the face.

■ OTHER MOTOR DISORDERS OF THE FACE

Hemifacial spasm consists of painless irregular involuntary contractions on one side of the face. Most cases appear related to vascular compression of the exiting facial nerve in the pons. Other cases develop as a sequela to Bell's palsy or are secondary to compression and/or demyelination of the nerve by tumor, infection, or MS. Local injections of botulinum toxin into affected muscles can relieve spasms for 3–4 months, and the injections can be repeated. Refractory cases due to vascular compression usually respond to surgical decompression of the facial nerve. Anecdotal reports describe success using carbamazepine, gabapentin, or baclofen. Blepharospasm is an involuntary recurrent spasm of both eyelids that usually occurs in elderly persons as an isolated phenomenon or with varying degrees of spasm of other facial muscles. Severe, persistent cases of blepharospasm can be treated by local injection of botulinum toxin into the orbicularis oculi. Clonazepam, baclofen, and trihexyphenidyl have also been used to treat this disorder. Facial myokymia refers to a fine rippling activity of the facial muscles; it may be caused by MS or follow Guillain-Barré syndrome (Chap. 447).

OTHER CRANIAL NERVE DISORDERS

■ GLOSSOPHARYNGEAL NEURALGIA

The ninth cranial (glossopharyngeal) nerve (Fig. 441-5) conveys somatic sensation from the pharynx, middle ear, tympanic membrane, eustachian tube, and posterior third of the tongue to the spinal trigeminal nucleus. It also relays taste from the posterior third of the tongue and information about blood pressure from baroreceptors in the carotid sinus to the nucleus solitarius, which also serves as the sensory nucleus for the vagus nerve. Motor function originates in the nucleus ambiguus and is limited to the stylopharyngeus muscle. Parasympathetic fibers from the medullary inferior salivatory nucleus synapse in the otic ganglion with postganglionic fibers that innervate the parotid gland. Glossopharyngeal neuralgia resembles trigeminal neuralgia in many respects but is much less common. Sometimes it involves portions of the tenth (vagus) nerve. The pain is intense and paroxysmal; it originates on one side of the throat, approximately in the tonsillar fossa. In some cases, the pain is localized in the ear or may radiate from the throat to the ear because of involvement of the tympanic branch of the glossopharyngeal nerve. Spasms of pain may be initiated by

swallowing or coughing. There is no demonstrable motor or sensory deficit. Cardiac symptoms—bradycardia or asystole, hypotension, and fainting—have been reported. Glossopharyngeal neuralgia can result from vascular compression, MS, or tumors, but many cases are idiopathic. Medical therapy is similar to that for trigeminal neuralgia, and carbamazepine is generally the first choice. If drug therapy is unsuccessful, surgical procedures—including microvascular decompression if vascular compression is evident—or rhizotomy of glossopharyngeal and vagal fibers in the jugular bulb is frequently successful.

■ DYSPHAGIA AND DYSPHONIA

The tenth cranial (vagus) nerve (Fig. 441-6) carries somatic sensation from the posterior aspect of the external auditory canal, laryngopharynx, superior larynx, and meninges of the posterior fossa to the spinal trigeminal nucleus, as well as taste from the epiglottis and pharynx and visceral sensation from chemoreceptors and baroreceptors in the aortic arch, heart, and gastrointestinal tract to the splenic flexure to the nucleus solitarius. The motor part originates in the nucleus ambiguus and innervates most muscles of the oropharynx and soft palate as well as all laryngeal muscles. Parasympathetic fibers originate in the dorsal motor nucleus of the vagus nerve and decrease the heart rate through action at the sino-atrial and atrioventricular nodes; others promote peristalsis and secretion of the alimentary tract from the esophagus to the splenic flexure. When the intracranial portion of one vagus (tenth cranial) nerve is interrupted, the soft palate droops ipsilaterally and does not rise in phonation. There is loss of the gag reflex on the affected side, as well as of the “curtain movement” of the lateral wall of the pharynx, whereby the faecal pillars move medially as the palate rises in saying “ah.” The voice is hoarse and slightly nasal, and the vocal cord lies immobile midway between abduction and adduction. Loss of sensation at the external auditory meatus and the posterior pinna may also be present.

The vagus nerve may be involved at the meningeal level by neoplastic and infectious processes and within the medulla by tumors, vascular lesions (e.g., the lateral medullary syndrome), and motor neuron disease. The nerve may be involved by infection with varicella zoster virus. Injury to the vagus nerve in the carotid sheath can occur with carotid dissection or following endarterectomy. The pharyngeal branches of both vagal nerves may be affected in diphtheria; the voice has a nasal quality, and regurgitation of liquids through the nose occurs during swallowing. Polymyositis and dermatomyositis, which cause hoarseness and dysphagia by direct involvement of laryngeal and pharyngeal muscles, may be confused with diseases of the vagus nerves. Dysphagia is also a symptom in some patients with myotonic dystrophy. **Nonneurologic causes of dysphagia are discussed in Chap. 44.**

The recurrent laryngeal nerves, especially the left, are most often damaged as a result of intrathoracic disease. Aneurysm of the aortic arch, an enlarged left atrium, and tumors of the mediastinum and

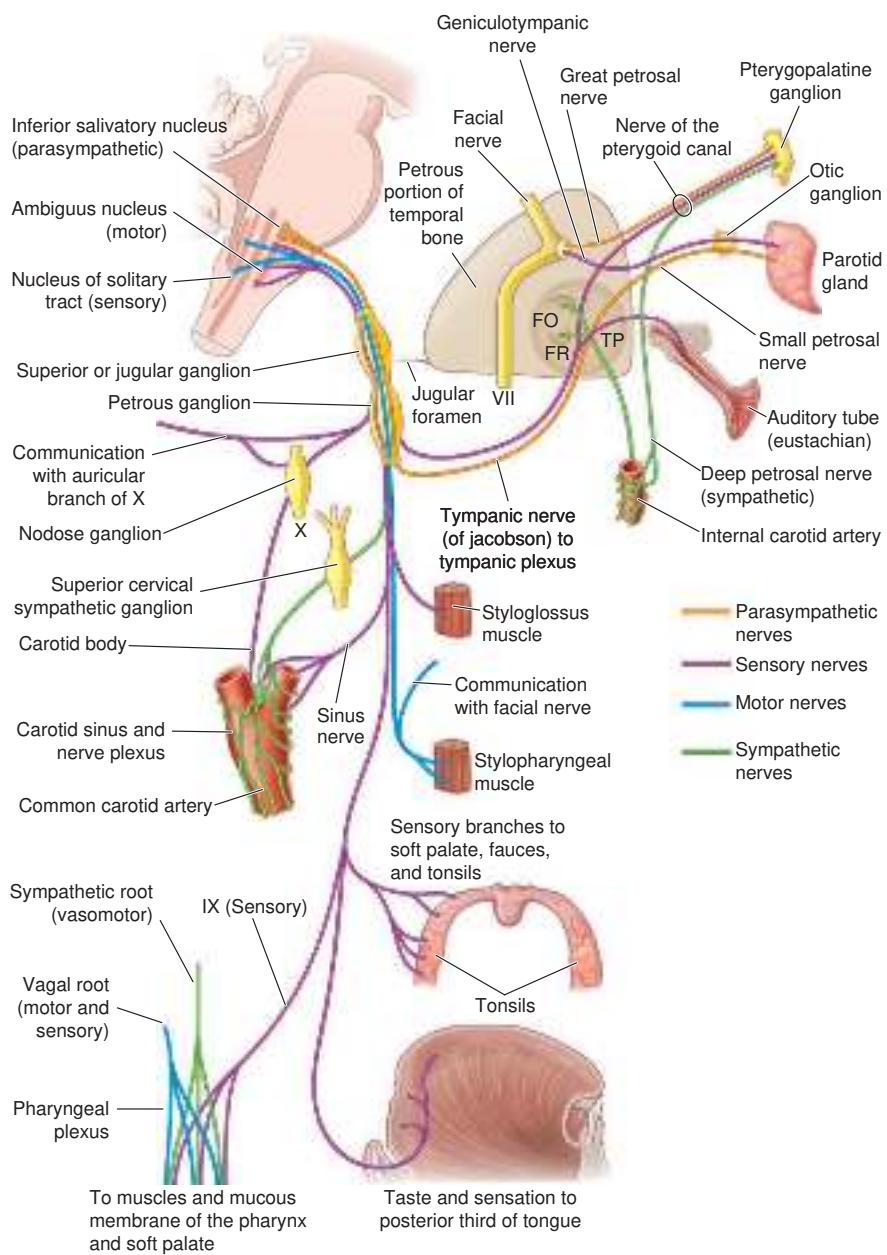


FIGURE 441-5 The ninth cranial (glossopharyngeal) nerve. TP, tympanum plexus; FR, foramen rotundum; FO, foramen ovale. (Reproduced with permission from SG Waxman: Clinical Neuroanatomy, 29th ed. New York, McGraw Hill, 2020.)

bronchi are much more frequent causes of an isolated vocal cord palsy than are intracranial disorders. However, a substantial number of cases of recurrent laryngeal palsy remain idiopathic.

When confronted with a case of laryngeal palsy, the physician must attempt to determine the site of the lesion. If it is intramedullary, there are usually other signs, such as ipsilateral cerebellar dysfunction, loss of pain and temperature sensation over the ipsilateral face and contralateral arm and leg, and an ipsilateral Horner's syndrome. If the lesion is extramedullary, the glossopharyngeal and spinal accessory nerves are frequently involved (jugular foramen syndrome). If it is extracranial in the posterior laterocondylar or retroparotid space, there may be a combination of ninth, tenth, eleventh, and twelfth cranial nerve palsies and Horner's syndrome (Table 441-2). If there is no sensory loss over the palate and pharynx and no palatal weakness or dysphagia, the lesion is below the origin of the pharyngeal branches,

which leave the vagus nerve high in the cervical region; the usual site of disease is then the mediastinum.

■ NECK WEAKNESS

The eleventh cranial nerve (spinal accessory) is a pure motor nerve arising from the nucleus ambiguus and the ventral horn of the spinal cord from C1–C6. The nerve travels superiorly through the foramen magnum and exits through the jugular foramen to innervate the ipsilateral sternocleidomastoid and trapezius muscles. Isolated involvement of the accessory (eleventh cranial) nerve can occur anywhere along its route, resulting in partial or complete paralysis of the sternocleidomastoid and trapezius muscles. Spinal accessory nerve palsy does not result in significant neck weakness because several other muscles also turn the head and flex the neck; therefore, detection of accessory nerve injury relies on palpating the absence of sternocleidomastoid contraction

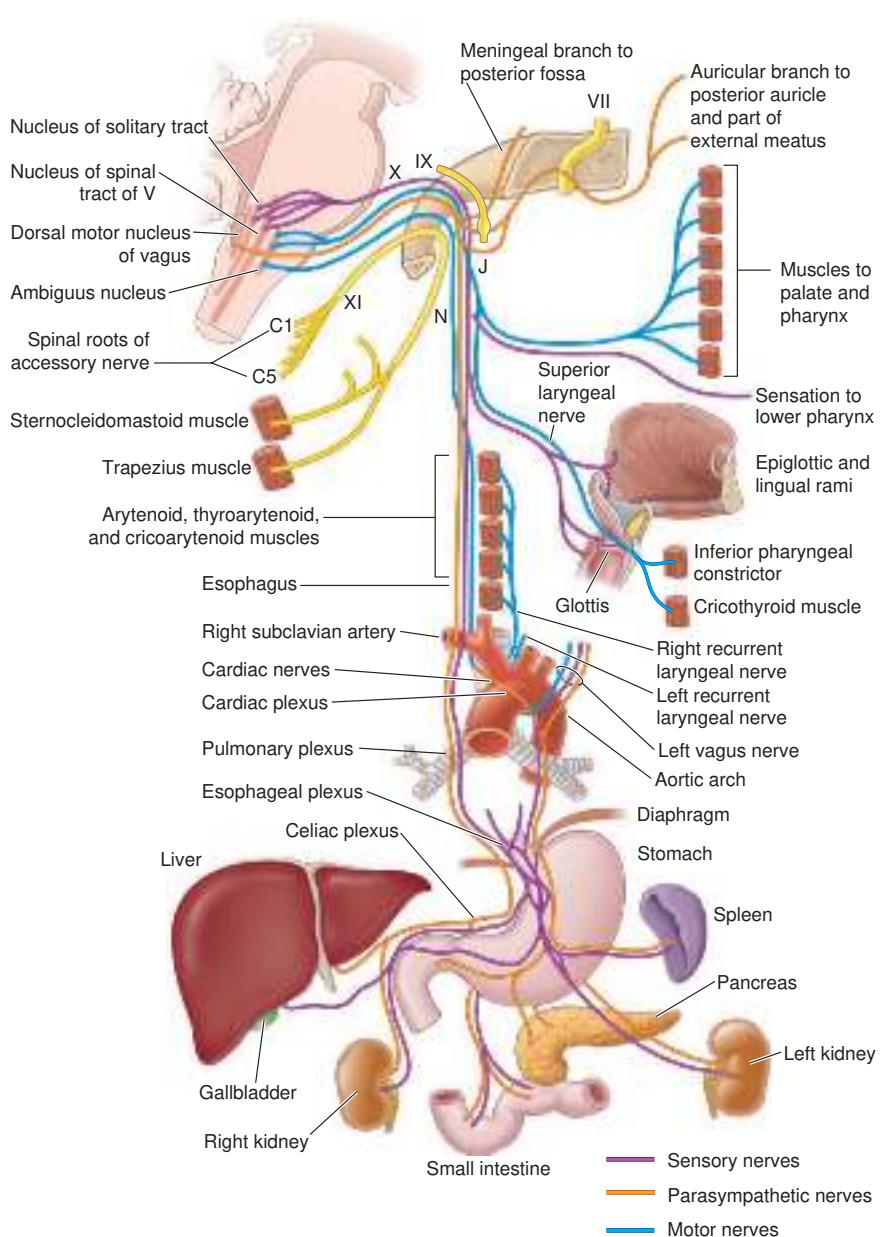


FIGURE 441-6 The vagus nerve. J, jugular (superior) ganglion; N, nodose (inferior) ganglion. (Reproduced with permission from SG Waxman: Clinical Neuroanatomy, 29th ed. New York, McGraw Hill, 2020.)

during head turning. Similarly, shoulder shrug is only slightly impacted by trapezius weakness, although the affected shoulder is lower at rest, scapular winging occurs, and the arm cannot abduct beyond 90°. Isolated spinal accessory nerve palsy is often iatrogenic due to neck surgery or jugular vein cannulation, or traumatic. An idiopathic form of accessory neuropathy, akin to Bell's palsy, has been described, and it may be recurrent in some cases. Most but not all patients recover.

TONGUE PARALYSIS

The twelfth cranial nerve (hypoglossal) supplies the ipsilateral muscles of the tongue. Nerve lesions cause the tongue to deviate toward the ipsilateral side during protrusion due to ipsilateral genioglossus weakness, in addition to weakness of tongue movements toward the affected side to weakness of ipsilateral intrinsic tongue musculature. Atrophy and fasciculation of the tongue develop weeks to months after interruption of the nerve. The nucleus of the nerve or its fibers of exit

may be involved by intramedullary lesions such as tumor, poliomyelitis, or most often motor neuron disease. Lesions of the basal meninges and the occipital bones (platybasia, invagination of occipital condyles, Paget's disease) may compress the nerve in its extramedullary course or as it exits the skull in the hypoglossal canal. Isolated lesions of unknown cause can occur.

MULTIPLE CRANIAL NERVE PALSYES

Several cranial nerves may be affected by the same disease process. In this situation, the main clinical problem is to determine whether the lesion lies within the brainstem or outside it. Lesions that lie on the surface of the brainstem are characterized by involvement of adjacent cranial nerves (often occurring in succession) and late and rather slight involvement of the long sensory and motor pathways and segmental structures lying within the brainstem. The opposite is true of primary lesions within the brainstem. The extramedullary lesion is more likely

TABLE 441-2 Cranial Nerve Syndromes

SITE	CRANIAL NERVES	USUAL CAUSE
Orbital apex	II, III, IV, first division V, VI	Invasive fungal infections, amyloidosis, granulomatous disease
Sphenoid fissure (superior orbital)	III, IV, first division V, VI	Invasive tumors of sphenoid bone; aneurysms
Lateral wall of cavernous sinus	III, IV, first division V, VI, often with proptosis	Infection, thrombosis, aneurysm or fistula of cavernous sinus; invasive tumors from sinuses and sella turcica; benign granuloma responsive to glucocorticoids
Retrosphenoid space	II, III, IV, V, VI	Large tumors of middle cranial fossa
Apex of petrous bone	V, VI	Petrositis; tumors of petrous bone
Internal auditory meatus	VII, VIII	Tumors of petrous bone (dermoids, etc.); infectious processes; acoustic neuroma
Pontocerebellar angle	V, VI, VII, VIII, and sometimes IX	Acoustic neuroma; meningioma
Jugular foramen	IX, X, XI	Tumors and aneurysms
Posterior laterocondylar space	IX, X, XI, XII	Tumors of parotid gland and carotid body and metastatic tumors
Posterior retroparotid space	IX, X, XI, XII, and Horner's syndrome	Tumors of parotid gland, carotid body, lymph nodes; metastatic tumor; tuberculous adenitis

to cause bone erosion or enlargement of the foramen of exit of cranial nerves. The intramedullary lesion involving cranial nerves often produces a crossed sensory or motor paralysis (cranial nerve signs on one side of the body and tract signs on the opposite side).

Involvement of multiple cranial nerves outside the brainstem is frequently the result of trauma, localized infections including varicella-zoster virus, infectious and noninfectious (especially carcinomatous) causes of meningitis (Chaps. 138 and 139), granulomatous diseases such as granulomatosis with polyangiitis (Chap. 363), Behcet's disease, vascular disorders including those associated with diabetes, enlarging aneurysms, or locally infiltrating tumors. Among the tumors, nasopharyngeal cancers, lymphomas, neurofibromas, meningiomas, chordomas, cholesteatomas, carcinomas, and sarcomas have all been observed to involve a succession of lower cranial nerves. Owing to their anatomic relationships, the multiple cranial nerve palsies form a number of distinctive syndromes, listed in Table 441-2. Sarcoidosis is the cause of some cases of multiple cranial neuropathy; tuberculosis, the Chiari malformation, platybasia, and basilar invagination of the skull are additional causes.

Cavernous sinus syndrome (Fig. 441-7) is a distinctive and frequently life-threatening disorder. It often presents as orbital or facial pain; orbital swelling, chemosis due to occlusion of the ophthalmic veins; fever; oculomotor neuropathy affecting the third, fourth, and sixth cranial nerves; and trigeminal neuropathy affecting the ophthalmic (V1) and occasionally the maxillary (V2) divisions of the trigeminal nerve. Cavernous sinus thrombosis, often secondary to infection from orbital cellulitis (frequently *Staphylococcus aureus*), a cutaneous source on the face, or sinusitis (especially with mucormycosis in diabetic patients), is the most frequent cause; other etiologies include aneurysm of the carotid artery, a carotid-cavernous fistula (orbital bruit may be present), meningioma, nasopharyngeal carcinoma, other tumors, or an idiopathic granulomatous disorder (Tolosa-Hunt syndrome). The two cavernous sinuses directly communicate via intercavernous channels; thus, involvement on one side may extend to become bilateral. Early diagnosis is essential, especially when due to infection, and treatment depends on the underlying etiology.

In infectious cases, prompt administration of broad-spectrum antibiotics, drainage of any abscess cavities, and identification of the offending organism are essential. Anticoagulant therapy may benefit cases of primary thrombosis. Repair or occlusion of the carotid artery may be required for treatment of fistulas or aneurysms. Tolosa-Hunt

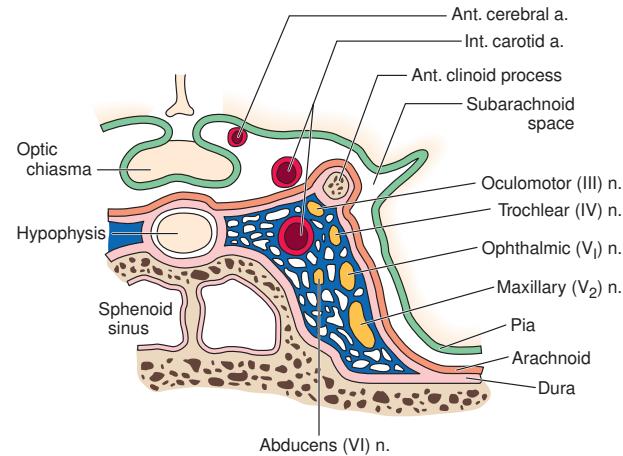


FIGURE 441-7 Anatomy of the cavernous sinus in coronal section, illustrating the location of the cranial nerves in relation to the vascular sinus, internal carotid artery (which loops anteriorly to the section), and surrounding structures.

syndrome generally responds to glucocorticoids. A dramatic improvement in pain is usually evident within a few days; oral prednisone (60 mg daily) is usually continued for 2 weeks and then gradually tapered over a month, or longer if pain recurs. Occasionally an immunosuppressive medication, such as azathioprine or methotrexate, needs to be added to maintain an initial response to glucocorticoids.

Lesions in the superior orbital fissure and orbital apex cause more prominent vision loss than those in the cavernous sinus due to compression of the optic nerve; the second branch of the trigeminal nerve is usually spared. The cause is often an invasive fungal infection, frequently due to osseous erosion through the wall of the maxillary, sphenoid, or ethmoid sinuses. Infiltrative processes such as amyloidosis, granulomatosis with polyarteritis, and an idiopathic inflammatory syndrome similar to Tolosa-Hunt are additional causes, and biopsy is often necessary for diagnosis.

As noted above, Guillain-Barré syndrome commonly affects the facial nerves bilaterally. In the Fisher variant of Guillain-Barré syndrome, oculomotor paresis occurs with ataxia and areflexia in the limbs (Chap. 447). Wernicke's encephalopathy can cause a severe ophthalmoplegia combined with other brainstem signs (Chap. 307).

Progressive bulbar palsy is a slowly progressive purely motor disorder affecting multiple cranial nerve nuclei. Weakness of the face, jaw, pharynx, neck and tongue is usually present accompanied by atrophy and fasciculations. It is a form of motor neuron disease (Chap. 437). Pure motor syndromes without atrophy raise the question of myasthenia gravis (Chap. 448), and with rapidly evolving Guillain Barre syndrome, diphtheria and poliomyelitis are additional considerations.

Glossopharyngeal neuropathy in conjunction with vagus and accessory nerve palsies may occur with herpes zoster infection or with a tumor or aneurysm in the posterior fossa or in the jugular foramen, through which all three nerves exit the skull. Hoarseness due to vocal cord paralysis, some difficulty in swallowing, deviation of the soft palate to the intact side, anesthesia of the posterior wall of the pharynx, and weakness of the upper part of the trapezius and sternocleidomastoid muscles make up jugular foramen syndrome.

Paralysis of the vagus and hypoglossal nerves (Tapia syndrome) can rarely follow endotracheal intubation and has been reported during the COVID-19 pandemic; symptoms consist of dysphonia and tongue deviation, and usually resolve within a few months.

An idiopathic form of multiple cranial nerve involvement on one or both sides of the face is occasionally seen. The syndrome consists of a subacute onset of boring facial pain, followed by paralysis of motor cranial nerves. The clinical features overlap those of Tolosa-Hunt syndrome and appear to be due to idiopathic inflammation of the dura mater, which may be visualized by MRI. The syndrome is usually responsive to glucocorticoids.

FURTHER READING

- B L et al: Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. *Lancet* 19:784, 2020.
- D P et al: Tapia syndrome at the time of the COVID-19 pandemic: Lower cranial neuropathy following prolonged intubation. *Neurology* 95:312, 2020.
- G I et al: Antiviral treatment of Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 9:CD001869, 2019.
- G S et al: Lower cranial nerve syndromes: A review. *Neurology* 44:1345, 2020.
- K HR, C HD: Imaging of skull base lesions. *Handb Clin Neurol* 135:637, 2016.
- M VB et al: Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 7:CD001942, 2016.

442

Diseases of the Spinal Cord

Stephen L. Hauser

Diseases of the spinal cord are frequently devastating. They produce quadriplegia, paraplegia, and sensory deficits far beyond the damage they would inflict elsewhere in the nervous system because the spinal cord contains, in a small cross-sectional area, almost the entire motor output and sensory input of the trunk and limbs. Many spinal cord diseases are reversible if recognized and treated at an early stage (**Table 442-1**); thus, they are among the most critical of neurologic emergencies. The efficient use of diagnostic procedures, guided by knowledge of the anatomy and the clinical features of spinal cord diseases, is required to maximize the likelihood of a successful outcome.

APPROACH TO THE PATIENT

Spinal Cord Disease

SPINAL CORD ANATOMY RELEVANT TO CLINICAL SIGNS

The spinal cord is a thin, tubular extension of the central nervous system contained within the bony spinal canal. It originates at the medulla and continues caudally to the conus medullaris at the lumbar level; its fibrous extension, the filum terminale, terminates at the coccyx. The adult spinal cord is ~46 cm (18 in.) long, oval in shape, and enlarged in the cervical and lumbar regions, where neurons that innervate the upper and lower extremities, respectively, are located. The white matter tracts containing ascending sensory and descending motor pathways are located peripherally, whereas nerve cell bodies are clustered in an inner region of gray matter shaped like a four-leaf clover that surrounds the central canal (anatomically an extension of the fourth ventricle). The membranes that cover the spinal cord—the pia, arachnoid, and dura—are continuous with those of the brain, and the cerebrospinal fluid is contained within the subarachnoid space between the pia and arachnoid.

The spinal cord has 31 segments, each defined by an exiting ventral motor root and entering dorsal sensory root. During embryologic development, growth of the cord lags behind that of the vertebral column, and the mature spinal cord ends at approximately the first lumbar vertebral body. The lower spinal nerves take an increasingly downward course to exit via intervertebral foramina. The first seven pairs of cervical spinal nerves exit above the same-numbered vertebral bodies, whereas all the subsequent nerves exit below the same-numbered vertebral bodies because of the presence of eight cervical spinal cord segments but only seven cervical vertebrae. The relationship between spinal cord segments

TABLE 442-1 Treatable Spinal Cord Disorders

Compressive	
Epidural, intradural, or intramedullary neoplasm	
Epidural abscess	
Epidural hemorrhage	
Cervical spondylosis	
Herniated disk	
Posttraumatic compression by fractured or displaced vertebra or hemorrhage	
Vascular	
Arteriovenous malformation and dural fistula	
Antiphospholipid syndrome and other hypercoagulable states	
Inflammatory	
Multiple sclerosis	
Neuromyelitis optica	
Sarcoidosis	
Systemic immune-mediated disorders: SLE, Sjögren's, Behcet's disease, APL antibody syndrome, others vasculitis	
Other CNS disorders: anti-MOG, anti-GFAP, paraneoplastic, ^a CLIPPERS, Erdheim-Chester	
Infectious	
Viral: VZV, HSV-1 and 2, CMV, HIV, HTLV-1, others	
Bacterial and mycobacterial: <i>Borrelia</i> , <i>Listeria</i> , syphilis, others	
<i>Mycoplasma pneumoniae</i>	
Parasitic: schistosomiasis, toxoplasmosis, cysticercosis	
Developmental	
Syringomyelia	
Meningomyelocele	
Tethered cord syndrome	
Metabolic	
Vitamin B ₁₂ deficiency (subacute combined degeneration)	
Folate deficiency	
Copper deficiency	

^aIncluding anti-amphiphysin, CRMP-5, Hu.

Abbreviations: CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CMV, cytomegalovirus; CNS, central nervous system; CRMP5, collapsin response mediator 5-1gg; GFAP, glial fibrillary acidic protein; HSV, herpes simplex virus; HTLV, human T-cell lymphotropic virus; MOG, myelin oligodendrocyte glycoprotein; SLE, systemic lupus erythematosus; VZV, varicella-zoster virus.

and the corresponding vertebral bodies is shown in **Table 442-2**. These relationships assume particular importance for localization of lesions that cause spinal cord compression. Sensory loss below the circumferential level of the umbilicus, for example, corresponds to the T10 cord segment but indicates involvement of the cord adjacent to the seventh or eighth thoracic vertebral body (**see Figs. 25-2 and 25-3**). In addition, at every level, the main ascending and descending tracts are somatotopically organized with a laminated distribution that reflects the origin or destination of nerve fibers.

Determining the Level of the Lesion The presence of a horizontally defined level below which sensory, motor, and autonomic function is impaired is a hallmark of a lesion of the spinal cord. This

TABLE 442-2 Spinal Cord Levels Relative to the Vertebral Bodies

SPINAL CORD LEVEL	CORRESPONDING VERTEBRAL BODY
Upper cervical	Same as cord level
Lower cervical	1 level higher
Upper thoracic	2 levels higher
Lower thoracic	2-3 levels higher
Lumbar	T10-T12
Sacral	T12-L1

sensory level is sought by asking the patient to identify a pinprick or cold stimulus applied to the proximal legs and lower trunk and successively moved up toward the neck on each side. Sensory loss below this level is the result of damage to the spinothalamic tract on the opposite side, one to two segments higher in the case of a unilateral spinal cord lesion, and at the level of a bilateral lesion. The discrepancy in the level of a unilateral lesion is the result of the course of the second-order sensory fibers, which originate in the dorsal horn, and ascend for one or two levels as they cross anterior to the central canal to join the opposite spinothalamic tract. Lesions that transect the descending corticospinal and other motor tracts cause paraplegia or quadriplegia with heightened deep tendon reflexes, Babinski signs, and eventual spasticity (upper motor neuron syndrome). Transverse damage to the cord also produces autonomic disturbances consisting of absent sweating below the implicated cord level and bladder, bowel, and sexual dysfunction.

The uppermost level of a spinal cord lesion can also be localized by attention to the *segmental signs* corresponding to disturbed motor or sensory innervation by an individual cord segment. A band of altered sensation (hyperesthesia or hyperpathia) at the upper end of the sensory disturbance, fasciculations or atrophy in muscles innervated by one or several segments, or a muted or absent deep tendon reflex may be noted at this level. These signs also can occur with focal root or peripheral nerve disorders; thus, they are most useful when they occur together with signs of long-tract damage. With severe and acute transverse lesions, the limbs initially may be flaccid rather than spastic. This state of "spinal shock" lasts for several days, rarely for weeks, and may be mistaken for extensive damage to the anterior horn cells over many segments of the cord or for an acute polyneuropathy.

The main features of transverse damage at each level of the spinal cord are summarized below.

Cervical Cord Upper cervical cord lesions produce quadriplegia and weakness of the diaphragm. The uppermost level of weakness and reflex loss with lesions at C5–C6 is in the biceps; at C7, in finger and wrist extensors and triceps; and at C8, finger and wrist flexion. Horner's syndrome (miosis, ptosis, and facial hypohidrosis) may accompany a cervical cord lesion at any level.

Thoracic Cord Lesions here are localized by the sensory level on the trunk and, if present, by the site of midline back pain. Useful markers of the sensory level on the trunk are the nipples (T4) and umbilicus (T10). Leg weakness and disturbances of bladder and bowel function accompany the paralysis. Lesions at T9–T10 paralyze the lower—but not the upper—abdominal muscles, resulting in upward movement of the umbilicus when the abdominal wall contracts (*Beevor's sign*).

Lumbar Cord Lesions at the L2–L4 spinal cord levels paralyze flexion and adduction of the thigh, weaken leg extension at the knee, and abolish the patellar reflex. Lesions at L5–S1 paralyze only movements of the foot and ankle, flexion at the knee, and extension of the thigh, and abolish the ankle jerks (S1).

Sacral Cord/Conus Medullaris The conus medullaris is the tapered caudal termination of the spinal cord, comprising the sacral and single coccygeal segments. The distinctive conus syndrome consists of bilateral saddle anesthesia (S3–S5), prominent bladder and bowel dysfunction (urinary retention and incontinence with lax anal tone), and impotence. The bulbocavernosus (S2–S4) and anal (S4–S5) reflexes are absent (Chap. 422). Muscle strength is largely preserved. By contrast, lesions of the cauda equina, the nerve roots derived from the lower cord, are characterized by low back and radicular pain, asymmetric leg weakness and sensory loss, variable areflexia in the lower extremities, and relative sparing of bowel and bladder function. Mass lesions in the lower spinal canal often produce a mixed clinical picture with elements of both cauda equina and conus medullaris syndromes. *Cauda equina syndromes are also discussed in Chap. 17.*

Special Patterns of Spinal Cord Disease The location of the major ascending and descending pathways of the spinal cord are shown in Fig. 442-1. Most fiber tracts—including the posterior columns and the spinocerebellar and pyramidal tracts—are situated on the side of the body they innervate. However, afferent fibers mediating pain and temperature sensation ascend in the spinothalamic tract contralateral to the side they supply. The anatomic configurations of these tracts produce characteristic syndromes that provide clues to the underlying disease process.

Brown-Séquard Hemicord Syndrome This consists of ipsilateral weakness (corticospinal tract) and loss of joint position and vibratory sense (posterior column), with contralateral loss of pain and temperature sense (spinothalamic tract) one or two levels below the lesion. Segmental signs, such as radicular pain, muscle atrophy, or loss of a deep tendon reflex, are unilateral. Partial forms are more common than the fully developed syndrome.

Central Cord Syndrome This syndrome results from selective damage to the gray matter nerve cells and crossing spinothalamic tracts surrounding the central canal. In the cervical cord, the central cord syndrome produces arm weakness out of proportion to leg weakness and a "dissociated" sensory loss, meaning loss of pain and temperature sensations over the shoulders, lower neck, and upper trunk (cape distribution), in contrast to preservation of light touch, joint position, and vibration sense in these regions. Spinal trauma, syringomyelia, and intrinsic cord tumors are the main causes.

Anterior Spinal Artery Syndrome Infarction of the cord is generally the result of occlusion or diminished flow in this artery. The result is bilateral tissue destruction at several contiguous levels that spares the posterior columns. All spinal cord functions—motor, sensory, and autonomic—are lost below the level of the lesion, with the striking exception of retained vibration and position sensation.

Foramen Magnum Syndrome Lesions in this area interrupt decussating pyramidal tract fibers destined for the legs, which cross caudal to those of the arms, resulting in weakness of the legs (*crural paresis*). Compressive lesions near the foramen magnum may produce weakness of the ipsilateral shoulder and arm followed by weakness of the ipsilateral leg, then the contralateral leg, and finally the contralateral arm, an "around-the-clock" pattern that may begin in any of the four limbs. There is typically suboccipital pain spreading to the neck and shoulders.

Intramedullary and Extramedullary Syndromes It is useful to differentiate *intramedullary* processes, arising within the substance of the cord, from *extramedullary* ones that lie outside the cord and compress the spinal cord or its vascular supply. The differentiating features are only relative and serve as clinical guides. With extramedullary lesions, radicular pain is often prominent, and there is early sacral sensory loss and spastic weakness in the legs with incontinence due to the superficial location of the corresponding sensory and motor fibers in the spinothalamic and corticospinal tracts (Fig. 442-1). Intramedullary lesions tend to produce poorly localized burning pain rather than radicular pain and to spare sensation in the perineal and sacral areas ("sacral sparing"), reflecting the laminated configuration of the spinothalamic tract with sacral fibers outermost; corticospinal tract signs appear later. Regarding extramedullary lesions, a further distinction is made between extradural and intradural masses, as the former are generally malignant and the latter benign (neurofibroma being a common cause). Consequently, a long duration of symptoms favors an intradural origin.

ACUTE AND SUBACUTE SPINAL CORD DISEASES

Symptoms of the cord diseases that evolve over days or weeks are focal neck or back pain, followed by various combinations of paresthesias, sensory loss, motor weakness, and sphincter disturbance. There may be mild sensory symptoms only or a devastating functional transection of the cord. When paresthesias begin in the feet and then ascend a

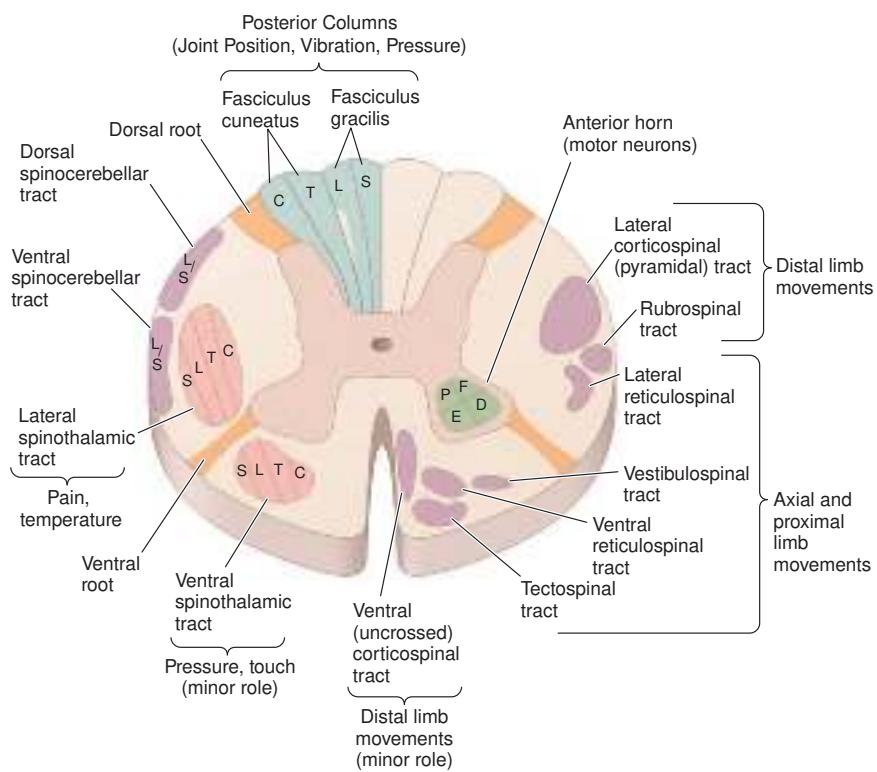


FIGURE 442-1 Transverse section through the spinal cord, composite representation, illustrating the principal ascending (left) and descending (right) pathways. The lateral and ventral spinothalamic tracts ascend contralateral to the side of the body that is innervated. In humans, the lateral corticospinal (pyramidal) tract is thought to lack strict somatotopic organization in the spinal cord. C, cervical; D, distal; E, extensors; F, flexors; L, lumbar; P, proximal; S, sacral; T, thoracic.

Polyneuropathy is often considered, and in such cases the presence of bladder disturbances and a sharply demarcated spinal cord level provide important clues to the spinal cord origin of the disease.

In severe and abrupt cases, areflexia reflecting spinal shock may be present, but hyperreflexia supervenes over days or weeks; persistent areflexic paralysis with a sensory level usually indicates necrosis over multiple segments of the spinal cord.

APPROACH TO THE PATIENT

Compressive and Noncompressive Myelopathy

DISTINGUISHING COMPRESSIVE FROM NONCOMPRESSIVE MYELOPATHY

The first priority is to exclude treatable compression of the cord by a mass lesion. The common causes are tumor, epidural abscess or hematoma, herniated disk, and spondylitic vertebral pathology. Epidural compression due to malignancy or abscess often causes warning signs of neck or back pain, bladder disturbances, and sensory symptoms that precede the development of paralysis. Spinal subluxation, hemorrhage, and noncompressive etiologies such as infarction are more likely to produce myelopathy without antecedent symptoms. MRI with gadolinium, centered on the clinically suspected level, is the initial diagnostic procedure if it is available; it is often appropriate to image the entire spine (cervical through sacral regions) to search for additional clinically silent lesions. Once compressive lesions have been excluded, noncompressive causes of acute myelopathy that are intrinsic to the cord are considered, primarily vascular, inflammatory, and infectious etiologies.

■ COMPRESSIVE MYELOPATHIES

Neoplastic Spinal Cord Compression In adults, most neoplasms are epidural in origin, resulting from metastases to the adjacent

vertebral column. The propensity of solid tumors to metastasize to the vertebral column probably reflects the high proportion of bone marrow located in the axial skeleton. Almost any malignant tumor can metastasize to the spinal column, with breast, lung, prostate, kidney, lymphoma, and myeloma being particularly frequent. The thoracic spinal column is most commonly involved; exceptions are metastases from prostate and ovarian cancer, which occur disproportionately in the sacral and lumbar vertebrae, probably from spread through Batson's plexus, a network of veins along the anterior epidural space. Retroperitoneal neoplasms (especially lymphomas or sarcomas) enter the spinal canal laterally through the intervertebral foramina and produce radicular pain with signs of weakness that corresponds to the level of involved nerve roots.

Pain is usually the initial symptom of spinal metastasis; it may be aching and localized or sharp and radiating in quality and typically worsens with movement, coughing, or sneezing and characteristically awakens patients at night. A recent onset of persistent back pain, particularly if in the thoracic spine (which is uncommonly involved by spondylosis), should prompt consideration of vertebral metastasis. Rarely, pain is mild or absent. Plain radiographs of the spine and radionuclide bone scans have a limited role in diagnosis because they do not identify 15–20% of metastatic vertebral lesions and fail to detect paravertebral masses that reach the epidural space through the intervertebral foramina. MRI provides excellent anatomic resolution of the extent of spinal tumors (Fig. 442-2) and is able to distinguish between malignant lesions and other masses—epidural abscess, tuberculoma, lipoma, or epidural hemorrhage, among others—that present in a similar fashion. Vertebral metastases are usually hypointense relative to a normal bone marrow signal on T1-weighted MRI; after the administration of gadolinium, contrast enhancement may deceptively “normalize” the appearance of the tumor by increasing its intensity to that of normal bone marrow. Infections of the spinal column (osteomyelitis and related disorders) are distinctive in that, unlike tumor, they often cross the disk space to involve the adjacent vertebral body.

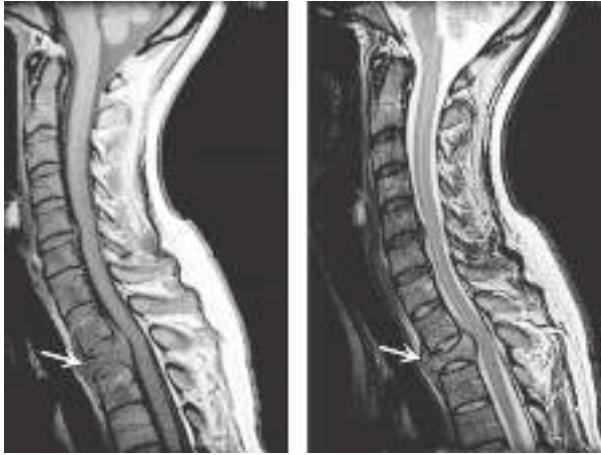


FIGURE 442-2 Epidural spinal cord compression due to breast carcinoma. Sagittal T1-weighted (*A*) and T2-weighted (*B*) magnetic resonance imaging scans through the cervicothoracic junction reveal an infiltrated and collapsed second thoracic vertebral body with posterior displacement and compression of the upper thoracic spinal cord. The low-intensity bone marrow signal in *A* signifies replacement by tumor.

If spinal cord compression is suspected, imaging should be obtained promptly. If there are radicular symptoms but no evidence of myelopathy, it may be safe to defer imaging for 24–48 h. Up to 40% of patients who present with cord compression at one level are found to have asymptomatic epidural metastases elsewhere; thus, imaging of the entire length of the spine is important to define the extent of disease.

TREATMENT

Neoplastic Spinal Cord Compression

Proper management of cord compression is based on multiple considerations, including radiosensitivity of the primary tumor, extent of compression, prior therapy to the site, and stability of the spine. Treatment includes glucocorticoids to reduce cord edema, surgery and/or local radiotherapy (initiated as early as possible) to the symptomatic lesion, and specific therapy for the underlying tumor type. Glucocorticoids (typically dexamethasone, 10 mg intravenously) can be administered before an imaging study if there is clinical suspicion of cord compression and continued at a lower dose (4 mg every 6 h orally) until definitive treatment with radiotherapy and/or surgical decompression is completed. In one trial, initial management with surgery followed by radiotherapy was more effective than radiotherapy alone for patients with a single area of spinal cord compression by extradural tumor; however, patients with recurrent cord compression, brain metastases, radiosensitive tumors, or severe motor symptoms of >48 h in duration were excluded from this study. Stereotactic body radiotherapy, which delivers high doses of focused radiation, is preferred for radioresistant tumor types and for patients requiring re-irradiation.

Biopsy of the epidural mass is unnecessary in patients with known primary cancer, but it is indicated if a history of underlying cancer is lacking. Surgical treatment, either decompression by laminectomy or a spinal fixation procedure, is also indicated when signs of cord compression worsen despite radiotherapy; the maximum-tolerated dose of radiotherapy has been delivered previously to the site; a vertebral compression fracture or spinal instability contributes to cord compression; or in cases of high-grade spinal cord compression from a radioresistant tumor.

A good response to therapy can be expected in individuals who are ambulatory at presentation. Treatment usually prevents new weakness, and some recovery of motor function occurs in up to one-third of patients. Motor deficits (paraplegia or quadriplegia),

once established for >12 h, do not usually improve, and beyond 48 h the prognosis for substantial motor recovery is poor. Although most patients do not experience recurrences in the months following radiotherapy, with survival beyond 2 years recurrence becomes increasingly likely and can be managed with additional radiotherapy.

In contrast to tumors of the epidural space, most intradural mass lesions are slow-growing and benign. Meningiomas and neurofibromas account for most of these, with occasional cases caused by chordoma, lipoma, dermoid, or sarcoma. Meningiomas (Fig. 442-3) are often located posterior to the thoracic cord or near the foramen magnum, although they can arise from the meninges anywhere along the spinal canal. Neurofibromas are benign tumors of the nerve sheath that typically arise from the posterior root; when multiple, neurofibromatosis is the likely etiology. Symptoms usually begin with radicular sensory symptoms followed by an asymmetric, progressive spinal cord syndrome. Therapy is surgical resection.

Primary intramedullary tumors of the spinal cord are uncommon. They present as central cord or hemicord syndromes, often in the cervical region. There may be poorly localized burning pain in the extremities and sparing of sacral sensation. In adults, these lesions are ependymomas, hemangioblastomas, or low-grade astrocytomas (Fig. 442-4). Complete resection of an intramedullary ependymoma is often possible with microsurgical techniques. Debulking of an intramedullary astrocytoma can also be helpful, as these are often slowly growing lesions; the value of adjunctive radiotherapy and chemotherapy is uncertain. Secondary (metastatic) intramedullary tumors also occur, especially in patients with advanced metastatic disease (Chap. 90), although these are not nearly as frequent as brain metastases.

Spinal Epidural Abscess Spinal epidural abscess presents with midline back or neck pain, fever, and progressive limb weakness. Prompt recognition of this distinctive process may prevent permanent sequelae. Aching pain is almost always present, either over the spine or in a radicular pattern. The duration of pain prior to presentation is generally 2 weeks but may on occasion be several months or longer.



FIGURE 442-3 Magnetic resonance imaging of a thoracic meningioma. Coronal T1-weighted postcontrast image through the thoracic spinal cord demonstrates intense and uniform enhancement of a well-circumscribed extramedullary mass (arrows) that displaces the spinal cord to the left.



FIGURE 442-4 Magnetic resonance imaging of an intramedullary astrocytoma. Sagittal T1-weighted postcontrast image through the cervical spine demonstrates expansion of the upper cervical spine by a mass lesion emanating from within the spinal cord at the cervicomедullary junction. Irregular peripheral enhancement occurs within the mass (arrows).

Fever is typically but not invariably present, accompanied by elevated white blood cell count, sedimentation rate, and C-reactive protein. As the abscess expands, further spinal cord damage results from venous congestion and thrombosis. Once weakness and other signs of myelopathy appear, progression may be rapid and irreversible. A more chronic sterile granulomatous form of abscess is also known, usually after treatment of an acute epidural infection.

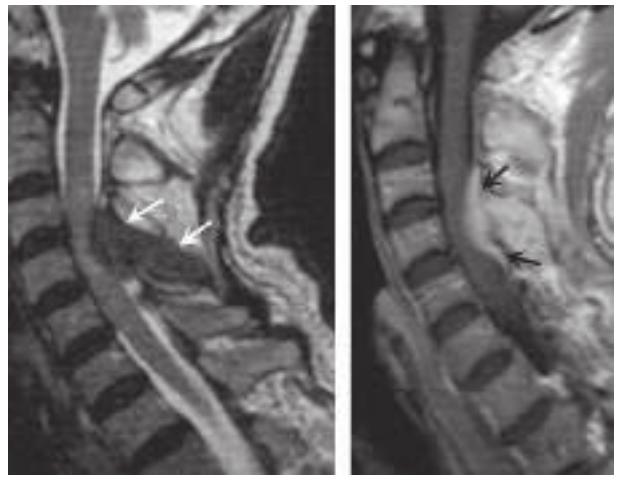
Risk factors include an impaired immune status (HIV, diabetes mellitus, renal failure, alcoholism, malignancy), intravenous drug abuse, and infections of the skin or other tissues. Two-thirds of epidural infections result from hematogenous spread of bacteria from the skin (furunculosis), soft tissue (pharyngeal or dental abscesses; sinusitis), or deep viscera (bacterial endocarditis). The remainder arises from direct extension of a local infection to the subdural space; examples of local predisposing conditions are vertebral osteomyelitis, decubitus ulcers, lumbar puncture, epidural anesthesia, or spinal surgery. Most cases are due to *Staphylococcus aureus*; gram-negative bacilli, *Streptococcus*, anaerobes, and fungi can also cause epidural abscesses. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important consideration, and therapy should be tailored to this possibility. Tuberculosis from an adjacent vertebral source (Pott's disease) remains an important cause in the developing world.

MRI (Fig. 442-5) localizes the abscess and excludes other causes of myelopathy. Blood cultures are positive in more than half of cases, but direct aspiration of the abscess at surgery is often required for a microbiologic diagnosis. Lumbar puncture is only required if encephalopathy or other clinical signs raise the question of associated meningitis, a feature that is found in <25% of cases. The level of the puncture should be planned to minimize the risk of meningitis due to passage of the needle through infected tissue. A high cervical tap is sometimes the safest approach. Cerebrospinal fluid (CSF) abnormalities in epidural and subdural abscesses consist of pleocytosis with a preponderance of polymorphonuclear cells, an elevated protein level, and a reduced glucose level, but the responsible organism is not cultured unless there is associated meningitis.

TREATMENT

Spinal Epidural Abscess

Treatment is by decompressive laminectomy with debridement combined with long-term antibiotic treatment. Surgical evacuation prevents development of paralysis and may improve or reverse



A **B**

FIGURE 442-5 Magnetic resonance (MR) imaging of a spinal epidural abscess due to tuberculosis. **A**, Sagittal T2-weighted free spin-echo MR sequence. A hypointense mass replaces the posterior elements of C3 and extends epidurally to compress the spinal cord (arrows). **B**, Sagittal T1-weighted image after contrast administration reveals a diffuse enhancement of the epidural process (arrows) with extension into the epidural space.

paralysis in evolution, but it is unlikely to improve deficits of more than several days in duration. Broad-spectrum antibiotics typically vancomycin 15–20 mg/kg q12h (staphylococcus including MRSA, streptococcus), ceftriaxone 2 gm q24h (gram-negative bacilli), and when indicated metronidazole 30 mg/kg per day divided into q6h intervals (anaerobes) should be started empirically before surgery and then modified on the basis of culture results; medication is generally continued for 6–8 weeks. If surgery is contraindicated or if there is a fixed paraparesis or quadriplegia that is unlikely to improve following surgery, long-term administration of systemic and oral antibiotics can be used; in such cases, the choice of antibiotics may be guided by results of blood cultures. Surgical management remains the treatment of choice unless the abscess is limited in size and causes few or no neurologic signs.

With prompt diagnosis and treatment of spinal epidural abscess, up to two-thirds of patients experience significant recovery.

Spinal Epidural Hematoma Hemorrhage into the epidural (or subdural) space causes acute focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder. Therapeutic anticoagulation, trauma, tumor, or blood dyscrasias are predisposing conditions. Rare cases complicate lumbar puncture or epidural anesthesia. MRI and CT confirm the clinical suspicion and can delineate the extent of the bleeding. Treatment consists of prompt reversal of any underlying clotting disorder and surgical decompression. Surgery may be followed by substantial recovery, especially in patients with some preservation of motor function preoperatively. Because of the risk of hemorrhage, lumbar puncture should be avoided whenever possible in patients with severe thrombocytopenia or other coagulopathies.

Hematomyelia Hemorrhage into the substance of the spinal cord is a rare result of trauma, intraparenchymal vascular malformation (see below), vasculitis due to polyarteritis nodosa or systemic lupus erythematosus (SLE), bleeding disorders, or a spinal cord neoplasm. Hematomyelia presents as an acute painful transverse myelopathy. With large lesions, extension into the subarachnoid space results in subarachnoid hemorrhage (Chap. 302). Diagnosis is by MRI or CT. Therapy is supportive, and surgical intervention is generally not useful. An exception is hematomyelia due to an underlying vascular malformation, for which spinal angiography and endovascular occlusion may be indicated, or surgery to evacuate the clot and remove the underlying vascular lesion.

Acute Spondylytic Myelopathy Of particular concern are hyperextension injuries in patients with underlying degenerative cervical spine disease (Chap. 17). The provoking stimulus may be obvious such as a forward fall, or occur after seemingly innocuous low-impact movements of the neck. A preexisting stenotic spinal canal is often present and “buckling” of the posterior ligamentum flavum (less commonly acute disc herniation or subluxation) is believed to produce the cord compression, sometimes with a central cord syndrome (see above) and involvement of the upper, more than lower, limbs. Deficits can be transient, resulting in a “concussion” of the spinal cord, or permanent. *The more common syndrome of chronic spondylitic myelopathy is discussed below.*

■ NONCOMPRESSIVE MYELOPATHIES

Once a compressive etiology has been excluded as the cause of an acute myelopathy, the principal challenge is to distinguish vascular/ischemic from inflammatory/infectious causes. This is often not straightforward, because clinical presentations can overlap. Moreover, findings that usually point to an inflammatory etiology—such as focal gadolinium enhancement on MRI scans or pleocytosis in the CSF—can also occur with spinal cord ischemia. Ischemia is likely in hyperacute presentations with back or neck pain, and when an anterior pattern of spinal cord injury is identified on clinical examination or by MRI. By contrast, inflammation is more likely in cases that develop subacutely, or when systemic symptoms, CSF oligoclonal bands, or multiple discrete spinal cord MRI lesions are present. The most frequent inflammatory causes of acute myelopathy are multiple sclerosis (MS); neuromyelitis optica (NMO); sarcoidosis; systemic inflammatory diseases such as SLE and Behcet's disease; postinfectious or idiopathic transverse myelitis, which is presumed to be an immune condition related to acute disseminated encephalomyelitis (Chap. 441); and infectious (primarily viral) causes.

The evaluation generally requires a lumbar puncture and a search for underlying systemic disease (Table 442-3).

Spinal Cord Infarction The cord is supplied by three arteries that course vertically over its surface: a single anterior spinal artery and

paired posterior spinal arteries. The anterior spinal artery originates in paired branches of the vertebral arteries at the craniocervical junction and is fed by additional radicular vessels that arise at C6, at an upper thoracic level, and, most consistently, at T11–L2 (artery of Adamkiewicz). At each spinal cord segment, paired penetrating vessels branch from the anterior spinal artery to supply the anterior two-thirds of the cord; the posterior spinal arteries, which often become less distinct below the midthoracic level, supply the posterior columns.

Spinal cord ischemia can occur at any level; however, the presence of the artery of Adamkiewicz below, and the anterior spinal artery circulation above, creates a region of marginal blood flow in the upper thoracic segments. With hypotension or cross-clamping of the aorta, cord infarction typically occurs at the level of T3–T4, and also at boundary zones between the anterior and posterior spinal artery territories. The latter may result in a rapidly progressive syndrome over hours of weakness and spasticity with little sensory change.

Acute infarction in the territory of the *anterior spinal artery* produces paraplegia or quadriplegia, dissociated sensory loss affecting pain and temperature sense but sparing vibration and position sense, and loss of sphincter control (“anterior cord syndrome”). Onset may be sudden but more typically is progressive over minutes or a few hours, unlike stroke in the cerebral hemispheres. Sharp midline or radiating back pain localized to the area of ischemia is frequent. Areflexia due to spinal shock is often present initially; with time, hyperreflexia and spasticity appear. Less common is infarction in the territory of the *posterior spinal arteries*, resulting in loss of posterior column function either on one side or bilaterally.

Causes of spinal cord infarction include aortic atherosclerosis, dissecting aortic aneurysm, vertebral artery occlusion or dissection in the neck, aortic surgery, or profound hypotension from any cause. A *surfer's myelopathy* usually in the thoracic region, has been associated with prolonged back extension due to lifting the upper body off the board while waiting for waves; it typically manifests as back pain followed by an anterior cord syndrome with progressive paralysis and loss of sphincter control, and is likely vascular in origin. Cardiogenic emboli, vasculitis (Chap. 363), and collagen vascular disease (particularly SLE [Chap. 356], Sjögren's syndrome [Chap. 361], and the antiphospholipid antibody syndrome [Chap. 357]) are other etiologies. Occasional cases develop from *embolism of nucleus pulposus* material into spinal vessels, usually from local spine trauma. In a substantial number of cases, no cause can be found, and thromboembolism in arterial feeders is suspected. MRI may fail to demonstrate infarctions of the cord, especially in the first day, but often the imaging becomes abnormal at the affected level. MRI features suggestive of cord infarction include diffusion weighted restriction; longitudinally extensive anterior T2 signal brightness on sagittal images (“pencil-like sign”); focal enhancement in the anterior horns; and paired areas of focal T2 hyperintensity in the anterior medial cord on axial images (“owl's eyes”). When present, infarction of a vertebral body adjacent to the area of cord involvement is diagnostically helpful.

With cord infarction due to presumed thromboembolism, acute anticoagulation is not indicated, with the possible exception of the unusual transient ischemic attack or incomplete infarction with a stuttering or progressive course. The antiphospholipid antibody syndrome is treated with anticoagulation (Chap. 357). Increasing systemic blood pressure to a mean arterial pressure of >90 mmHg, or lumbar drainage of spinal fluid, was reportedly helpful in a few published cases of cord infarction, but neither of these approaches has been studied systematically. Prognosis following spinal cord infarction is influenced by the severity of the deficits at presentation; patients with severe motor weakness and those with persistent areflexia usually do poorly, but in one recent large series some improvement over time occurred in many patients, with more than half ultimately regaining some ambulation.

Inflammatory and Immune Myopathies (Myelitis) This broad category includes the demyelinating conditions MS, NMO, and postinfectious myelitis, as well as sarcoidosis, systemic autoimmune disease, and infections. In approximately one-quarter of cases of myelitis, no underlying cause can be identified. Some will later manifest

TABLE 442-3 Evaluation of Myelopathy

1. MRI of spinal cord with and without contrast (exclude compressive causes).
2. CSF studies: Cell count, protein, glucose, IgG index/synthesis rate, oligoclonal bands, VDRL; Gram's stain, acid-fast bacilli, and India ink stains; PCR for VZV, HSV-2, HSV-1, EBV, CMV, HHV-6, enteroviruses, HIV; antibody for HTLV-1, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*; viral, bacterial, mycobacterial, and fungal cultures.
3. Blood studies for infection: HIV; RPR; IgG and IgM enterovirus antibody; IgM mumps, measles, rubella, group B arbovirus, *Brucella melitensis*, *Chlamydia psittaci*, *Bartonella henselae*, schistosomal antibody; cultures for *B. melitensis*. Also consider nasal/pharyngeal/anal cultures for enteroviruses; stool O&P for *Schistosoma* ova.
4. Vascular causes: MRI, CT myelogram; spinal angiogram.
5. Multiple sclerosis: Brain MRI scan; evoked potentials.
6. Neuromyelitis optica and related disorders: Serum anti-aquaporin-4 antibody, anti-MOG antibody, anti-GFAP antibody.
7. Sarcoidosis: Serum angiotensin-converting enzyme; serum Ca; 24-h urine Ca; chest x-ray; chest CT; slit-lamp eye examination; total-body gallium scan; lymph node biopsy.
8. Systemic immune-mediated disorders: ESR; ANA; ENA; dsDNA; rheumatoid factor; anti-SSA; anti-SSB; complement levels; antiphospholipid and anticardiolipin antibodies; p-ANCA; antimicrosomal and antithyroglobulin antibodies; if Sjögren's syndrome suspected, Schirmer test, salivary gland scintigraphy, and salivary/lacrimal gland biopsy.
9. Paraneoplastic disorders: Antibody for amphiphysin, CRMP5, Hu, others.
10. Other: vitamin B₁₂, copper, zinc.

Abbreviations: ANA, antinuclear antibodies; CMV, cytomegalovirus; CRMP5, collapsin response mediator 5-IgG; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ENA, epithelial neutrophil-activating peptide; ESR, erythrocyte sedimentation rate; GFAP, glial fibrillary acidic protein; HHV, human herpes virus; HSV, herpes simplex virus; HTLV, human T-cell leukemia/lymphoma virus; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; O&P, ova and parasites; p-ANCA, perinuclear antineutrophilic cytoplasmic antibodies; PCR, polymerase chain reaction; RPR, rapid plasma reagent (test); VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus.

additional symptoms of an immune-mediated disease. *Transverse myelitis* refers to a pattern of extensive spinal cord injury, clinically manifest as bilateral sensory symptoms, unilateral or bilateral weakness, and bladder and/or bowel disturbance. In most of the developed world MS is the most common inflammatory cause of an acute myelitis but involvement is usually partial and not transverse. *Recurrent episodes of myelitis* are usually due to one of the immune-mediated diseases or to infection with herpes simplex virus (HSV) type 2 (below).

MULTIPLE SCLEROSIS MS may present with acute myelitis, particularly in individuals of Asian or African ancestry. In whites, MS attacks rarely cause a transverse myelopathy (i.e., attacks of bilateral sensory disturbances, unilateral or bilateral weakness, and bladder or bowel symptoms), but MS is among the most common causes of a partial cord syndrome. MRI findings in MS-associated myelitis typically consist of mild swelling of the cord and diffuse or multifocal "shoddy" areas of abnormal signal on T2-weighted sequences. Contrast enhancement, indicating disruption in the blood-brain barrier associated with inflammation, is present in many acute cases. In one study 68% of patients presenting with partial myelitis developed MS after a mean follow-up of 4 years; risk factors for conversion to MS included age <40 years; inflammatory CSF, and >3 periventricular lesions on brain MRI.

Treatment of acute episodes of MS-associated myelitis consists of intravenous methylprednisolone (500 mg qd for 3 days) followed by oral prednisone (1 mg/kg per day for several weeks, then gradual taper). A course of plasma exchange may be indicated for severe cases if glucocorticoids are ineffective. **MS is discussed in Chap. 444.**

NEUROMYELITIS OPTICA NMO is an immune-mediated demyelinating disorder consisting of a severe myelopathy that is typically longitudinally extensive, meaning that the lesion spans three or more vertebral segments. NMO is associated with optic neuritis that is often bilateral and may precede or follow myelitis by weeks or months, and also by brainstem and, in some cases, hypothalamic or focal cerebral white matter involvement. Recurrent myelitis without optic nerve or other involvement can also occur in NMO. CSF studies reveal a variable mononuclear pleocytosis of up to several hundred cells per microliter (higher than in typical MS) with occasional cases showing polymorphonuclear predominant pattern; oligoclonal bands are present in <20% of NMO cases. Diagnostic serum autoantibodies against the water channel protein aquaporin-4 (AQP-4) are present in 90% of patients with NMO; in some AQP-4 negative cases autoantibodies against the CNS myelin protein myelin oligodendrocyte glycoprotein (MOG) are found. NMO has also been associated with SLE (see below) as well as with other systemic autoimmune diseases; rare cases are paraneoplastic. Acute relapses of NMO are treated with glucocorticoids and, for severe or refractory cases, plasma exchange. Three monoclonal antibodies are now available for prophylactic treatment: eculizumab, a terminal complement inhibitor; inebilizumab, a B-cell depleter; and satralizumab, an IL-6 receptor blocker. Off-label use of azathioprine, mycophenolate, or rituximab are other options. Treatment for 5 years or longer is generally recommended. **NMO is discussed in Chap. 445.**

SARCOIDOSIS Sarcoid myopathy may present as a slowly progressive or relapsing disorder. Clinically, sensory involvement often predominates. MRI reveals edematous swelling of the spinal cord that may mimic tumor and subpial gadolinium enhancement of active lesions typically along the dorsal surface of the cord. In some cases nodular enhancing lesions can be seen; lesions may be single or multiple, and on axial images enhancement of the central cord is often present. The typical CSF profile consists of a mild lymphocyte-predominant pleocytosis and elevated protein level; in a minority of cases, reduced glucose and oligoclonal bands are found. The diagnosis is particularly difficult when systemic manifestations of sarcoid are minor or absent (nearly 50% of cases) or when other typical neurologic manifestations of the disease, such as cranial neuropathy, hypothalamic involvement, or meningeal enhancement visualized by MRI, are lacking. A slit-lamp examination of the eye to search for uveitis, chest x-ray and CT to assess pulmonary involvement and mediastinal lymphadenopathy, serum or CSF angiotensin-converting enzyme (ACE; lacks specificity

and values are elevated in only a minority of cases), serum calcium, and a gallium scan may assist in the diagnosis. Initial treatment is with high doses of glucocorticoids, which need to be administered long term and tapered slowly while monitoring resolution of clinical and MRI signs of active disease; relapses are managed with high-dose glucocorticoids plus a steroid-sparing immunosuppressant drug (typically mycophenolate mofetil, azathioprine, or methotrexate), or with the tumor necrosis factor α -inhibitor infliximab. **Sarcoidosis is discussed in Chap. 367.**

SYSTEMIC IMMUNE MEDIATED DISORDERS Myelitis occurs in a small number of patients with SLE, many cases of which are associated with antibodies to AQP-4 and satisfy diagnostic criteria for NMO (discussed above). These patients are at high risk of developing future episodes of myelitis and/or optic neuritis. In others the etiology of SLE-associated myelitis is uncertain; antiphospholipid antibodies have been suggested to play a role; however, the presence of these antibodies appears to be no more frequent in SLE patients with and without myelitis. The CSF in NMO-associated myelitis typically shows a pleocytosis often with polymorphonuclear leukocytes, and no oligoclonal bands; in cases not due to NMO a mild lymphocytic pleocytosis and oligoclonal bands are variable findings. Although there are no systematic trials of therapy for SLE myelitis, based on limited data high-dose glucocorticoids followed by cyclophosphamide have been recommended. Severe episodes that do not initially respond to glucocorticoids are often treated with a course of plasma exchange. Sjögren's syndrome (Chap. 361) can also be associated with NMO and also with cases of chronic progressive myelopathy. Other immune-mediated myelitides include Behcet's disease (Chap. 364), antiphospholipid antibody syndrome (Chap. 357), mixed connective tissue disease (Chap. 360), and vasculitis related to polyarteritis nodosa, perinuclear antineutrophilic cytoplasmic (p-ANCA) antibodies, or primary central nervous system vasculitis (Chap. 363). Occasional cases of myelitis, often accompanied by other manifestations that can include encephalitis or optic neuritis, have been recently associated with autoantibodies against glial fibrillary acidic protein (GFAP) (Chap. 444). Other rare etiologies are chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), and Erdheim-Chester disease producing inflammatory masslike lesions that can be intramedullary or extraaxial and compressive.

POSTINFECTIONOUS MYELITIS Many cases of myelitis, termed *postinfectious* or *postvaccinal*, follow an infection or vaccination. Numerous organisms have been implicated, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), mycoplasma, influenza, measles, varicella, mumps, and yellow fever. As in the related disorder acute disseminated encephalomyelitis (Chap. 444), postinfectious myelitis often begins as the patient appears to be recovering from an acute febrile infection, or in the subsequent days or weeks, but an infectious agent cannot be isolated from the nervous system or CSF. Serum anti-MOG antibodies are present acutely in about half of cases. The presumption is that the myelitis represents an autoimmune disorder triggered by infection and is not due to direct infection of the spinal cord. No randomized controlled trials of therapy exist; treatment is usually with glucocorticoids or, in fulminant cases, plasma exchange.

ACUTE INFECTIOUS MYELITIS Many viruses have been associated with an acute myelitis that is infectious in nature rather than postinfectious. Nonetheless, the two processes are often difficult to distinguish. Herpes zoster is the best characterized viral myelitis, but HSV types 1 and 2, EBV, CMV, and rabies virus are other well-described causes and Zika virus has also been recognized as a cause of infectious myelitis. HSV-2 (and less commonly HSV-1) produces a distinctive syndrome of recurrent sacral cauda equina neuritis in association with outbreaks of genital herpes (Elsberg's syndrome). Poliomyelitis is the prototypic viral myelitis, but it is more or less restricted to the anterior gray matter of the cord containing the spinal motoneurons. A polio-like syndrome can also be caused by a large number of enteroviruses (including enterovirus A-71 and coxsackie), and with Japanese encephalitis and other flaviviruses such as West Nile virus. Beginning in 2012, cases of acute flaccid paralysis in children and adolescents have appeared

associated with enterovirus A-71 and D-68 infection. Chronic viral myelitic infections, such as those due to HIV or human T-cell lymphotropic virus type 1 (HTLV-1), are discussed below.

Bacterial and mycobacterial myelitis (most are essentially abscesses) are less common than viral causes and much less frequent than cerebral bacterial abscess. Almost any pathogenic species may be responsible, including *Borrelia burgdorferi* (Lyme disease), *Listeria monocytogenes*, *Mycobacterium tuberculosis*, and *Treponema pallidum* (syphilis). *Mycoplasma pneumoniae* may be a cause of myelitis, but its status is uncertain because many cases are more properly classified as postinfectious.

Schistosomiasis ([Chap. 234](#)) is an important cause of parasitic myelitis in endemic areas. The process is intensely inflammatory and granulomatous, caused by a local response to tissue-digesting enzymes from the ova of the parasite, typically *Schistosoma haematobium* or *Schistosoma mansoni*. Toxoplasmosis ([Chap. 228](#)) can occasionally cause a focal myopathy, and this diagnosis should especially be considered in patients with AIDS ([Chap. 202](#)). Cysticercosis ([Chap. 235](#)) is another consideration, although myelitis from this helminth is far less common than parenchymal brain or meningeal involvement.

In cases of suspected viral myelitis, it may be appropriate to begin specific therapy pending laboratory confirmation. Herpes zoster, HSV, and EBV myelitis are treated with intravenous acyclovir (10 mg/kg q8h) or oral valacyclovir (2 g tid) for 10–14 days; CMV is treated with ganciclovir (5 mg/kg IV bid) plus foscarnet (60 mg/kg IV tid) or cidofovir (5 mg/kg per week for 2 weeks).

High-Voltage Electrical Injury Spinal cord injuries are prominent following electrocution from lightning strikes or other accidental electrical exposures. The syndrome consists of transient weakness acutely (often with an altered sensorium and focal cerebral disturbances), sometimes followed several days or even weeks later by a myopathy that can be severe and permanent. This is a rare injury type, and limited data incriminate a vascular pathology involving the anterior spinal artery and its branches in some cases. Therapy is supportive.

CHRONIC MYELOPATHIES

■ SPONDYLOTIC MYELOPATHY

Spondylotic myelopathy is the most common cause of myopathy and of gait difficulty in the elderly, accounting for more than half of non-traumatic spinal cord injuries in some series. Neck and shoulder pain with stiffness are early symptoms; impingement of bone and soft tissue overgrowth on nerve roots results in radicular arm pain, most often in a C5 or C6 distribution. Compression of the cervical cord, which occurs in fewer than one-third of cases, produces a slowly progressive spastic paraparesis, at times asymmetric and often accompanied by paresthesias in the feet and hands. Vibratory sense is diminished in the legs, there is a Romberg sign, and occasionally there is a sensory level for vibration or pinprick on the upper thorax. In some cases, coughing or straining produces leg weakness or radiating arm or shoulder pain. Dermatomal sensory loss in the arms, atrophy of intrinsic hand muscles, increased deep-tendon reflexes in the legs, and extensor plantar responses are common. Urinary urgency or incontinence occurs in advanced cases, but there are many alternative causes of these problems in older individuals. A tendon reflex in the arms is often diminished at some level; most often at the biceps (C5-C6). In individual cases, radicular, myelopathic, or combined signs may predominate. The diagnosis should be considered in appropriate cases of progressive cervical myelopathy, paresthesias of the feet and hands, or wasting of the hands.

Diagnosis is usually made by MRI and may be suspected from CT images; plain x-rays are less helpful. Extrinsic cord compression and deformation are appreciated on axial MRI views, and T2-weighted sequences may reveal areas of high signal intensity within the cord adjacent to the site of compression. A cervical collar may be helpful in milder cases, but the likelihood of progression of medically treated myelopathy is high, estimated at 8% over 1 year. Definitive therapy consists of surgical decompression, either posterior laminectomy or an anterior approach with resection of the protruded disk and bony material. [Cervical spondylosis and related degenerative diseases of the spine](#) are discussed in [Chap. 17](#).

■ VASCULAR MALFORMATIONS OF THE CORD AND DURA

Vascular malformations, comprising ~4% of all mass lesions of the cord and overlying dura, are treatable causes of progressive myopathy. Most common are fistulas located within the dura or posteriorly along the surface of the cord. Most dural arteriovenous (AV) fistulas are located at or below the midthoracic level, usually consisting of a direct connection between a radicular feeding artery in the nerve root sleeve with dural veins. The typical presentation is a middle-aged man with a progressive myopathy that worsens slowly or intermittently and may have periods of remission, sometimes mimicking MS. Acute deterioration due to hemorrhage into the spinal cord (hematomyelia) or subarachnoid space may also occur but is rare. In many cases, progression results from local ischemia and edema due to venous congestion. Most patients have incomplete sensory, motor, and bladder disturbances. The motor disorder may predominate and produce a mixture of upper and restricted lower motor neuron signs, simulating amyotrophic lateral sclerosis (ALS). Pain over the dorsal spine, dysesthesias, or radicular pain may be present. Other symptoms suggestive of AV malformation (AVM) or dural fistula include intermittent claudication; symptoms that change with posture, exertion, Valsalva maneuver, or menses; and fever.

Less commonly, AVM disorders are intramedullary rather than dural. One unusual disorder is a progressive thoracic myopathy with paraparesis developing over weeks or months, characterized pathologically by abnormally thick, hyalinized vessels within the cord (subacute necrotic myopathy or Foix-Alajouanine syndrome).

Spinal bruits are infrequent but may be sought at rest and after exercise in suspected cases. A vascular nevus on the overlying skin may indicate an underlying vascular malformation as occurs with Klippel-Trenaunay-Weber syndrome. MR angiography and CT angiography can detect the draining vessels of many AVMs ([Fig. 442-6](#)). Definitive diagnosis requires selective spinal angiography, which defines the feeding vessels and the extent of the malformation. Treatment is tailored to the anatomy and location of the lesion, and generally consists of microsurgical resection, endovascular embolization of the major feeding vessels, or a combination of the two approaches.



FIGURE 442-6 Arteriovenous malformation. Sagittal magnetic resonance scans of the thoracic spinal cord: T2 fast spin-echo technique (*left*) and T1 postcontrast image (*right*). On the T2-weighted image (*left*), abnormally high signal intensity is noted in the central aspect of the spinal cord (*arrowheads*). Numerous punctate flow voids indent the dorsal and ventral spinal cord (*arrow*). These represent the abnormally dilated venous plexus supplied by a dural arteriovenous fistula. After contrast administration (*right*), multiple, serpentine, enhancing veins (*arrows*) on the ventral and dorsal aspect of the thoracic spinal cord are visualized, diagnostic of arteriovenous malformation. This patient was a 54-year-old man with a 4-year history of progressive paraparesis.

■ RETROVIRUS ASSOCIATED MYELOPATHIES

The myelopathy associated with HTLV-1, formerly called tropical spastic paraparesis, is a slowly progressive spastic syndrome with variable sensory and bladder disturbance. Approximately half of patients have mild back or leg pain. The neurologic signs may be asymmetric, often lacking a well-defined sensory level; the only sign in the arms may be hyperreflexia after several years of illness. The onset is usually insidious, and the tempo of progression of the illness occurs at a variable rate; in one study, median time for progression to cane-, walker-, or wheelchair-dependent state was 6, 13, and 21 years, respectively. Progression appears to be more rapid in older patients and those with higher viral loads. Diagnosis is made by demonstration of HTLV-1-specific antibody in serum by enzyme-linked immunosorbent assay (ELISA), confirmed by radioimmunoprecipitation or Western blot analysis. Especially in endemic areas, a finding of HTLV-1 seropositivity in a patient with myelopathy does not necessarily prove that HTLV-1 is causative. The CSF/serum antibody index may provide support by establishing intrathecal synthesis of antibodies, including oligoclonal antibodies, favoring HTLV-1 myelopathy over asymptomatic carriage. Measuring proviral DNA by polymerase chain reaction (PCR) in serum and CSF cells can be useful as an ancillary part of diagnosis. The pathogenesis of the myelopathy is uncertain. It could result from an immune response directed against HTLV-1 antigens in the nervous system, or alternatively to secondary autoimmunity triggered by the viral infection. There is no proven effective treatment. Based on limited evidence, the use of chronic low-dose oral glucocorticoids can be tried; interferon is of uncertain value, and antiviral treatment is ineffective. Symptomatic therapy for spasticity and bladder symptoms may be helpful.

A progressive myelopathy can also result from HIV infection (Chap. 197). It is characterized by vacuolar degeneration of the posterior and lateral tracts, resembling subacute combined degeneration (see below).

SYRINGOMYELIA

Syringomyelia is a developmental cavity in the cervical cord that may enlarge and produce progressive myelopathy or may remain asymptomatic. Symptoms begin insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years. Many young patients acquire a cervical-thoracic scoliosis. More than half of all cases are associated with Chiari type 1 malformations in which the cerebellar tonsils protrude through the foramen magnum and into the cervical spinal canal. The pathophysiology of syrinx expansion is controversial, but some interference with the normal flow of CSF seems likely, perhaps by the Chiari malformation. Acquired cavitations of the cord in areas of necrosis are also termed *syrinx cavities*; these follow trauma, myelitis, necrotic spinal cord tumors, and chronic arachnoiditis due to tuberculosis and other etiologies.

The presentation is a central cord syndrome consisting of a regional dissociated sensory loss (loss of pain and temperature sensation with sparing of touch and vibration) and areflexic weakness in the upper limbs. The sensory deficit has a distribution that is “suspended” over the nape of the neck, shoulders, and upper arms (cape distribution) or in the hands. Most cases begin asymmetrically with unilateral sensory loss in the hands that leads to injuries and burns that are not appreciated by the patient. Muscle wasting in the lower neck, shoulders, arms, and hands with asymmetric or absent reflexes in the arms reflects expansion of the cavity in the gray matter of the cord. As the cavity enlarges and compresses the long tracts, spasticity and weakness of the legs, bladder and bowel dysfunction, and Horner’s syndrome appear. Some patients develop facial numbness and sensory loss from damage to the descending tract of the trigeminal nerve (C2 level or above). In cases with Chiari malformations, cough-induced headache and neck, arm, or facial pain may be reported. Extension of the syrinx into the medulla, syringobulbia, causes palatal or vocal cord paralysis, dysarthria, horizontal or vertical nystagmus, episodic dizziness or vertigo, and tongue weakness with atrophy.

MRI accurately identifies developmental and acquired syrinx cavities and their associated spinal cord enlargement (Fig. 442-7). Images



FIGURE 442-7 Magnetic resonance imaging of syringomyelia associated with a Chiari malformation. Sagittal T1-weighted image through the cervical and upper thoracic spine demonstrates descent of the cerebellar tonsils below the level of the foramen magnum (black arrows). Within the substance of the cervical and thoracic spinal cord, a cerebrospinal fluid collection dilates the central canal (white arrows).

of the brain and the entire spinal cord should be obtained to delineate the full longitudinal extent of the syrinx, assess posterior fossa structures for the Chiari malformation, and determine whether hydrocephalus is present.

TREATMENT

Syringomyelia

Treatment of syringomyelia is generally unsatisfactory. The Chiari tonsillar herniation may be decompressed, generally by suboccipital craniectomy, upper cervical laminectomy, and placement of a dural graft. Fourth ventricular outflow is reestablished by this procedure. If the syrinx cavity is large, some surgeons recommend direct decompression or drainage, but the added benefit of this procedure is uncertain, and complications are common. With Chiari malformations, shunting of hydrocephalus generally precedes any attempt to correct the syrinx. Surgery may stabilize the neurologic deficit, and some patients improve. Patients with few symptoms and signs from the syrinx do not require surgery and are followed by serial clinical and imaging examinations.

Syrinx cavities secondary to trauma or infection, if symptomatic, are treated with a decompression and drainage procedure in which a small shunt is inserted between the cavity and subarachnoid space; alternatively, the cavity can be fenestrated. Cases due to intramedullary spinal cord tumor are generally managed by resection of the tumor.

■ CHRONIC MYELOPATHY OF MULTIPLE SCLEROSIS

A chronic progressive myelopathy is the most frequent cause of disability in both primary progressive and secondary progressive forms of MS. Involvement is typically bilateral but asymmetric and produces motor, sensory, and bladder/bowel disturbances. Fixed motor disability appears to result from extensive loss of axons in the corticospinal tracts. Diagnosis is facilitated by identification of earlier attacks such as optic neuritis. MRI, CSF, and evoked-response testing are confirmatory. Treatment with ocrelizumab, an anti-CD20 B-cell monoclonal antibody, is effective in patients with primary progressive MS, and disease-modifying therapy is also indicated in patients with secondary

SUBACUTE COMBINED DEGENERATION VITAMIN B₁₂ DEFICIENCY

This treatable myopathy presents with subacute paresthesias in the hands and feet, loss of vibration and position sensation, and a progressive spastic and ataxic weakness. Loss of reflexes due to an associated peripheral neuropathy in a patient who also has Babinski signs is a helpful diagnostic clue. Optic atrophy and irritability or other cognitive changes may be prominent in advanced cases and are occasionally the presenting symptoms. The myopathy of subacute combined degeneration tends to be diffuse rather than focal; signs are generally symmetric and reflect predominant involvement of the posterior and lateral tracts, including Romberg sign. Causes include dietary deficiency, especially in vegans, and gastric malabsorption syndromes including pernicious anemia (Chap. 99). The diagnosis is confirmed by the finding of macrocytic red blood cells, a low serum B₁₂ concentration, and elevated serum levels of homocysteine and methylmalonic acid. Treatment is by replacement therapy, beginning with 1000 µg of intramuscular vitamin B₁₂ daily for 5 days and then continued as a once monthly maintenance dose; oral maintenance is also reasonable, except in cases of pernicious anemia.

Two closely related conditions deserve mention here. The first is *folate deficiency*–associated myopathy, now only rarely seen since widespread programs of dietary fortification with folate have been implemented. A second is due to inhalation with *nitrous oxide* (laughing gas), an irreversible inhibitor of vitamin B₁₂, which also produces a myopathy identical to subacute combined degeneration. Exposure to nitrous oxide may occur during dental or surgical procedures or from recreational inhalation (“doing whippets”).

HYPOCUPRIC MYELOPATHY

This myopathy is similar to subacute combined degeneration (described above), except serum levels of B₁₂ are normal. Low levels of serum copper are found, and often there is also a low level of serum ceruloplasmin. Some cases follow gastrointestinal procedures, particularly bariatric surgery, that result in impaired copper absorption; others have been associated with excess zinc from health food supplements or in the past zinc-containing denture creams, all of which impair copper absorption via induction of metallothionein, a copper-binding protein. Many cases are idiopathic. There is often a coexisting anemia. Improvement or at least stabilization may be expected with reconstitution of copper stores by oral supplementation.

TABES DORSALIS

The classic syphilitic syndromes of tabes dorsalis and meningovascular inflammation of the spinal cord are now less frequent than in the past but must be considered in the differential diagnosis of spinal cord disorders. The characteristic symptoms of tabes are fleeting and repetitive lancinating pains, primarily in the legs or less often in the back, thorax, abdomen, arms, and face. Ataxia of the legs and gait due to loss of position sense occurs in half of patients. Paresthesias, bladder disturbances, and acute abdominal pain with vomiting (visceral crisis) occur in 15–30% of patients. The cardinal signs of tabes are loss of reflexes in the legs; impaired position and vibratory sense; Romberg sign; and, in almost all cases, bilateral Argyll Robertson pupils, which fail to constrict to light but accommodate. Diabetic polyradiculopathy may simulate this condition. Treatment of tabes dorsalis and other forms of neurosyphilis consists of penicillin G administered intravenously, or intramuscularly in combination with oral probenecid (Chap. 182).

HEREDITARY SPASTIC PARAPLEGIA

Many cases of slowly progressive myopathy are genetic in origin (Chap. 437). More than 80 different causative loci have been identified, including autosomal dominant, autosomal recessive, and X-linked forms. Especially for the recessive and X-linked forms, a family history of myopathy may be lacking. Most patients present with almost imperceptibly progressive spasticity and weakness in the legs, usually but not always symmetrical. Sensory symptoms and signs are absent

or mild, but sphincter disturbances may be present. In some families, additional neurologic signs are prominent, including nystagmus, ataxia, or optic atrophy. The onset may be as early as the first year of life or as late as middle adulthood. Only symptomatic therapies are available.

PRIMARY LATERAL SCLEROSIS

This is a mid- to late-life onset degenerative disorder characterized by progressive spasticity with weakness, eventually accompanied by dysarthria and dysphonia; bladder symptoms occur in approximately half of patients. Sensory function is spared. The disorder resembles ALS and is considered a variant of the motor neuron degenerations, but without the characteristic lower motor neuron disturbance and with typically a slower progression. Some cases may represent late-onset cases of familial spastic paraparesis, particularly autosomal recessive or X-linked varieties in which a family history may be absent. (See also Chap. 437.)

ADRENOMYELOEUROPATHY

This X-linked disorder is a variant of adrenoleukodystrophy (ALD). Most affected males have a history of adrenal insufficiency and then develop a progressive spastic (or ataxic) paraparesis beginning in early or sometimes middle adulthood; some patients also have a mild peripheral neuropathy. Female heterozygotes may develop a slower, insidiously progressive spastic myopathy beginning later in adulthood and without adrenal insufficiency. Diagnosis is usually made by demonstration of elevated levels of very-long-chain fatty acids in plasma and in cultured fibroblasts. The responsible gene encodes the adrenoleukodystrophy protein (ALDP), a peroxisomal membrane transporter involved in carrying long-chain fatty acids to peroxisomes for degradation. Corticosteroid replacement is indicated if hypoadrenalinism is present. Allogeneic bone marrow transplantation has been successful in slowing progression of cognitive decline in some patients with ALD treated early in their disease but appears to be ineffective for the myopathy of ALD. Nutritional supplements (Lorenzo’s oil) have also been attempted for this condition without evidence of efficacy.

CANCER RELATED SYNDROMES

Cancer-related causes of chronic myopathy, besides the common neoplastic compressive myopathy discussed earlier, include radiation injury (Chap. 90), and a myopathy resembling subacute combined degeneration that can follow intrathecal administration of methotrexate (a folate antagonist). Rare paraneoplastic myopathies are most often associated with lung cancer and anti-amphiphysin (also breast), anti-collapsin response mediator 5 (CRMP5) (also lymphoma), or anti-Hu antibodies (Chap. 94). Another uncommon lymphoma-associated paraneoplastic syndrome is a progressive flaccid paresis with destruction of anterior horn cells. NM_O with aquaporin-4 antibodies (Chap. 445) can also rarely be paraneoplastic in origin. Metastases to the cord are probably more common than any of these disorders in patients with cancer.

OTHER CHRONIC MYELOPATHIES

Tethered cord syndrome is a developmental disorder of the lower spinal cord and nerve roots that rarely presents in adulthood as low back pain accompanied by a progressive lower spinal cord and/or nerve root syndrome. Some patients have a small leg or foot deformity indicating a long-standing process, and in others, a dimple, patch of hair, or sinus tract on the skin overlying the lower back is the clue to a congenital lesion. Diagnosis is made by MRI, which demonstrates a low-lying conus medullaris and thickened filum terminale. The MRI may also reveal diastematomyelia (division of the lower spinal cord into two halves), lipomas, cysts, or other congenital abnormalities of the lower spine coexisting with the tethered cord. Treatment is with surgical release.

There are a number of rare toxic causes of spastic myopathy, including lathyrism due to ingestion of chickpeas containing the excitotoxin β -N-oxalylamino-L-alanine (BOAA), seen primarily in the developing world or during famines, and Konzo due to ingestion of the cyanogen-containing cassava plant found in sub-Saharan Africa.

TABLE 442-4 Expected Neurologic Function Following Complete Cord Lesions

LEVEL	SELF-CARE	TRANSFERS	MAXIMUM MOBILITY
High quadriplegia (C1–C4)	Dependent on others; requires respiratory support	Dependent on others	Motorized wheelchair
Low quadriplegia (C5–C8)	Partially independent with adaptive equipment	May be dependent or independent	May use manual wheelchair, drive an automobile with adaptive equipment
Paraplegia (below T1)	Independent	Independent	Ambulates short distances with aids

Source: Adapted from JF Ditunno, CS Formal: Chronic spinal cord injury. *N Engl J Med* 330:550, 1994.

Often, a cause of intrinsic myelopathy can be identified only through periodic reassessment.

REHABILITATION OF SPINAL CORD DISORDERS

The prospects for recovery from an acute destructive spinal cord lesion fade after ~6 months. There are currently no effective means to promote repair of injured spinal cord tissue; promising but entirely experimental approaches include the use of factors that influence reinnervation by axons of the corticospinal tract, nerve and neural sheath graft bridges, forms of electrical stimulation at the site of injury, and the local introduction of stem cells. The disability associated with irreversible spinal cord damage is determined primarily by the level of the lesion and by whether the disturbance in function is complete or incomplete (Table 442-4). Even a complete high cervical cord lesion may be compatible with a productive life. The primary goals are development of a rehabilitation plan framed by realistic expectations and attention to the neurologic, medical, and psychological complications that commonly arise.

Many of the usual symptoms associated with medical illnesses, especially somatic and visceral pain, may be lacking because of the destruction of afferent pain pathways. Unexplained fever, worsening of spasticity, or deterioration in neurologic function should prompt a search for infection, thrombophlebitis, or an intraabdominal pathology. The loss of normal thermoregulation and inability to maintain normal body temperature can produce recurrent fever (*quadriplegic fever*), although most episodes of fever are due to infection of the urinary tract, lung, skin, or bone.

Bladder dysfunction generally results from loss of supraspinal innervation of the detrusor muscle of the bladder wall and the sphincter musculature. Detrusor spasticity is treated with anticholinergic drugs (oxybutynin, 2.5–5 mg qid) or tricyclic antidepressants with anticholinergic properties (imipramine, 25–200 mg/d). Failure of the sphincter muscle to relax during bladder emptying (urinary dyssynergia) may be managed with the α -adrenergic blocking agent terazosin hydrochloride (1–2 mg tid or qid), with intermittent catheterization, or, if that is not feasible, by use of a condom catheter in men or a permanent indwelling catheter. Surgical options include the creation of an artificial bladder by isolating a segment of intestine that can be catheterized intermittently (enterocystoplasty) or can drain continuously to an external appliance (urinary conduit). Bladder areflexia due to acute spinal shock or conus lesions is best treated by catheterization. Bowel regimens and disimpaction are necessary in most patients to ensure at least biweekly evacuation and avoid colonic distention or obstruction.

Patients with acute cord injury are at risk for venous thrombosis and pulmonary embolism. Use of calf-compression devices and anticoagulation with low-molecular-weight heparin are recommended. In cases of persistent paralysis, anticoagulation should probably be continued for 3 months.

Prophylaxis against decubitus ulcers should involve frequent changes in position in a chair or bed, the use of special mattresses, and cushioning of areas where pressure sores often develop, such as the sacral prominence and heels. Early treatment of ulcers with careful cleansing, surgical or enzyme debridement of necrotic tissue, and appropriate dressing and drainage may prevent infection of adjacent soft tissue or bone.

Spasticity is aided by stretching exercises to maintain mobility of joints. Drug treatment is effective but may result in reduced function, as some patients depend on spasticity as an aid to stand, transfer, or walk. Baclofen (up to 240 mg/d in divided doses) is effective; it acts

by facilitating γ -aminobutyric acid-mediated inhibition of motor reflex arcs. Diazepam acts by a similar mechanism and is useful for leg spasms that interrupt sleep (2–4 mg at bedtime). Tizanidine (2–8 mg tid), an α_2 adrenergic agonist that increases presynaptic inhibition of motor neurons, is another option. For nonambulatory patients, the direct muscle inhibitor dantrolene (25–100 mg qid) may be used, but it is potentially hepatotoxic. In refractory cases, intrathecal baclofen administered via an implanted pump, botulinum toxin injections, or dorsal rhizotomy may be required to control spasticity.

Despite the loss of sensory function, many patients with spinal cord injury experience chronic pain sufficient to diminish their quality of life. Randomized controlled studies indicate that gabapentin or pregabalin is useful in this setting. Epidural electrical stimulation and intrathecal infusion of pain medications have been tried with some success.

Management of chronic pain is discussed in Chap. 13.

A paroxysmal autonomic hyperreflexia may occur following lesions above the major splanchnic sympathetic outflow at T6. Headache, flushing, and diaphoresis above the level of the lesion, as well as hypertension with bradycardia or tachycardia, are the major symptoms. The trigger is typically a noxious stimulus—for example, bladder or bowel distention, a urinary tract infection, or a decubitus ulcer—below the level of the cord lesion. Treatment consists of removal of offending stimuli; ganglionic blocking agents (mecamylamine, 2.5–5 mg) or other short-acting antihypertensive drugs are useful in some patients.

Attention to these details allows longevity and a productive life for patients with complete transverse myelopathies.

FURTHER READING

- B JH et al: Degenerative cervical myelopathy—update and future directions. *Nat Rev Neurol* 16:108, 2020.
- B P et al: Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy. *Neurology* 90:12, 2018.
- K JS et al: Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy. *Brain* 140:953, 2017.
- L AD, S JM: A critical reappraisal of corticospinal tract somatotopy and its role in traumatic cervical spinal cord syndromes. *J Neurosurg Spine* 12:1, 2021.
- O A et al: Epidemiology, clinical presentation, diagnostic evaluation, and prognosis of spinal arteriovenous malformations. *Handb Clin Neurol* 143:145, 2017.
- P NE: Metabolic and toxic myopathies. *Continuum (Minneapolis Minn)* 27:143, 2021.
- P RA et al: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: A randomised trial. *Lancet* 366:643, 2005.
- R CE et al: Recovery after spinal cord infarcts: Long-term outcome in 115 patients. *Neurology* 78:114, 2012.
- R AE, R AH: Acute spinal cord compression. *N Engl J Med* 376:1358, 2017.
- R A et al: Predictive factors for multiple sclerosis in patients with clinically isolated spinal cord syndrome. *Mult Scler* 17:312, 2011.
- Y ML et al: Diagnosis and treatment of epidural metastases. *Cancer* 123:1106, 2017.
- Z NL, F EP: Autoimmune and paraneoplastic myopathies. *Semin Neurol* 38:278, 2018.
- Z NL et al: Characteristics of spontaneous spinal cord infarction and proposed diagnostic criteria. *JAMA Neurol* 76:56, 2019.



Geoffrey T. Manley, Benjamin L. Brett,
Michael McCrea

INTRODUCTION

Traumatic brain injury (TBI) represents a significant global public health problem. In the United States, estimates of the frequency of TBI range between 2.5 and 4 million cases per year, depending on the study and methods used to define and include cases. Age-specific rates show a bimodal distribution, with highest risk in younger individuals and older adults. The most common mechanism of injury in the young is motor vehicle accidents and is more common in men, whereas in older adults, falls are the major cause of injury and are more likely to occur in women.

TBI imposes substantial demands on health care systems. Worldwide, at least 10 million TBIs are serious enough to result in death or hospitalization, producing a global economic burden of \$400 billion annually. In the United States, the estimated annual cost is >\$76 billion. Due to advances in medical care and other factors, more people are surviving TBI than ever before. Brain injury accounts for more lost productivity at work among Americans than any other form of injury. An estimated 5.3 million Americans are living with significant disabilities resulting from TBI that complicate their return to a full and productive life. Increased media attention to military and sports-related TBI has highlighted the growing concern that injuries that were previously dismissed can have lifelong consequences for some individuals.

Head injuries are so common that almost all physicians will be called upon to provide some aspect of immediate care or to see patients who are suffering from various sequelae. Patients and their families initially need education regarding the natural history of TBI along with treatment of acute symptoms such as headache. Continued follow-up is important to ensure that the sequelae experienced by some patients—such as postconcussive disorder (PCD), depression, or sleep disorder—are identified and treated appropriately. Effective management of TBI and its consequences often requires a coordinated multidisciplinary care team.

DEFINITION AND CLASSIFICATION

TBI is commonly defined as *an alteration in brain function, or other evidence of brain pathology, caused by an external force, and characterized by the following: (1) any period of loss or decreased level of consciousness (LOC), (2) any loss of memory for events immediately before (retrograde) or after (posttraumatic) the injury, (3) any neurologic deficits, and/or (4) any alteration in mental state at the time of injury.*

Evidence of TBI can include visual, neuroradiologic, or laboratory confirmation of damage to the brain, but TBI is more often diagnosed on the basis of acute clinical criteria. In addition to standard CT imaging, structural MRI and functional imaging (resting-state functional MRI) techniques show increasing sensitivity, and it is likely that sensitive blood-based biomarkers will play an increasingly important role in the diagnosis and treatment of these patients (described below).

MECHANISMS OF TBI Common mechanisms of TBI include the head being struck by an object, the head striking an object, the brain undergoing an acceleration/deceleration movement, a foreign body penetrating the brain, or forces generated from events such as a blast or explosion. Motor vehicle crashes have historically been cited as the most common cause of TBI. All forms of transportation, however, are common causes of TBI, including motorcycle crashes, bicycle accidents, skateboarding, and pedestrian injuries. The other leading causes of TBI are falls, assaults, and sports, with varied frequency across the lifespan. Certainly, there has been an increased focus on the high frequency of mild TBI (mTBI), often referred to as concussion, encountered by athletes participating in contact and collision sports

at all competitive levels, as well as the potential short-term effects and long-term risks associated with sport-related concussion.

CLASSIFICATION OF TBI SEVERITY Numerous systems have been developed over the years to define and classify TBI severity along a continuum from mild to moderate to severe. These systems are usually most applicable to closed head injuries. In nearly all classification systems, TBI severity is graded based on acute injury characteristics rather than postacute injury status, as other factors can intervene to influence functional outcome. This can be problematic, as some patients with severe TBI will have a full recovery and some with mild TBI will be left with lifetime disability. Historically, the presence and duration of unconsciousness and amnesia have been the main points of distinction along the gradient of TBI severity. Current TBI classification systems remain symptom-based and do not incorporate patho-anatomical or molecular features, such as CT findings and blood-based biomarkers.

The Glasgow Coma Scale (GCS) is the most recognized and widely used method for grading TBI severity. The GCS provides a practical indicator of gross neurologic status by assessing motor function, verbal responses, and the patient's ability to open his or her eyes voluntarily or in response to external commands and stimuli. The grading is applied to the best response that can be elicited from the patient at the time of assessment, preferably before any paralyzing or sedating medication is administered or the patient is intubated, as these interventions confound interpretation of the score. The GCS assessment produces scores ranging from 3 to 15 (Table 443-1).

Upon the 40th anniversary of the GCS in 2014, the wording for responses was revised, and recommendations were made to improve its utility. Importantly, individual patients are best described by the three components of the coma scale (eye, verbal, motor, e.g., E3V4M6); the derived total coma score (e.g., 13) is less informative and should only be used to characterize groups of patients.

Several injury-classification systems have been developed to go beyond GCS score or acute injury characteristics and incorporate chief signs and symptoms in defining mTBI. The use of multiple severity indicators is intended to improve sensitivity in the detection of mTBI (GCS 13–15), while also taking into consideration traditional acute injury characteristics that have been presumed to predict outcome following mild and moderate brain injury. Loss of consciousness (LOC) and posttraumatic amnesia (PTA) remain the most common injury characteristics referenced in these classification systems. In the case of moderate (GCS 9–12) and severe (GCS 3–8) TBI, GCS score and the duration of LOC and PTA can be robust predictors of long-term outcome and morbidity. In cases of mTBI, however, while PTA and LOC are important indicators of acute injury, they are less predictive of eventual recovery time and outcome.

TABLE 443-1 Glasgow Coma Scale

EYE OPENING (E)	VERBAL RESPONSE (V)	MOTOR RESPONSE (M)
Spontaneous	4 Oriented	5
To speech	3 Confused	4
To pressure	2 Words	3
None	1 Sounds	2
		1 None
Best Motor Response (M)		
Obeying commands	6	
Localizing	5	
Normal flexion	4	
Abnormal flexion	3	
Extension	2	
None	1	

Note: Revised GCS (2014).

Source: Reproduced with permission from G Teasdale et al: The Glasgow Coma Scale at 40 years: Standing the test of time. Lancet Neurol 13:844, 2014.

TBI TYPES AND PATHOLOGIES

MILD TBI CONCUSSION It is estimated that 70–90% of all treated TBIs are mild in severity based on traditional case definitions and acute injury characteristics, with most reported estimates in the order of 85%. The published figures likely underrepresent the true incidence of mTBI because of variable case definitions and heterogeneous methods. Moreover, because a subgroup of individuals with milder brain injuries does not seek medical attention, epidemiologic studies that depend on hospital-based data also underestimate the true incidence.

The term *concussion*, while popular, is vague and is not based on widely accepted objective criteria, resulting in multiple definitions from various groups. There has been debate as to whether concussion is part of the TBI spectrum or a separate entity. In 2017, the Concussion in Sports Group issued a consensus statement that “concussion is a traumatic brain injury” (McCrory et al, 2017). By firmly placing concussion in the spectrum of TBI, the underlying pathophysiological processes common to all TBI presentations can now be considered together.

CT imaging is often normal in this population. However, emerging evidence indicates that 3-tesla (3T) MRI scans can identify pathology consistent with acute brain injury such as contusion and microhemorrhage. When patients with mTBI have CT and/or MRI abnormalities, they are often referred to as complicated mTBI and are more likely to have an unfavorable outcome.

SKULL FRACTURE, EXTRA AXIAL HEMATOMA, CONTUSION, AND AXONAL INJURY

Skull Fracture A blow to the skull that exceeds the elastic tolerance of the bone causes a fracture. Intracranial lesions accompany roughly two-thirds of skull fractures, and the presence of a fracture increases many-fold the chances of an underlying subdural or epidural hematoma. Consequently, fractures are primarily markers of the site and severity of injury. If the underlying arachnoid membrane has been torn, fractures also provide potential pathways for entry of bacteria to the cerebrospinal fluid (CSF) with a risk of meningitis and for leakage of CSF outward through the dura. If there is leakage of CSF, severe orthostatic headache results from lowered pressure in the spinal fluid compartment.

Most fractures are linear and extend from the point of impact toward the base of the skull. Basilar skull fractures are often extensions of adjacent linear fractures over the convexity of the skull but may occur independently owing to stresses on the floor of the middle cranial fossa or occiput. Basilar fractures are usually parallel to the petrous bone or along the sphenoid bone and directed toward the sella turcica and ethmoidal groove. Although most basilar fractures are uncomplicated, they can cause CSF leakage, pneumocephalus, and delayed cavernous-carotid fistulas. Hemotympanum (blood behind the tympanic membrane), ecchymosis over the mastoid process (Battle sign), and periorbital ecchymosis (“raccoon sign”) are clinical signs associated with basilar fractures.

EPIDURAL AND SUBDURAL HEMATOMAS

Hemorrhages between the dura and skull (epidural) or beneath the dura (subdural) have characteristic clinical and imaging features. They are sometimes associated with underlying brain contusions and other injuries, often making it difficult to determine the relative contribution of each component to the clinical state. The mass effect of raised intracranial pressure (ICP) caused by these hematomas can be life threatening, making it imperative to identify them rapidly by CT or MRI scan and to surgically remove them when appropriate.

Epidural Hematoma (Fig. 443-1) These highly dangerous lesions usually arise from an injury to a meningeal arterial vessel and evolve rapidly. They are often accompanied by a “lucid interval” of several minutes to hours prior to neurologic deterioration. They occur in up to 10% of cases of severe head injury, but are less often associated with underlying cortical damage compared to subdural hematomas. Rapid surgical evacuation and ligation or cauterization of the damaged vessel, usually the middle meningeal artery that has been lacerated by an overlying skull fracture, is indicated. If recognized and treated rapidly, patients often have a favorable outcome.

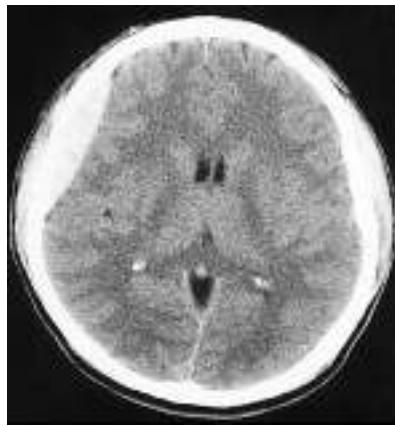


FIGURE 443-1 Acute epidural hematoma. The tightly attached dura is stripped from the inner table of the skull, producing a characteristic lenticular-shaped hemorrhage on noncontrast CT scan. Epidural hematomas are usually caused by tearing of the middle meningeal artery following fracture of the temporal bone.

Acute Subdural Hematoma (Fig. 443-2) Direct cranial trauma may be minor and is not always required for acute subdural hemorrhage to occur, especially in the elderly and those taking anticoagulant medications. Acceleration forces alone, as from whiplash, are sometimes sufficient to produce subdural hematoma. Up to one-third of patients have a lucid interval lasting minutes to hours before coma supervenes, but most are drowsy or comatose from the moment of injury. A unilateral headache and slightly enlarged pupil on the side of the hematoma are frequently, but not invariably, present. Small subdural hematomas may be asymptomatic and usually do not require surgical evacuation if they do not enlarge. Stupor or coma, hemiparesis, and unilateral pupillary enlargement are signs of larger hematomas. The bleeding that causes larger subdural hematomas is primarily venous in origin, although arterial bleeding sites are sometimes found at operation, and a few large hematomas have a purely arterial origin. In an acutely deteriorating patient, an emergency craniotomy is required. In contrast to epidural hematomas, there is significant morbidity and mortality associated with acute subdural hematomas that require surgery.

Chronic Subdural Hematoma A subacutely evolving syndrome due to subdural hematoma occurs days or weeks after injury with drowsiness, headache, confusion, or mild hemiparesis, usually in the elderly with age-related atrophy and often after only minor or unnoticed trauma. On imaging studies, chronic subdural hematomas appear as crescentic clots over the convexity of one or both hemispheres, most



FIGURE 443-2 Acute subdural hematoma. Noncontrast CT scan reveals a hyperdense clot that has an irregular border with the brain and causes more horizontal displacement (mass effect) than might be expected from its thickness. The disproportionate mass effect is the result of the large rostral-caudal extent of these hematomas. Compare to Fig. 443-1.



FIGURE 443-3 CT scan of chronic bilateral subdural hematomas of different ages. The collections began as acute hematomas and have become hypodense in comparison to the adjacent brain after a period during which they were isodense and difficult to appreciate. Some areas of resolving blood are contained on the more recently formed collection on the left (arrows).

commonly in the frontotemporal region ([Fig. 443-3](#)). A history of trauma may or may not be elicited in relation to chronic subdural hematoma; the injury may have been trivial and forgotten, particularly in the elderly and those with clotting disorders. Headache is common but not invariable. Additional features that may appear weeks later include slowed thinking, vague change in personality, seizure, or a mild hemiparesis. The headache typically fluctuates in severity, sometimes with changes in head position. Drowsiness, inattentiveness, and incoherence of thought are generally more prominent than focal signs such as hemiparesis. Rarely, chronic hematomas cause brief episodes of hemiparesis or aphasia that are indistinguishable from transient ischemic attacks.

CT without contrast initially shows a low-density mass over the convexity of the hemisphere. Between 2–6 weeks after the initial bleeding, the clot becomes isodense compared to adjacent brain and may be inapparent. Many subdural hematomas that are several weeks in age contain areas of blood and intermixed serous fluid. Infusion of contrast material demonstrates enhancement of the vascular fibrous capsule surrounding the collection. MRI reliably identifies both subacute and chronic hematomas.

Clinical observation coupled with serial imaging is a reasonable approach to patients with few symptoms and small chronic subdural collections that do not cause mass effect. Treatment with surgical evacuation through burr holes is usually successful, if a cranial drain is used postoperatively. The fibrous membranes that grow from the dura and encapsulate the collection may require removal with a craniotomy to prevent recurrent fluid accumulation.

■ TRAUMATIC SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) is common in TBI. Rupture of small cortical arteries or veins can cause bleeding into the subarachnoid space. Traumatic SAH is often seen in the sulci and is frequently the only radiographic finding on CT following mild TBI. SAH occurs diffusely after severe TBI and confers an increase in mortality. In mild TBI, SAH provides an objective imaging biomarker for TBI, and in some patients is associated with unfavorable outcomes.

Contusion ([Fig. 443-4](#)) A surface bruise of the brain, or contusion, consists of varying degrees of petechial hemorrhage, edema, and tissue destruction. Contusions and deeper hemorrhages result from mechanical forces that displace and compress the hemispheres forcefully and by deceleration of the brain against the inner skull, either under a point of impact (coup lesion) or, as the brain swings back, in the antipolar area (contrecoup lesion). Trauma sufficient to cause prolonged unconsciousness usually produces some degree of contusion. Blunt deceleration impact, as occurs against an automobile dashboard or from falling forward onto a hard surface, causes contusions on the orbital surfaces of the frontal lobes and the anterior and basal portions of the temporal



FIGURE 443-4 Traumatic cerebral contusion. Noncontrast CT scan demonstrating a hyperdense hemorrhagic region in the anterior temporal lobe.

lobes. With lateral forces, as from impact on an automobile door frame, contusions are situated on the lateral convexity of the hemisphere. The clinical signs of contusion are determined by the location and size of the lesion; often, there are no focal abnormalities with a routine neurologic exam, but these injured regions are later the sites of gliotic scars that may produce seizures. A hemiparesis or gaze preference is fairly typical of moderately sized contusions. Large bilateral contusions produce stupor with extensor posturing, while those limited to the frontal lobes cause a taciturn state. Contusions in the temporal lobe may cause delirium or an aggressive, combative syndrome. Torsional or shearing forces within the brain can cause hemorrhages of the basal ganglia and other deep regions. Large contusions and hemorrhages after minor trauma should raise concerns for coagulopathy due to an underlying disease or more commonly anticoagulant therapy.

Acute contusions are easily visible on CT and MRI scans, appearing as inhomogeneous hyperdensities on CT and as hyperintensities on T2 and fluid-attenuated inversion recovery (FLAIR) MRI sequences; there is usually surrounding localized brain edema and some subarachnoid bleeding. Blood in the CSF due to trauma may provoke a mild inflammatory reaction. Over a few days, contusions acquire a surrounding contrast enhancement and edema that may be mistaken for tumor or abscess.

Axonal Injury ([Fig. 443-5](#)) Traumatic axonal injury (TAI) is one of the most common injuries after TBI. There is disruption, or shearing, of axons at the time of impact and this is associated with



FIGURE 443-5 Multiple small areas of hemorrhage and tissue disruption in the white matter of the frontal lobes on noncontrast CT scan. These appear to reflect an extreme type of the diffuse axonal shearing lesions that occur with closed head injury.

microhemorrhages. It occurs following high-speed deceleration injuries, such as motor vehicle collisions (Johnson et al, 2013). The presence of ≥ 4 areas of TAI is called diffuse axonal injury (DAI), and when widespread, has been proposed to explain persistent coma and the vegetative state after TBI (Chap. 28). Only severe TAI lesions that contain substantial blood are visualized by CT, usually in the corpus callosum and centrum semiovale. More commonly, the CT will be negative for TAI, but subsequent MRI, particularly gradient-echo or susceptibility-weighted imaging, will show hemosiderin deposits reflective of microhemorrhages in addition to the axonal damage on diffusion sequences. Traditionally, TAI and DAI have been considered as sequelae much more likely to result from moderate and severe injuries. Accumulating evidence has demonstrated that diffuse white matter abnormalities purportedly reflective of axonal injury, such as changes in microstructure and neurite density, are quite common in mild TBI as well. The degree of these changes correlates with metrics of injury severity (e.g., symptom burden) and recovery duration.

■ CRANIAL NERVE INJURIES

The cranial nerves most often injured with TBI are the olfactory, optic, oculomotor, and trochlear nerves; the first and second branches of the trigeminal nerve; and the facial and auditory nerves. Anosmia and an apparent loss of taste (actually a loss of perception of aromatic flavors, with retained elementary taste perception) occur in $\sim 10\%$ of persons with serious head injuries, particularly from falls on the back of the head. This is the result of displacement of the brain and shearing of the fine olfactory nerve filaments that course through the cribriform bone. At least partial recovery of olfactory and gustatory function is expected, but if bilateral anosmia persists for several months, the prognosis is poor. Partial optic nerve injuries from closed trauma result in blurring of vision, central or paracentral scotomas, or sector defects. Direct orbital injury may cause short-lived blurred vision for close objects due to reversible iridoplegia. Diplopia limited to downward gaze and corrected when the head is tilted away from the side of the affected eye indicates trochlear (fourth nerve) nerve damage. It occurs frequently as an isolated problem after minor head injury or may develop for unknown reasons after a delay of several days. Facial nerve injury caused by a basilar fracture is present immediately in up to 3% of severe injuries; it may also be delayed for 5–7 days. Fractures through the petrous bone, particularly the less common transverse type, are liable to produce facial palsy. Delayed facial palsy occurring up to a week after injury, the mechanism of which is unknown, has a good prognosis. Injury to the eighth cranial nerve from a fracture of the petrous bone causes loss of hearing, vertigo, and nystagmus immediately after injury. Deafness from eighth nerve injury is rare and must be distinguished from blood in the middle ear or disruption of the middle ear ossicles. Dizziness, tinnitus, and high-tone hearing loss occur from cochlear concussion.

■ SEIZURES

Convulsions are surprisingly uncommon immediately after TBI, but a brief period of tonic extensor posturing or a few clonic movements of the limbs just after the moment of impact can occur. However, the cortical scars that evolve from contusions are highly epileptogenic and may later manifest as seizures, even after many months or years (Chap. 425). The severity of injury roughly determines the risk of future seizures. It has been estimated that 17% of individuals with brain contusion, subdural hematoma, or prolonged LOC will develop a seizure disorder and that this risk extends for an indefinite period of time, whereas the risk is $\leq 2\%$ after mild injury. The majority of convulsions in the latter group occur within 5 years of injury but may be delayed for decades. Penetrating injuries have a much higher rate of subsequent epilepsy.

CLINICAL SYNDROMES AND TREATMENT OF HEAD INJURY

■ CONCUSSION/ MILD TBI

The patient who has briefly lost consciousness or been stunned after a minor head injury usually becomes fully alert and attentive within minutes but may complain of headache, dizziness, faintness, nausea, a

single episode of emesis, difficulty with concentration, a brief amnesia period, or slight blurring of vision. This typical concussion syndrome has a good prognosis with little risk of subsequent deterioration. Children are particularly prone to drowsiness, vomiting, and irritability, symptoms that are sometimes delayed for several hours after apparently minor injuries. Vasovagal syncope that follows injury may cause undue concern. Generalized or frontal headache is common in the following days. It may be migrainous (throbbing and hemicranial) in nature or aching and bilateral. After several hours of observation, patients with minor injury may be accompanied home and observed for a day by a family member or friend, with written instructions to return if symptoms worsen.

Persistent severe headache and repeated vomiting in the context of normal alertness and no focal neurologic signs is usually benign, but CT should be obtained and a longer period of observation is appropriate. The decision to perform imaging tests also depends on clinical signs that indicate that the impact was severe (e.g., persistent confusion, repeated vomiting, palpable skull fracture); the presence of other serious bodily injuries, an underlying coagulopathy, or age >65 years; and on the degree of surveillance that can be anticipated after discharge. Guidelines have also indicated that older age (>65 years), two or more episodes of vomiting, >30 min of retrograde or persistent anterograde amnesia, seizure, and concurrent drug or alcohol intoxication are sensitive (but not specific) indicators of intracranial hemorrhage that justify CT scanning.

Though not incorporated into conventional clinical practice guidelines, growing evidence suggests that MRI improves sensitivity for detection of small intracranial hemorrhages and other lesions in mild TBI patients, particular among those with negative findings on CT. Specifically, intracranial abnormalities are fairly common on MRI (27%) in CT-negative patients. Further, acute MRI findings have prognostic utility in predicting recovery and outcome after mTBI/concussion (e.g., risk of functional impairment, time to return to activity).

Blood-based (serum and plasma) biomarkers of astrocyte damage/astrogliosis (glial fibrillary acidic protein [GFAP]) and neuronal injury (ubiquitin carboxy-terminal hydrolase L1 [UCHL1]) also hold promise in improving detection and outcome prediction across the full spectrum of TBI. With development of new rapid assay systems, these can now be used for real-time point-of-care assessment; GFAP in particular has high discriminant ability to detect intracranial abnormalities, as well as potential to differentiate CT+, CT-/MRI+, and CT-/MRI-patients. Similar to MRI, emerging biomarkers appear to have not only diagnostic but also prognostic utility in predicting the trajectory of recovery and functional impairments weeks and months after TBI.

■ SPORT RELATED CONCUSSION

Based on its reported prevalence, acute effects, and fears over potential long-term neurologic consequences, sport-related concussion has become the focus of increasing concern from clinicians, researchers, sporting organizations, and athletes themselves. Concussion is a frequent injury in contact and collision sports (e.g., football, hockey, wrestling) at all levels of participation, including youth sports. Head injury associated with sport and recreational activity accounts for 45% of TBI-related emergency department visits in children age 17 years and under. Between 1997 to 2007, emergency department visits for 8- to 13-year-old children affected by concussion in organized team sports doubled, and increased by $>200\%$ in the 14- to 19-year-old group. Over the last decade, data from the Centers for Disease Control and Prevention indicate that this trend has reversed, with a 27% decrease in emergency department visits for sport- and recreation-related TBI in the United States between 2012 and 2018. Given that national and state surveillance systems continue to report increased sport-related concussion rates over the same time period, it could be inferred that diagnosis and management of sport-related concussion outside of the emergency department has increased.

The natural history of clinical recovery following sport-related concussion has been a subject of substantial ongoing research. In general, the findings on acute recovery are favorable. A 2003 report was the first to chart the continuous time course of acute recovery within several

days after concussion, indicating that >90% of athletes reported symptom recovery within 1 week. Several other prospective studies have since demonstrated that the overwhelming majority of athletes achieve a complete recovery in symptoms, cognitive functioning, postural stability, and other functional impairments over a period of 1–3 weeks following concussion.

In recent years, a paradigm shift toward a more rapid return to activity and a focus on rehabilitation has occurred. Specifically, while experts agree that initial rest post-injury is beneficial for recovery, extended inactivity beyond 5 days can be detrimental and increase risk for protracted recovery. Rather, active rehabilitation involving supervised subthreshold exercise has been shown to improve duration of symptoms and decrease risk of protracted recovery.

There are many anecdotal reports, however, of athletes who remain symptomatic or impaired on functional testing well beyond the window of recovery commonly reported in group studies. The greatest challenge arguably still facing sport medicine clinicians and public health experts is how to most effectively manage and reduce risk in this subset of athletes who do not follow the “typical” course of recovery. The precise frequency of athletes who do not follow the typical course of rapid, spontaneous recovery and instead exhibit prolonged postconcussive symptoms or other functional impairments after concussion remains unclear. Postinjury symptom burden is the most robust predictor of recovery and risk of prolonged symptoms. Preinjury mental health diagnosis and history of prior concussion are two factors that have been consistently identified as being associated with potential for prolonged recovery as well.

Following acute concussion, multimodal advanced neuroimaging has demonstrated a variety of changes, including decreased cerebral blood flow, increased global and local functional connectivity, and alterations in white matter microstructure reflecting axonal organization. In general, these metrics correlate with measures of injury severity, and resolution of these changes tends to parallel clinical recovery. However, a number of studies have shown that slight changes on advanced multimodal imaging can persist even after symptoms have fully resolved, supporting the concept that the “tail” of neurobiologic recovery may extend beyond the time course of apparent clinical recovery.

In the current absence of adequate data, a commonsense approach to athletic concussion has been to remove the individual from play immediately and avoid contact sports for at least several days after a mild injury, and for a longer period if there are more severe injuries or if there are protracted neurologic symptoms such as headache and difficulty concentrating. No individual should return to play unless all concussion-related symptoms have resolved and an assessment has been made by a health care professional who has experience with treatment of concussion. Validated symptom inventories, such as the Rivermead Post-Concussion Symptom Questionnaire (Table 443-2), have been developed to aid clinicians with recording and quantifying the diverse range of physical, cognitive, and behavioral symptoms that can occur following concussion. In addition to characterizing the constellation of acute symptoms and their severity, symptom inventories can be beneficial to track the course and resolution of symptoms through recovery. Differentiating concussion-related symptoms from factors that may be also influencing endorsement (e.g., preinjury mood difficulties) is an important component of managing recovery from sport-related concussion. Once cleared, the individual can then begin a graduated program of increasing activity. Younger athletes are particularly likely to experience protracted concussive symptoms, and a slower return to play in this age group may be reasonable. These guidelines are designed in part to avoid a perpetuation of symptoms but also to prevent the rare *second-impact syndrome*, in which diffuse and fatal cerebral swelling follows a second minor head injury.

■ POSTCONCUSSIVE STATES

The *postconcussion syndrome* (PCS) refers to a state following mild TBI consisting of combinations of fatigue, dizziness, headache, and difficulty in concentration. Management is difficult and generally requires the identification and management of the specific problem or

TABLE 443-2 Review of Concussion Symptoms

PHYSICAL	COGNITIVE	BEHAVIORAL
Headaches	Forgetfulness or poor memory	Being irritable, easily angered
Dizziness	Poor concentration	Feeling depressed or tearful
Nausea and/or vomiting	Taking longer to think	Feeling frustrated or impatient
Noise sensitivity		Restlessness
Sleep disturbance		
Fatigue		
Blurred vision		
Light sensitivity		
Double vision		

Note: Items were adapted from the Rivermead Post-Concussion Symptom Questionnaire. Each item is rated on a 5-point Likert scale (0–4), as follows: 0 = Not experienced at all; 1 = No more of a problem now than preinjury; 2 = A mild problem; 3 = A moderate problem; 4 = A severe problem. Total scores can range from 0–64.

problems that are most troubling to the individual. A clear explanation and education around the symptoms that may follow concussion has been shown to reduce subsequent complaints. Care is taken to avoid prolonged use of drugs that produce dependence. Headache may initially be treated with acetaminophen and small doses of amitriptyline. Vestibular exercises (Chap. 22) and small doses of vestibular suppressants such as promethazine (Phenergan) may be helpful when dizziness is the main problem. Patients, who after mild or moderate injury have difficulty with memory or with complex cognitive tasks at work, may be reassured to know that these problems usually improve over several months, and a reduced workload or other accommodations may be prescribed in the interim.

For the vast majority of individuals with mTBI, the symptoms of PCS subside and resolve within a few weeks of injury. For a subset of individuals with mTBI, however, complaints of postconcussion symptoms persist beyond the expectation derived from TBI severity markers. The term *postconcussion disorders* (PCDs) has been proposed for diagnostic use and to improve characterization of specific symptoms or types of sequelae following mTBI. These include neurologic, cognitive, behavioral, or somatic complaints that continue beyond the acute and subacute periods, becoming chronic and often operationalized as persisting beyond 3 months. Although the overall risk of developing PCD following mTBI is low, the frequency of mTBI patients who meet criteria for a diagnosis of PCD and present in a clinical setting is believed to be higher.

mTBI patients with PCD frequently present to the outpatient clinics of primary care physicians, physiatrists, or neurologists seeking relief for lingering PCD-related symptoms. While some patients will have already received an initial medical workup to rule out a more serious brain injury during the acute phase, many patients will have had no prior contact with health care specialists. A medical workup ordered in the outpatient setting for PCD-related complaints is typically unremarkable for any identifiable neurologic cause to account for the persisting symptoms reported by the patient. The development of uniform decision trees or “standard of care” treatment regimens for PCD-related symptoms has been limited by the diversity of symptoms that patients experience, even within mTBI subgroups that have sustained very similar injury patterns. While some patients experience somatic symptoms, others complain of subjective cognitive or behavioral changes. Symptom inventories (Table 443-2) can be helpful in documenting the broad range of these symptoms and serve as a metric for improvement following symptom-based treatment.

Active rehabilitation for the treatment of PCD involving subthreshold exercise has increased in popularity over recent years and has gained empirical support for its effectiveness as a useful intervention for protracted recovery.

PCD is not a unidimensional condition but rather an outcome influenced by diverse cognitive, emotional, medical, psychosocial, and motivational factors. Because of this complexity, treatments targeting

persistent and refractory PCD-related symptoms should be tailored to the needs and expectations of the individual patient, with referrals to specialists as needed for assistance with management of headache, neck and back pain, dizziness and vertigo, and other symptoms reported within the context of PCD. A comprehensive review of concussion- and PCD-related symptoms presented in Table 443-2 allows for development of an individualized approach that leverages currently available treatment for those sequelae that are most bothersome to the patient (e.g., vestibular rehabilitation therapy for vertigo, melatonin for sleep disturbance). Patients are frequently referred to behavioral health providers such as neuropsychologists, rehabilitation psychologists, health psychologists, and/or psychiatrists for a variety of reasons, but particularly when they are experiencing cognitive, emotional, or behavioral changes that accompany PCD. Patients with mood disorders (e.g., depression), anxiety disorders (e.g., posttraumatic stress disorder), or adjustment reactions may benefit from psychiatric consultation for appropriate medication trials or from time-limited psychotherapy such as cognitive behavioral therapy.

Due to the complexity of presentation and varying diagnostic criteria, there are limited studies regarding overall prognosis of PCD. However, treatment of PCD-related symptoms targeted to the individual's specific difficulties can improve functional outcomes and patient-rated quality of life. Further, collaborative care has been shown to improve outcomes among patients experiencing persistent postconcussion symptoms. These improved outcomes are likely due to a multidisciplinary team's ability to simultaneously address the diverse set of symptoms that can occur with PCD.

■ INJURY OF INTERMEDIATE SEVERITY

Patients who are not fully alert or have persistent confusion, behavioral changes, extreme dizziness, or focal neurologic signs such as hemiparesis should be admitted to the hospital and undergo a cerebral imaging study. A cerebral contusion or hematoma will usually be found. Common syndromes include: (1) delirium with a disinclination to be examined or moved, expletive speech, and resistance if disturbed (anterior temporal lobe contusions); (2) a quiet, disinterested, slowed mental state (abulia) alternating with irascibility (inferior frontal and frontopolar contusions); (3) a focal deficit such as aphasia or mild hemiparesis (due to subdural hematoma or convexity contusion or, less often, carotid artery dissection); (4) confusion and inattention, poor performance on simple mental tasks, and fluctuating orientation (associated with several types of injuries, including those described above, and with medial frontal contusions and interhemispheric subdural hematoma); (5) repetitive vomiting, nystagmus, drowsiness, and unsteadiness (labyrinthine concussion, but occasionally due to a posterior fossa subdural hematoma or vertebral artery dissection); and (6) diabetes insipidus (damage to the median eminence or pituitary stalk). Injuries of this degree can be complicated by drug or alcohol intoxication, and clinically inapparent cervical spine injury may be present. Blast injuries are often accompanied by rupture of the tympanic membranes.

After surgical removal of hematomas, patients in this category improve over weeks to months. During the first week, the state of alertness, memory, and other cognitive functions often fluctuate, and agitation and somnolence are common. Behavioral changes tend to be worse at night, as with many other encephalopathies, and may be treated with small doses of antipsychotic medications. Subtle abnormalities of attention, intellect, spontaneity, and memory return toward normal weeks or months after the injury, sometimes abruptly. However, the full extent of recovery may not be realized for several years. Persistent cognitive problems are discussed below.

■ SEVERE INJURY

Patients who are comatose from the moment of injury require immediate neurologic attention and resuscitation. After intubation, with care taken to immobilize the cervical spine, the depth of coma, pupillary size and reactivity, limb movements, and Babinski responses are assessed. As soon as vital functions permit and cervical spine x-rays and a CT scan have been obtained, the patient should be transported

to a critical care unit. Hypoxia should be reversed, and normal saline used as the resuscitation fluid in preference to albumin. The finding of an epidural or subdural hematoma or large intracerebral hemorrhage is usually an indication for prompt surgery and intracranial decompression in an otherwise salvageable patient. Measurement of ICP with a ventricular catheter or fiberoptic device in order to guide treatment has been favored by many units but has not improved outcome. Similarly, induced hypothermia has shown no benefit. Hyperosmolar intravenous solutions are used in various regimens to limit intracranial pressure. Prophylactic antiepileptic medications are recommended for 7 days and should be discontinued unless there are multiple seizures postinjury. Management of raised ICP, a frequent feature of severe head injury, is discussed in Chap. 307.

Despite the improvement in mortality for severe TBI over the past few decades, a great deal of therapeutic nihilism persists in TBI. The common use of a 6-month outcome for TBI clinical studies reinforces this misconception. The recovery from severe TBI can take years. Furthermore, the ability to predict long-term outcome is limited and frequently incorrect. Best-practice guidelines recommend, in the absence of brain death, that aggressive therapy be instituted for at least 72 h in the acute injury period.

■ LONG TERM OUTCOMES IN TBI

TBI (aggregated mild to severe) is associated with a 63–96% increased risk of all-cause dementia. The degree of risk for dementia ranges along the gradient of TBI severity (i.e., greatest risk among severe injuries). To date, investigations have less reliably established mTBI as a robust risk factor for dementia, likely due to methodologic heterogeneity (e.g., use of different diagnostic criteria, exposure misclassification, self-report vs. physician diagnoses of TBI or dementia). Though an identified risk factor for all-cause dementia, pathophysiologic and epidemiologic factors that underlie the association between TBI with risk of specific neurodegenerative pathologies and dementia-subtypes are not well understood. As a result, associations between TBI with clinical syndromes (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis) or distinct neuropathologies (e.g., beta-amyloid, Lewy bodies, transactive response DNA-binding protein 43) have been inconsistently reported in the literature. In a large study involving clinical and neuropathologic data from three pooled prospective studies of community-based cohorts, a significant relationship was found between TBI with LOC > 1 h and subsequent Parkinson's disease diagnosis, progression rate of parkinsonism, and Lewy body accumulation at postmortem examination.

There is some evidence that repeated mTBI or sport-related concussions, particularly among boxing and professional American football athletes, are associated with delayed and potentially progressive neurobehavioral changes. The brains of these patients display a characteristic deposition of tau protein in neurons located in the superficial cortical layers and perivascular regions, and particularly in the depths of sulci. This pattern has been defined as the pathognomonic lesion of *chronic traumatic encephalopathy* (CTE). A variety of neurodegenerative pathologies are commonly found in the presence of CTE, adding to the complexity of diagnosis. While staging criteria for this neuropathologic entity have yet to be established, a consensus meeting to define the neuropathologic criteria for CTE proposed an algorithm assessing CTE as "low" or "high" in severity. Overall, its contribution, if any, to late-life dementia and parkinsonism in former athletes, soldiers, or others who have sustained repeated concussive injuries is unknown.

Research criteria for the clinical diagnosis of CTE have been proposed, and include a range of cognitive and/or behavioral symptoms, including executive dysfunction, depression, insomnia, and behavioral dyscontrol. Multiple studies have suggested that these proposed criteria lack specificity (i.e., they are frequent in other conditions and non-CTE cases). As such, CTE remains a postmortem diagnosis. Advances in positron emission tomography (PET) have allowed for *in vivo* investigation of tau deposition. Significant correlations between greater years of football participation and greater standardized uptake value ratio (SUVR) of ¹⁸F-flortaucipir (purportedly representative of tau deposition) in the bilateral superior frontal, bilateral medial temporal, and left

parietal regions have been reported. However, increased SUVR in these regions was not significantly associated with neuropsychologic and neuropsychiatric function. Taken together, further study is required to better refine the clinical and postmortem diagnostic criteria of CTE, enhance clinicopathologic correlation, and ultimately improve patient care and management. CTE is also discussed in Chap. 424.

FURTHER READING

- J VE et al: Axonal pathology in traumatic brain injury. *Exp Neurol* 246:35, 2013.
- K R et al: Recovery of consciousness and functional outcome in moderate and severe traumatic brain injury. *JAMA Neurol* 78:548, 2021.
- M C P et al: Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med* 51:838, 2017.
- M J et al: Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA* 318:360, 2017.
- N L et al: Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. *JAMA Neurol* 76:1049, 2019.
- T CA et al: Traumatic brain injury-related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. *MMWR Surveill Summ* 66:1, 2017.

444

Multiple Sclerosis

Bruce A. C. Cree, Stephen L. Hauser

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by chronic inflammation, demyelination, gliosis (plaques or scarring), and neuronal loss; the course can be relapsing or progressive. MS plaques typically develop at different times and in different CNS locations (i.e., MS is said to be disseminated in time and space). More than 900,000 individuals in the United States and millions of individuals worldwide are affected. The clinical course is extremely variable, ranging from a relatively benign condition to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments.

CLINICAL MANIFESTATIONS

The onset of MS may be abrupt or insidious. Symptoms may be severe or seem so trivial that a patient may not seek medical attention for months or years. Indeed, at autopsy, ~0.1% of individuals who were asymptomatic during life will be found, unexpectedly, to have pathologic evidence of MS. Similarly, an MRI scan obtained for an unrelated reason may show evidence of asymptomatic MS. Symptoms of MS are extremely varied and depend on the location and severity of lesions within the CNS (Table 444-1). Examination often reveals evidence of neurologic dysfunction, often in asymptomatic locations. For example, a patient may present with symptoms in one leg but signs in both.

Sensory symptoms are varied and include both paresthesias (e.g., tingling, prickling sensations, formications, “pins and needles,” or painful burning) and hypesthesia (e.g., reduced sensation, numbness, or a “dead” feeling). Unpleasant sensations (e.g., feelings that body parts are swollen, wet, raw, or tightly wrapped) are also common. Sensory impairment of the trunk and legs below a horizontal line on the torso (a sensory level) indicates that the spinal cord is the origin of the

TABLE 444-1 Initial Symptoms of Multiple Sclerosis (MS)

SYMPOTM	PERCENTAGE OF CASES	SYMPOTM	PERCENTAGE OF CASES
Sensory loss	37	Lhermitte	3
Optic neuritis	36	Pain	3
Weakness	35	Dementia	2
Paresthesias	24	Visual loss	2
Diplopia	15	Facial palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal attacks	4	Epilepsy	1
Bladder	4	Falling	1

Source: Data from RJ Swingler, DA Compston: The morbidity of multiple sclerosis. *Q J Med* 83:325, 1992.

sensory disturbance. It is often accompanied by a bandlike sensation of tightness around the torso. Pain is a common symptom of MS, experienced by >50% of patients. Pain can occur anywhere on the body and can change locations over time.

Optic neuritis (ON) presents as diminished visual acuity, dimness, or decreased color perception (desaturation) in the central field of vision. These symptoms can be mild or may progress to severe visual loss. Rarely, there is complete loss of light perception. Visual symptoms are generally monocular but may be bilateral. Periorbital pain (aggravated by eye movement) often precedes or accompanies the visual loss. An afferent pupillary defect (Chap. 32) is usually present. Fundoscopic examination may be normal or reveal optic disc swelling (papillitis). Pallor of the optic disc (optic atrophy) commonly follows ON. Uveitis is uncommon and should raise the possibility of alternative diagnoses such as sarcoidosis or lymphoma.

Weakness of the limbs may manifest as loss of strength, speed, or dexterity; as fatigue; or as a disturbance of gait. Exercise-induced weakness is a characteristic symptom of MS. The weakness is of the upper motor neuron type (Chap. 24) and is usually accompanied by other pyramidal signs such as spasticity, hyperreflexia, and Babinski signs. Occasionally, a tendon reflex may be lost (simulating a lower motor neuron lesion) if an MS lesion disrupts the afferent reflex fibers in the spinal cord (see Fig. 24-2).

Facial weakness due to a lesion in the pons may resemble idiopathic Bell’s palsy (Chap. 441). Unlike Bell’s palsy, facial weakness in MS is usually not associated with ipsilateral loss of taste sensation or retroauricular pain.

Spasticity (Chap. 24) is commonly associated with spontaneous and movement-induced muscle spasms. More than 30% of MS patients have moderate to severe spasticity, especially in the legs. This is often accompanied by painful spasms interfering with ambulation, work, or self-care. Occasionally, spasticity provides support for the body weight during ambulation, and in these cases, treatment of spasticity may actually do more harm than good.

Visual blurring in MS may result from ON or diplopia (double vision); if the symptom resolves when either eye is covered, the cause is diplopia. *Diplopia* may be caused by internuclear ophthalmoplegia (INO) or palsy of the sixth cranial nerve (rarely the third or fourth). An INO consists of impaired adduction of one eye due to a lesion in the ipsilateral medial longitudinal fasciculus (Chaps. 32 and V3). Prominent nystagmus is often observed in the abducting eye, along with a small skew deviation. A bilateral INO is particularly suggestive of MS. Other common gaze disturbances in MS include (1) a horizontal gaze palsy, (2) a “one and a half” syndrome (horizontal gaze palsy plus an INO), and (3) acquired pendular nystagmus.

Ataxia usually manifests as cerebellar tremors (Chap. 439). Ataxia may also involve the head and trunk or the voice, producing a characteristic cerebellar dysarthria (scanning speech).

Vertigo may appear suddenly from a brainstem lesion, superficially resembling acute labyrinthitis (Chap. 22). *Hearing loss* (Chap. 34) may also occur in MS but is uncommon.

■ ANCILLARY SYMPTOMS

Paroxysmal symptoms are distinguished by their brief duration (10 s to 2 min), high frequency (5–40 episodes per day), lack of any alteration of consciousness or change in background electroencephalogram during episodes, and a self-limited course (generally lasting weeks to months). They may be precipitated by hyperventilation or movement. These syndromes may include Lhermitte's symptom; tonic contractions of a limb, face, or trunk (tonic seizures); paroxysmal dysarthria and ataxia; paroxysmal sensory disturbances; and several other less well-characterized syndromes. Paroxysmal symptoms probably result from spontaneous discharges, arising at the edges of demyelinated plaques and spreading to adjacent white matter tracts.

Lhermitte's symptom is an electric shock-like sensation (typically induced by flexion or other movements of the neck) that radiates down the back into the legs. Rarely, it radiates into the arms. It is generally self-limited but may persist for years. Lhermitte's symptom can also occur with other disorders of the cervical spinal cord (e.g., cervical spondylosis).

Trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia (Chap. 441) can occur when the demyelinating lesion involves the root entry (or exit) zone of the fifth, seventh, and ninth cranial nerve, respectively. Trigeminal neuralgia (tic douloureux) is a very brief lancinating facial pain often triggered by an afferent input from the face or teeth. Most cases of trigeminal neuralgia are not MS related; however, atypical features such as onset before age 50 years, bilateral symptoms, objective sensory loss, or nonparoxysmal pain should raise the possibility that MS could be responsible.

Facial myokymia consists of either persistent rapid flickering contractions of the facial musculature (especially the lower portion of the orbicularis oculus) or a contraction that slowly spreads across the face. It results from lesions of the corticobulbar tracts or brainstem course of the facial nerve.

Heat sensitivity refers to neurologic symptoms produced by an elevation of the body's core temperature. For example, unilateral visual blurring may occur during a hot shower or with physical exercise (*Uhthoff's symptom*). It is also common for MS symptoms to worsen transiently, sometimes dramatically, during febrile illnesses. Such heat-related symptoms probably result from transient conduction block.

Bladder dysfunction is present in >90% of MS patients, and in one-third of patients, dysfunction results in weekly or more frequent episodes of incontinence. During normal reflex voiding, relaxation of the bladder sphincter (α -adrenergic innervation) is coordinated with contraction of the detrusor muscle in the bladder wall (muscinic cholinergic innervation). *Detrusor hyperreflexia*, due to impairment of suprasegmental inhibition, causes urinary frequency, urgency, nocturia, and uncontrolled bladder emptying. *Detrusor sphincter dyssynergia*, due to loss of synchronization between detrusor and sphincter muscles, causes difficulty in initiating and/or stopping the urinary stream, producing hesitancy, urinary retention, overflow incontinence, and recurrent infection.

Constipation occurs in >30% of patients. Fecal urgency or *bowel incontinence* is less common (<15%) but can be socially debilitating.

Sexual dysfunction may manifest as decreased libido, impaired genital sensation, impotence in men, and diminished vaginal lubrication or adductor spasms in women.

Cognitive dysfunction can include memory loss; impaired attention; difficulties in executive functioning, memory, and problem solving; slowed information processing; and problems shifting between cognitive tasks. Euphoria (elevated mood) was once thought to be characteristic of MS but is actually uncommon, occurring in <20% of patients. Cognitive dysfunction sufficient to impair activities of daily living is rare.

Depression, experienced by approximately half of patients, can be reactive, endogenous, or part of the illness itself and can contribute to fatigue.

Fatigue (Chap. 23) is experienced by 90% of patients; this symptom is the most common reason for work-related disability in MS. Fatigue can be exacerbated by elevated temperatures, depression, expending exceptional effort to accomplish basic activities of daily living, or sleep disturbances (e.g., from frequent nocturnal awakenings to urinate).

DISEASE COURSE

Three clinical types of MS exist (Fig. 444-1):

1. *Relapsing or bout onset MS* (RMS) accounts for 90% of MS cases and is characterized by discrete attacks of neurologic dysfunction that generally evolve over days to weeks (rarely over hours). With initial attacks, there is often substantial or complete recovery over the ensuing weeks to months. However, as attacks continue, recovery may be less evident (Fig. 444-1A). Between attacks, patients were traditionally thought to be neurologically stable; however it is now clear that many patients with RMS experience subtle "silent" progression even when relapse-free.

2. *Secondary progressive MS* (SPMS) always begins as RMS (Fig. 444-1B). At some point, however, the clinical course changes so that the patient experiences progressive deterioration in function unassociated with acute attacks. SPMS produces a greater amount of fixed neurologic disability than RMS. For a patient with RMS, the risk of developing SPMS was approximately 3% each year in the pre-treatment era, meaning that the great majority of RMS would ultimately evolve into SPMS. However, recent case series have indicated a much lower rate of evolution to SPMS, estimated at slightly >1% each year, likely due to widespread use of effective therapies for MS.

3. *Primary progressive MS* (PPMS) accounts for ~10% of cases. These patients do not experience attacks but rather steadily decline in function from disease onset (Fig. 444-1C). Compared to RMS, the sex distribution is more even, the disease begins later in life (mean age ~40 years), and disability develops faster (relative to the onset of the first clinical symptom). Despite these differences, PPMS appears to represent the same underlying illness as RMS.

Progressive MS and Disease Activity Patients with SPMS or even PPMS will occasionally experience relapses, albeit less often than in RMS. Progressive MS patients experiencing relapses or who are found to have acute new lesions on MRI are considered to have "active" progressive MS.

■ EPIDEMIOLOGY

MS is approximately threefold more common in women than men. The age of onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present across the lifespan. Approximately 10% of cases begin before the age of 18 years, and a small percentage of cases begin before the age of 10 years.

Geographic gradients are observed in MS, with the highest known prevalence for MS (250 per 100,000) in the Orkney Islands, located north of Scotland. In other temperate zone areas (e.g., northern

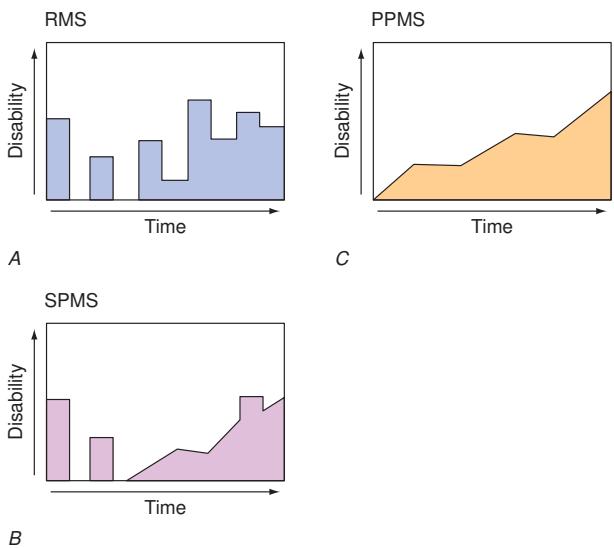


FIGURE 444-1 Clinical course of multiple sclerosis (MS). A. Relapsing MS (RMS). B. Secondary progressive MS (SPMS). C. Primary progressive MS (PPMS).

North America, northern Europe, southern Australia, and southern New Zealand), the prevalence of MS is 0.1–0.2%. By contrast, in the tropics (e.g., Asia, equatorial Africa, and the Middle East), the prevalence is often tenfold to twentyfold less.

The prevalence of MS has increased steadily (and dramatically) in several regions around the world over the past half-century, presumably reflecting the impact of some environmental shift. Moreover, the fact that this increase appears to have occurred primarily in women indicates that women are more responsive to this environmental change.

Well-established risk factors for MS include a genetic predisposition, vitamin D deficiency, Epstein-Barr virus (EBV) exposure after early childhood, and cigarette smoking.

Vitamin D deficiency is associated with an increase in MS risk, and data suggest that ongoing deficiency also increases disease activity after MS begins. Immunoregulatory effects of vitamin D could explain these apparent relationships. Exposure of the skin to ultraviolet-B (UVB) radiation from the sun is essential for the biosynthesis of vitamin D, and this endogenous production is the most important source of vitamin D in most individuals. A diet rich in fatty fish represents another source of vitamin D. At high latitudes, the amount of UVB radiation reaching the earth's surface is often insufficient, particularly during winter months, and consequently, low serum levels of vitamin D are common in temperate zones. The common practice to avoid direct sun exposure and the widespread use of sunblock would be expected to exacerbate any population-wide vitamin D deficiency (sun protection factor [SPF] 15 blocks 94% of incoming UVB radiation).

Evidence of a remote EBV infection playing some role in MS is supported by numerous epidemiologic and laboratory studies. A higher risk of infectious mononucleosis (associated with relatively late EBV infection) and higher antibody titers to latency-associated EBV nuclear antigen have been repeatedly associated with MS risk, although a causal role for EBV is not established.

A history of cigarette smoking also is associated with MS risk. Interestingly, in an animal model of MS, the lung was identified as a critical site for activation of pathogenic T lymphocytes responsible for autoimmune demyelination.

GENETIC CONSIDERATIONS

 Whites are inherently at higher risk for MS than Africans or Asians, even when residing in a similar environment. Recent studies in the United States, however, have shown that MS risk in persons of African descent is as high, and possibly higher, than in whites. MS also aggregates within some families, and adoption, half-sibling, twin, and spousal studies indicate that familial aggregation is primarily due to genetic factors. Nonetheless, family studies also support a contribution of environment, as fraternal twins of MS patients are at higher risk than nontwin siblings (Table 444-2).

Susceptibility to MS is polygenic, with each gene contributing a relatively small amount to the overall risk. The strongest susceptibility signal genome-wide maps to the human leukocyte antigen (HLA)-DRB1 gene in the class II region of the major histocompatibility complex (MHC) and specifically to HLA-DR15 (formerly designated DR2), and this association accounts for ~10% of the disease risk. This HLA association, first described in the early 1970s, suggests that MS, at its core, is an autoimmune disease. Whole-genome association studies have now identified ~230 other MS susceptibility variants, each of which individually has only a very small effect on MS risk. Many

TABLE 444-2 Risk of Developing Multiple Sclerosis (MS)

1 in 3	If an identical twin has MS
1 in 15	If a fraternal twin has MS
1 in 25	If a sibling has MS
1 in 50	If a parent or half-sibling has MS
1 in 100	If a first cousin has MS
1 in 1000	If a spouse has MS
1 in 1000	If no one in the family has MS

of these MS-associated genes have known roles in the adaptive and innate immune system, for example the genes for the interleukin (IL)-7 receptor (CD127), IL-2 receptor (CD25), and T-cell costimulatory molecule LFA-3 (CD58); some variants also influence susceptibility to other autoimmune diseases in addition to MS. The variants identified so far all lack specificity and sensitivity for MS; thus, at present, they are not useful for diagnosis or prediction of the future disease course.

PATHOGENESIS

■ PATHOLOGY

Demyelination New MS lesions begin with perivenular cuffing by inflammatory mononuclear cells, predominantly T cells and macrophages, which also infiltrate the surrounding white matter. At sites of inflammation, the blood-brain barrier (BBB) is disrupted, but unlike in vasculitis, the vessel wall is preserved. At the leading edge of lesions, large numbers of cytotoxic CD8 cells are found. Involvement of the humoral immune system is also evident; small numbers of B lymphocytes infiltrate the nervous system, myelin-specific autoantibodies are present on degenerating myelin sheaths, and complement is activated.

Sharply demarcated areas of demyelination are the pathologic hallmark of MS lesions, and evidence of myelin degeneration is found at the earliest time points of tissue injury. Although relative sparing of axons is typical, partial or total axonal destruction can also occur, especially within highly inflammatory lesions. In some lesions, surviving oligodendrocytes or those that differentiate from precursor cells partially remyelinate the surviving axons, producing so-called *shadow plaques*. However, in many lesions oligodendrocyte precursor cells are present but they fail to differentiate into mature myelin-producing cells. Therefore, promoting remyelination to protect axons remains an important therapeutic goal. As lesions evolve, there is prominent astrocytic proliferation (gliosis) and the term *sclerosis* refers to these gliotic plaques that have a rubbery or hardened texture at autopsy.

Neurodegeneration Cumulative axonal and neuronal loss is the most important contributor to irreversible neurologic disability and progressive symptoms. With paraplegia due to MS, as many as 70% of axons are ultimately lost from the lateral corticospinal (e.g., motor) tracts. Demyelination can reduce trophic support for axons, redistribute ion channels, and destabilize action potential membrane potentials. Axons can adapt initially to these injuries, but over time distal and retrograde degeneration ("dying-back" axonopathy) occurs.

Multiple pathologies appear to contribute to progressive symptoms in longstanding MS. *Chronic active plaques* are preexisting white matter lesions that show evidence of persistent inflammation, progressive axonal loss, and gradual concentric expansion, with large numbers of microglial cells at the leading edge of enlarging lesions but without BBB disruption. Recent studies have also highlighted the importance of a primary injury to the cerebral cortex. Cortical plaques are frequent in MS but are generally not well visualized by MRI; these can extend upward from adjacent white matter lesions, or may be located within the cortex or underneath the pia. *Ectopic lymphoid follicles* are aggregates of B, T, and plasma cells located in the superficial meninges, especially overlying deep cortical sulci; similar clusters are also present in perivascular spaces. Ectopic lymphoid follicles are topographically associated with underlying demyelination and neuronal loss in the cerebral cortex, and diffusible factors from these lymphoid cells are believed to mediate subpial cortical demyelination and neurodegeneration. Neuronal and axonal death may result from glutamate-mediated excitotoxicity, oxidative injury, iron accumulation, and/or mitochondrial failure.

In relapsing MS, inflammation is associated with focal perivenular parenchymal infiltration of lymphocytes and monocytes associated with BBB disruption and active demyelination. By contrast, inflammation in progressive MS is more diffuse and is characterized by widespread microglial activation across large areas of white matter, associated with reduced myelin staining and axonal injury ("dirty white matter"). Activated astrocytes induced by microglia may also contribute to tissue damage (Chap. 425). These observations imply

that ongoing inflammation occurs behind an intact BBB in many patients with progressive MS, and this feature could explain the failure of immunotherapies not capable of crossing the BBB to benefit patients with progressive MS.

■ PHYSIOLOGY

Nerve conduction in myelinated axons occurs in a saltatory manner, with the nerve impulse jumping from one node of Ranvier to the next without depolarization of the axonal membrane underlying the myelin sheath between nodes (Fig. 444-2). This produces faster conduction velocities (~70 m/s) than the slow velocities (~1 m/s) produced by continuous propagation in unmyelinated nerves. Conduction block occurs when the nerve impulse is unable to traverse the demyelinated segment. This can happen when the resting axon membrane becomes hyperpolarized due to exposure of voltage-dependent potassium channels that are normally buried underneath the myelin sheath. A temporary conduction block often follows a demyelinating event before sodium channels (originally concentrated at the nodes) redistribute along the naked axon (Fig. 444-2). This redistribution ultimately allows continuous propagation of nerve action potentials through the demyelinated segment. Conduction block may be incomplete, affecting high- but not low-frequency volleys of impulses. Variable conduction block can occur with raised body temperature or metabolic alterations and may explain clinical fluctuations that vary from hour to hour or appear with fever or exercise. Conduction slowing occurs when the demyelinated segments of the axonal membrane are reorganized to support continuous (slow) nerve impulse propagation.

■ IMMUNOLOGY

A proinflammatory autoimmune response directed against a component of CNS myelin, and perhaps other neural elements as well, remains the cornerstone of current concepts of MS pathogenesis.

■ AUTOREACTIVE T LYMPHOCYTES

Myelin basic protein (MBP), an intracellular protein involved in myelin compaction, is an important T-cell antigen in experimental allergic encephalomyelitis (EAE), a laboratory model, and possibly also in human MS. Activated MBP-reactive T cells have been identified in the blood, in cerebrospinal fluid (CSF), and within MS lesions. The MS associated HLA-DR15 protein binds with high affinity to a fragment of MBP (spanning amino acids 89–96), potentially stimulating T-cell responses to this self-protein. Several different populations of proinflammatory T cells are likely to mediate autoimmunity in MS. T-helper type 1 (T_H1) cells producing interferon γ (IFN- γ) are one

key effector population; T_H1 cytokines, including IL-2, tumor necrosis factor (TNF)- α , and IFN- γ , also play key roles in activating and maintaining autoimmune responses, and TNF- α and IFN- γ may directly injure oligodendrocytes or the myelin membrane. As noted above, CD8 cytotoxic T cells are present at the active edges of expanding MS lesions, and activated CD8 cells also appear to be enriched for reactivity against myelin antigens in MS patients.

■ HUMORAL AUTOIMMUNITY

B-cell activation and antibody responses are centrally involved in the development of demyelinating lesions, as evidenced by the efficacy of B cell-based treatments in all forms of MS (see “Treatment” below). Clonally restricted populations of activated, antigen-experienced, memory B cells and plasma cells are present in MS lesions, in meningeal lymphoid follicle-like structures overlying the cerebral cortex, and in the CSF. Similar populations are found in each compartment, indicating that a highly focused B-cell response occurs locally within the CNS. Myelin-specific autoantibodies, some directed against an extracellular myelin protein, myelin oligodendrocyte glycoprotein (MOG), have been detected bound to vesiculated myelin debris in MS plaques. In the CSF elevated levels of locally synthesized immunoglobulins and oligoclonal antibodies, derived from clonally restricted CNS B cells and plasma cells, are also characteristic of MS. The pattern of oligoclonal banding is unique to each individual, and attempts to identify the targets of these antibodies have been largely unsuccessful; they appear to recognize a diverse array of antigens including intracellular ubiquitous proteins. Therefore, although intrathecal oligoclonal antibodies and elevated intrathecal synthesis of immunoglobulins are characteristic of MS, their role in disease pathogenesis remains uncertain.

Recent data suggest that the antigen presenting cell (APC) function of B cells may explain their role in MS pathogenesis. Remarkably, fragments of self-peptides derived from HLA-DR2 proteins themselves were found to bind intact DR2 molecules on B cells and serve as antigens for presentation to T cells. Memory CD4+ T cells derived from CSF responded to these self-peptides bound to DR2 molecules and, in some cases, these self-peptides were cross-reactive with myelin antigens, RAS guanyl-releasing protein 2 (RASGRP2) previously found to be a possible T-cell autoantigen in MS, EBV, and Akkermansia muciniphila, a commensal gut bacterium associated with dysbiosis in MS patients. Thus, the MS-associated HLA proteins contain fragments that might trigger autoimmunity through molecular mimicry with viral, bacterial, or cell-surface autoantigens.

DIAGNOSIS

There is no single diagnostic test for MS. Diagnostic criteria for clinically definite MS require documentation of two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS (Table 444-3). Symptoms must last for >24 h and occur as distinct episodes that are separated by a month or more. In patients who have only one of the two required signs on neurologic examination, the second may be documented by abnormal tests such as MRI or evoked potentials (EPs). Similarly, in the most recent diagnostic scheme, the second clinical event (in time) may be supported solely by MRI findings, consisting of either the development of new focal white matter lesions on MRI or the simultaneous presence of both an enhancing lesion and a nonenhancing lesion in an asymptomatic location. In patients whose course is progressive from onset for \geq 6 months without superimposed relapses, documentation of intrathecal IgG synthesis may be used to support a diagnosis of PPMS.

DIAGNOSTIC TESTS

■ MAGNETIC RESONANCE IMAGING

MRI has revolutionized the diagnosis and management of MS (Fig. 444-3); characteristic abnormalities are found in >95% of patients, although >90% of the lesions visualized by MRI are asymptomatic. An increase in vascular permeability from a breakdown of the BBB is detected by leakage of intravenous gadolinium (Gd) into

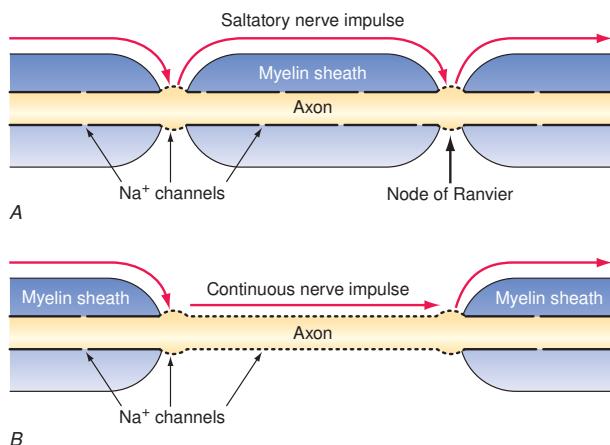


FIGURE 444-2 Nerve conduction in myelinated and demyelinated axons. **A.** Saltatory nerve conduction in myelinated axons occurs with the nerve impulse jumping from one node of Ranvier to the next. Sodium channels (shown as breaks in the solid black line) are concentrated at the nodes where axonal depolarization occurs. **B.** Following demyelination, additional sodium channels are redistributed along the axon itself, thereby allowing continuous propagation of the nerve action potential despite the absence of myelin.

TABLE 444-3 Diagnostic Criteria for Multiple Sclerosis (MS)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR DIAGNOSIS
2 or more attacks; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
2 or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by ≥ 1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a further clinical attack implicating a different CNS site
1 attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space • ≥ 1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a second clinical attack implicating a different CNS site AND • For dissemination in time • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack
Insidious neurologic progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) PLUS 2 out of the 3 following criteria: • Evidence for dissemination in space in the brain based on ≥ 1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions • Evidence for dissemination in space in the spinal cord based on ≥ 2 T2+ lesions in the cord • Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis.

Source: Reproduced with permission from AJ Thompson et al: Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17:162, 2018.

the parenchyma. Such leakage occurs early in the development of an MS lesion and serves as a useful marker of inflammation. Gd enhancement typically persists for <1 month, and the residual MS plaque remains visible indefinitely as a focal area of hyperintensity (a lesion) on T2-weighted images. Lesions are frequently oriented perpendicular to the ventricular surface, corresponding to the pathologic pattern of perivenous demyelination (Dawson's fingers). Lesions

are multifocal within the brain, brainstem, and spinal cord. Lesions >6 mm located in the corpus callosum, periventricular white matter, brainstem, cerebellum, or spinal cord are particularly helpful diagnostically. Current criteria for the use of MRI in the diagnosis of MS are shown in Table 444-3.

Serial MRI studies in early relapsing-remitting MS reveal that bursts of focal inflammatory disease activity occur far more frequently than would have been predicted by the frequency of relapses. Thus, early in MS, most disease activity is clinically silent.

The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical disability. Quantitative measures of brain and spinal cord atrophy are evidence of diffuse tissue injury and correlate more strongly with measures of disability or progressive MS. Serial MRI studies also indicate that progressive whole-brain atrophy occurs even in very early MS and continues throughout the disease course. Approximately one-third of T2-weighted lesions appear as hypointense lesions (black holes) on T1-weighted imaging. Black holes may be a marker of irreversible demyelination and axonal loss, although even this measure depends on the timing of the image acquisition (e.g., most acute Gd-enhancing T2 lesions are T1 dark).

■ EVOKED POTENTIALS

EP testing assesses function in afferent (visual, auditory, and somatosensory) or efferent (motor) CNS pathways. EPs use computer averaging to measure CNS electric potentials evoked by repetitive stimulation of selected peripheral nerves or of the brain. These tests provide the most information when the pathways studied are clinically uninvolved. For example, in a patient with a relapsing spinal cord syndrome with sensory deficits in the legs, an abnormal somatosensory EP following posterior tibial nerve stimulation provides little new information. By contrast, an abnormal visual EP in this circumstance would permit a diagnosis of clinically definite MS (Table 444-3). Abnormalities on one or more EP modalities occur in 80–90% of MS patients. EP abnormalities are not specific to MS, although a marked delay in the latency of a specific EP component (as opposed to a reduced amplitude or distorted wave-shape) is suggestive of demyelination.

■ CEREBROSPINAL FLUID

CSF abnormalities found in MS include a mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG. The total CSF protein is usually normal or mildly elevated. Various formulas distinguish intrathecally synthesized IgG from IgG that entered the CNS passively from the serum. The CSF IgG index expresses the ratio of IgG to albumin in the CSF divided by the same ratio in the serum. The IgG synthesis rate uses serum and CSF IgG and albumin measurements to calculate the rate of CNS IgG synthesis. The measurement of oligoclonal bands (OCBs) by agarose gel electrophoresis in the CSF also assesses intrathecal production of IgG. Two or more discrete OCBs, not present in a paired serum sample, are found in >90% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients, the number of bands may increase with time.

A mild CSF pleocytosis (>5 cells/ μ L) is present in ~25% of cases, usually in young patients with RMS. A pleocytosis of >75 cells/ μ L, the presence of polymorphonuclear leukocytes, or a protein concentration >1 g/L (>100 mg/dL) in CSF should raise concern that the patient may not have MS.

DIFFERENTIAL DIAGNOSIS

The possibility of an alternative diagnosis should always be considered (Table 444-4), particularly when (1) symptoms are localized exclusively to the posterior fossa, craniocervical junction, or spinal cord; (2) the patient is <15 or >60 years of age; (3) the clinical course is progressive from onset; (4) the patient has never experienced visual, sensory, or bladder symptoms; or (5) laboratory findings (e.g., MRI, CSF, or EPs) are atypical. Similarly, uncommon or rare symptoms in MS (e.g., aphasia, parkinsonism, chorea, isolated dementia, severe muscular atrophy, peripheral neuropathy, episodic loss of consciousness, fever, headache, seizures, or coma) should increase concern



FIGURE 444-3 Magnetic resonance imaging findings in multiple sclerosis (MS). *A*, Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. *B*, Sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) image in which the high signal of cerebrospinal fluid (CSF) has been suppressed. CSF appears dark, whereas areas of brain edema or demyelination appear high in signal, as shown here in the corpus callosum (arrows). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. *C*, Sagittal T2-weighted fast spin echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the midthoracic spinal cord. *D*, Sagittal T1-weighted image obtained after the intravenous administration of gadolinium DTPA reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (arrows).

about an alternative diagnosis. Diagnosis is also difficult in patients with a rapid or explosive (strokelike) onset or with mild symptoms and a normal neurologic examination. Rarely, intense inflammation and swelling may produce a mass lesion that mimics a primary or metastatic tumor. Disorders possibly mistaken for MS include: neuromyelitis optica (Chap. 437), sarcoidosis, vascular disorders (anti-phospholipid syndrome and vasculitis), rarely CNS lymphoma, and still more rarely infections such as syphilis or Lyme disease. The specific tests required to exclude alternative diagnoses will vary with each clinical situation; however, an erythrocyte sedimentation rate, serum B₁₂ level, antinuclear antibodies, and treponemal antibody should probably be obtained in all patients with suspected MS.

PROGNOSIS

Historically, most patients with MS ultimately experienced progressive neurologic disability. In older studies conducted before disease-modifying therapies for MS were available, 15 years after onset, only 20% of patients had no functional limitation, and between one-third and one-half of RMS patients progressed to SPMS and required

assistance with ambulation; furthermore, 25 years after onset, ~80% of MS patients reached this level of disability. The long-term prognosis for MS has improved substantially in recent years, and transition from RMS to SPMS now occurs at approximately a 1% annual rate compared with 2–3% in the pretreatment era. This improvement is almost certainly due, at least in part, to widespread use of disease-modifying therapies for RMS, and it is hoped that the prognosis will continue to improve as highly efficacious agents are increasingly employed early in the disease course.

Although the prognosis in an individual is difficult to establish, certain clinical features suggest a more favorable prognosis. These include ON or sensory symptoms at onset; fewer than two relapses in the first year of illness; and minimal impairment after 5 years. Predictors of an early aggressive course of the illness include older age at symptom onset and greater disability and the appearance of motor signs during the first year of the illness. By contrast, patients with truncal ataxia, action tremor, pyramidal symptoms, or a progressive disease course are more likely to become disabled. Patients with a long-term favorable course are likely to have developed fewer MRI lesions and have

TABLE 444-4 Disorders That Can Mimic Multiple Sclerosis (MS)

Acute disseminated encephalomyelitis (ADEM)
Antiphospholipid antibody syndrome
Behcet's disease
Cerebral autosomal-dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
Human immunodeficiency virus (HIV) infection
Ischemic optic neuropathy (arteritic and nonarteritic)
Lyme disease
Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
Neoplasms (e.g., lymphoma, glioma, meningioma)
Neuromyelitis optica
Sarcoidosis
Sjögren's syndrome
Stroke and ischemic cerebrovascular disease
Syphilis
Systemic lupus erythematosus and related collagen vascular disorders
Tropical spastic paraparesis (HTLV-1/2 infection)
Vascular malformations (especially spinal dural AV fistulas)
Vasculitis (primary CNS or other)
Vitamin B ₁₂ deficiency

Abbreviations: AV, arteriovenous; CNS, central nervous system; HTLV, human T-cell lymphotropic virus.

less brain atrophy during the early years of disease, and vice versa. Importantly, some MS patients have a benign variant of MS and never develop neurologic disability even when untreated. The likelihood of having benign MS is thought to be <10%. Patients with benign MS 15 years after onset who have entirely normal neurologic examinations are likely to maintain their benign course.

In patients with their first demyelinating event (i.e., a clinically isolated syndrome), the brain MRI provides prognostic information. With three or more typical T2-weighted lesions, the risk of developing MS after 20 years is ~80%. Conversely, with a normal brain MRI, the likelihood of developing MS is <20%. Similarly, the presence of two or more Gd-enhancing lesions at baseline is highly predictive of future MS, as is the appearance of either new T2-weighted lesions or new Gd enhancement ≥ months after the initial episode.

EFFECT OF PREGNANCY

Pregnant MS patients experience fewer attacks than expected during gestation (especially in the last trimester), but more attacks than expected in the first 3 months postpartum. When considering the pregnancy year as a whole (i.e., 9 months of pregnancy plus 3 months postpartum), the overall disease course is unaffected. Decisions about childbearing should thus be made based on (1) the mother's physical state, (2) her ability to care for the child, and (3) the availability of social support. Disease-modifying therapy is generally discontinued during pregnancy, although the actual risk from the interferons and glatiramer acetate (see below) appears to be low.

TREATMENT

Therapy for MS can be divided into several categories: (1) treatment of acute attacks, (2) treatment with disease-modifying agents that reduce the biologic activity of MS, and (3) symptomatic therapy. Treatments that promote remyelination or neural repair do not currently exist, but several promising approaches are being actively investigated.

The Expanded Disability Status Scale (EDSS) is a widely used measure of neurologic impairment in MS (Table 444-5). Most patients with EDSS scores <3.5 walk normally, and are generally not disabled; by contrast, patients with EDSS scores >4.0 have progressive MS (SPMS or PPMS), are gait-impaired, and often are occupationally disabled.

■ ACUTE ATTACKS OR INITIAL DEMYELINATING EPISODES

When patients experience acute deterioration, it is important to consider whether this change reflects new disease activity or a "pseudoexacerbation" resulting from an increase in ambient temperature, fever, or an infection. When the clinical change is thought to reflect a pseudoexacerbation, glucocorticoid treatment is inappropriate. Glucocorticoids are used to manage either first attacks or acute exacerbations. They provide short-term clinical benefit by reducing the severity and shortening the duration of attacks. Whether treatment provides any long-term benefit on the course of the illness is less clear. Therefore, mild attacks are often not treated. Physical and occupational therapy can help with mobility and manual dexterity.

Glucocorticoid treatment is usually administered as intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks. Orally administered methylprednisolone, prednisone, or dexamethasone (in equivalent dosages) can be substituted for the intravenous portion of the therapy. Outpatient treatment is almost always possible.

Side effects of short-term glucocorticoid therapy include fluid retention, potassium loss, weight gain, gastric disturbances, acne, and emotional lability. Concurrent use of a low-salt, potassium-rich diet and avoidance of potassium-wasting diuretics are advisable. Lithium carbonate (300 mg orally bid) may help manage emotional lability and insomnia associated with glucocorticoid therapy. Patients with a history of peptic ulcer disease may require cimetidine (400 mg bid) or ranitidine (150 mg bid). Proton pump inhibitors such as pantoprazole (40 mg orally bid) may reduce the likelihood of gastritis, especially when large doses are administered orally. Plasma exchange (five to seven exchanges: 40–60 mL/kg per exchange, every other day for 14 days) may benefit patients with fulminant attacks of demyelination that are unresponsive to glucocorticoids. However, the cost is high, and conclusive evidence of efficacy is lacking.

■ DISEASE MODIFYING THERAPIES FOR RELAPSING FORMS OF MS RMS, SPMS WITH EXACERBATIONS

Regulatory bodies have approved more than a dozen immunomodulatory and immunosuppressive agents for treatment of RMS. In phase 3 clinical trials, each was shown to reduce the frequency of clinical relapses and evolution of new brain MRI lesions in relapsing forms of MS (Table 444-6). Each can also be used in SPMS patients who continue to experience attacks, both because SPMS can be difficult to distinguish from relapsing MS and because the available clinical trials, although not all definitive, suggest that such patients may sometimes derive therapeutic benefit. Moreover, regulators now consider patients with recent relapses to be a "relapsing form of MS" regardless of whether these patients previously had progressive disability independent from relapses. When considering the data in Table 444-6, however, it is important to note that the relative efficacy of the different agents has not been directly tested in head-to-head studies and that cross-trial comparisons are inaccurate. However, given the increasingly complex landscape of therapeutics for MS, for convenience the discussion of these agents has been divided into those used more and less frequently; and also by an estimate of their relative (high, moderate, or modest) perceived level of efficacy. These are meant to serve as rough guides only, and considerable variance exists in practice patterns, as well as availability of these agents, in different parts of the world.

FREQUENTLY USED AGENTS FOR RMS

■ ANTI CD20 MONOCLONAL ANTIBODIES HIGHLY EFFECTIVE

Ocrelizumab is a humanized monoclonal antibody directed against the CD20 molecule present on the surface of mature B cells. CD20 is not expressed on early B-cell precursors or on antibody-producing plasma cells, thus treatment with ocrelizumab selectively depletes mature B cells while preserving preexisting humoral immunity and the capacity

TABLE 444-5 Scoring Systems for Multiple Sclerosis (MS)

Expanded Disability Status Scale (EDSS)

0.0 = Normal neurologic examination (all grade 0 in functional status [FS])	5.5 = Ambulatory without aid or rest for ~100 m
1.0 = No disability, minimal signs in one FS (i.e., grade 1)	6.0 = Unilateral assistance required to walk about 100 m with or without resting
1.5 = No disability, minimal signs in more than one FS (more than one grade 1)	6.5 = Constant bilateral assistance required to walk about 20 m without resting
2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1)	7.0 = Unable to walk beyond about 5 m even with aid; essentially restricted to wheelchair; wheels self and transfers alone
2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1)	7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer
3.0 = Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) although fully ambulatory	8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)	8.5 = Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
4.0 = Ambulatory without aid or rest for ~500 m	9.0 = Helpless bed patient; can communicate and eat
4.5 = Ambulatory without aid or rest for ~300 m	9.5 = Totally helpless bed patient; unable to communicate or eat
5.0 = Ambulatory without aid or rest for ~200 m	10.0 = Death due to MS
Functional Status (FS) Score	
A. Pyramidal functions	
0 = Normal	5 = Loss (essentially) of sensation in 1 or 2 limbs or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
1 = Abnormal signs without disability	6 = Sensation essentially lost below the head
2 = Minimal disability	E. Bowel and bladder functions
3 = Mild or moderate paraparesis or hemiparesis, or severe monoparesis	0 = Normal
4 = Marked paraparesis or hemiparesis, moderate quadriplegia, or monoplegia	1 = Mild urinary hesitancy, urgency, or retention
5 = Paraplegia, hemiplegia, or marked quadriplegia	2 = Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence
6 = Quadriplegia	3 = Frequent urinary incontinence
B. Cerebellar functions	4 = In need of almost constant catheterization
0 = Normal	5 = Loss of bladder function
1 = Abnormal signs without disability	6 = Loss of bowel and bladder function
2 = Mild ataxia	F. Visual (or optic) functions
3 = Moderate truncal or limb ataxia	0 = Normal
4 = Severe ataxia all limbs	1 = Scotoma with visual acuity (corrected) better than 20/30
5 = Unable to perform coordinated movements due to ataxia	2 = Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59
C. Brainstem functions	3 = Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99
0 = Normal	4 = Worse eye with marked decrease of fields and maximal acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
1 = Signs only	5 = Worse eye with maximal visual acuity (corrected) <20/200; grade 4 plus maximal acuity of better eye of ≤20/60
2 = Moderate nystagmus or other mild disability	6 = Grade 5 plus maximal visual acuity of better eye of ≤20/60
3 = Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves	G. Cerebral (or mental) functions
4 = Marked dysarthria or other marked disability	0 = Normal
5 = Inability to swallow or speak	1 = Mood alteration only (does not affect EDSS score)
D. Sensory functions	2 = Mild decrease in mentation
0 = Normal	3 = Moderate decrease in mentation
1 = Vibration or figure-writing decrease only, in 1 or 2 limbs	4 = Marked decrease in mentation
2 = Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in 1 or 2 limbs, or vibratory decrease alone in 3 or 4 limbs	5 = Chronic brain syndrome—severe or incompetent
3 = Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in 1 or 2 limbs, or mild decrease in touch or pain, and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs	
4 = Marked decrease in touch or pain or loss of proprioception, alone or combined, in 1 or 2 limbs or moderate decrease in touch or pain and/or severe proprioceptive decrease in >2 limbs	

Source: Adapted from JF Kurtzke: Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 33:1444, 1983.

for B-cell reconstitution by lymphoid stem cells. Ocrelizumab rapidly depletes circulating B cells through antibody-dependent cellular toxicity and complement-dependent cytotoxicity. The beneficial effects of B-cell depletion in MS may involve interruption in trafficking of B cells from the periphery to the CNS and reduction in antigen presentation and/or modulation of cytokine secretion by B cells (see “Immunology”, above). In two phase 3 trials, ocrelizumab demonstrated a

high degree of efficacy against RMS, reducing annualized relapse rates by 47%, reducing new MRI lesions by 95%, and improving other measures of inflammatory and degenerative disease activity, compared with three times per week interferon β-1a (Rebif). Ocrelizumab 600 mg is administered by intravenous infusion every 24 weeks (administered as two 300-mg infusions spaced 2 weeks apart for the first dose, and as a single 600-mg infusion thereafter); intravenous methylprednisolone

TABLE 444-6 Outcomes for FDA-Approved Therapies for Multiple Sclerosis^a

DOSE, ROUTE, AND SCHEDULE	STUDY DURATION (WEEKS)	COMPARATOR	CLINICAL OUTCOMES ^b		MRI OUTCOMES ^c	
			ATTACK RATE, MEAN	CHANGE IN DISEASE SEVERITY	NEW T2 LESIONS ^d	TOTAL BURDEN OF DISEASE
OCR, 600mg IV, Q6 mo	96	IFN-β-1a, 44 µg SC tiw	-46% ^{e,h}	-33% ^{e,h}	-80% ^{e,h}	NR
OFA	20 months ⁱ	TF 14 mg PO qd	-55% ^e	-34% ^j	-96% ^e	NR
NTZ, 300 mg IV qmo	96	PBO	-68% ^e	-42% ^e	-83% ^e	-18% ^e
FNG, 0.5 mg PO qd	96	PBO	-55% ^e	-34% ^j	-74% ^e	-23% ^e
FNG, 0.5 mg PO qd	48	IFN-β-1a, 30 µg IM qw	-52% ^e	NS	-35% ^e	NS
OZN, 1 mg PO qd	52	IFN-β-1a, 30 µg IM qw	-48% ^e	NS	-48% ^e	NR
OZN, 1 mg PO qd	104	IFN-β-1a, 30 µg IM qw	-38% ^e	NS	-42% ^e	NR
PNS, 20 mg PO qd	108	Teriflunomide 14 mg PO qd	-30% ^e	NS	-56% ^e	NR
DMF, 240 mg PO bid	96	PBO	-52% ^e	-40% ^j	-71% ^e	NR
IFN-β-1b, 250 µg SC qod	96	PBO	-34% ^e	-29% (NS)	-83% ^f	-17% ^e
IFN-β-1a, 30 µg IM qw	96	PBO	-18% ^g	-37% ^g	-36% ^f	NS
IFN-β-1a, 44 µg SC tiw	96	PBO	-32% ^e	-30% ^g	-78% ^e	-15% ^e
Peg- IFN-β-1a, 125 µg SC q2w	48	PBO	-36% ^e	-38% ^g	-67% ^e	-2% ^e
GA, 20 mg SC qd	96	PBO	-29% ^f	-12% (NS)	-38% ^f	-8% ^j
TF, 14 mg PO qd	96	PBO	-31% ^e	-26% ^g	-70% ^e	-20% ^g
CLAD 3.5 mg/kg PO	96	PBO	-43%	-23%	-73%	-24%
ALEM, 12mg/m ² IV/5d	104	IFN-β-1a, 44 µg SC tiw	-49% ^e	-42% ^j	-32% ^e	NS
MTX, 12 mg/m ² IV q3mo	96	PBO	-66% ^e	-75% ^g	-79% ^g	NR
Secondary Progressive MS						
SIP, 2 mg PO qd	12–36 months ⁱ	PBO	-55% ^e	-21% ^j	-81% ^e	-22% ^e
Primary Progressive MS						
OCR, 600 mg IV, Q6 mo	96	PBO	NR	-24% ^g	-92% ^e	-11% ^e

^aVariable duration study with median time in randomized controlled period of 20 months.

^bp = 0.002

^cPercentage reductions (or increases) have been calculated by dividing the reported rates in the treated group by the comparable rates in the placebo group, except for magnetic resonance imaging (MRI) disease burden, which was calculated as the difference in the median percent change between the treated and placebo groups.

^dSeverity = 1 point Expanded Disability Status Scale score progression, sustained for 3 months (in the IFN-β-1a 30 µg qw trial, this change was sustained for 6 months; in the IFN-β-1b trial, this was over 3 years). ^eDifferent studies measured these MRI measures differently, making comparisons difficult (numbers for new T2 represent the best-case scenario for each trial). ^fNew lesions seen on T2-weighted MRI. ^gp = .001. ^hp = .01. ⁱp = .05. ^jPooled analysis from OPERA 1 and 2 studies. ^kVariable duration study with median time in randomized controlled period of 18 months.

Abbreviations: ALEM, alemtuzumab; CLAD, cladribine; DMF, dimethyl fumarate; FDA, food and drug administration; FNG, fingolimod; GA, glatiramer acetate; IFN-β, interferon β; IM, intramuscular; IV, intravenous; MTX, mitoxantrone; NR, not reported; NS, not significant; NTZ, natalizumab; OFA, ofatumumab; OFF, ocrelizumab; OZN, ozanimod; PNS, ponemodip; PO, oral; q3mo, once every 3 months; qd, daily; qmo, once per month; qod, every other day; qw, once per week; qyr, once per year; SC, subcutaneous; SIP, siponimod; TF, teriflunomide; tiw, three times per week.

100 mg is given prior to each infusion and optional prophylaxis with analgesics/antipyretics and antihistamines is recommended, along with adjustment of the infusion rate to manage infusion-related reactions. Ocrelizumab is generally well tolerated with infusion-related reactions occurring in a minority of patients; these are most often observed with the first infusion and are usually mild in degree. Vaccination responses may be blunted in patients receiving ocrelizumab or other anti-CD20 based therapies; whenever possible, immunizations should be administered prior to initiating treatment, and live vaccines should not be given in actively treated patients.

Ofatumumab is a fully human anti-CD20 monoclonal antibody that can be self-administered at home by monthly 20 mg subcutaneous injection, after initial 20-mg loading doses on days 1, 7, and 14. Two pivotal phase 3 trials demonstrated superiority of ofatumumab tested against teriflunomide with an efficacy profile against relapses similar to ocrelizumab, reduction of new MRI lesions by 95%, reduction of disability, and lowering of serum neurofilament light chain levels, a biomarker of neuronal damage. A high degree of safety was also observed in the trials.

Rituximab, another anti-CD20 antibody, was tested against MS in preliminary trials, and appears also to be highly effective based on numerous reports of real-world experience with this agent; rituximab (1g IV Q6 mo) is used in some settings despite lack of pivotal

trial data. Rituximab is associated with a very small risk (estimated at <1:25,000/year) of progressive multifocal leukoencephalopathy (PML), a life-threatening condition resulting from infection by the John Cunningham (JC) virus, thus it is possible that ocrelizumab and ofatumumab will also carry a nonzero risk.

■ NATALIZUMAB HIGHLY EFFECTIVE

Natalizumab is a humanized monoclonal antibody directed against the α4 subunit of α4β1 integrin, a cellular adhesion molecule expressed on the surface of lymphocytes. It prevents lymphocytes from binding to endothelial cells, thereby preventing lymphocytes from penetrating the BBB and entering the CNS. Natalizumab is highly effective in reducing the attack rate and significantly improves all measures of disease severity in MS (both clinical and MRI). Moreover, it is well tolerated, and the dosing schedule of monthly intravenous infusions makes it convenient for patients. Natalizumab, 300 mg, is administered by IV infusion each month. Treatment is, in general, well tolerated. A small percentage (<10%) of patients experience hypersensitivity reactions (including anaphylaxis), and ~6% develop neutralizing antibodies to the molecule (only half of which persist).

The major concern is risk for PML, occurring in ~0.4% of patients treated with natalizumab. The incidence of PML is very low in the first year of treatment but then rises in subsequent years of treatment to

reach a level of about 2 cases per 1000 patients per year. Nevertheless, the measurement of antibodies against the JC virus in the serum can be used to stratify this risk. Approximately half of the adult population is JC antibody positive, indicating that they experienced an asymptomatic infection with the JC virus at some time in the past. Thus, in patients who do not have these antibodies, the risk of PML is minimal (<1:10,000 as long as they remain JC antibody free). Conversely, in patients who have these antibodies (especially those who have them in high titer), the risk may be as high as $\geq 1\%$. Up to 2% of seronegative MS patients undergoing treatment with natalizumab seroconvert annually; thus, it is recommended that JC antibody status be assessed at 6-month intervals in all patients receiving natalizumab. In antibody-positive patients, a change to another disease-modifying therapy should be strongly considered. The risk of PML is also high in patients who previously received immunosuppressive therapy. Natalizumab is generally recommended only for JC antibody-negative patients, unless they have failed alternative therapies or if they have a particularly aggressive disease course.

■ S1P RECEPTOR MODULATORS MODERATELY EFFECTIVE

Fingolimod is a sphingosine-1-phosphate (S1P) modulator that prevents the egress of lymphocytes from secondary lymphoid organs such as the lymph nodes and spleen. Fingolimod binds to S1P1, S1P3, S1P4, and S1P5 receptors. Its mechanism of action is probably due to sequestration of lymphocytes in the periphery, thereby inhibiting their trafficking to the CNS. Fingolimod reduces the attack rate and significantly improves all measures of disease severity in MS. It is well tolerated, and the daily oral dosing schedule makes it convenient for patients. A head-to-head phase 3 randomized study demonstrated the superiority of fingolimod over low-dose (weekly) IFN- β -1a. Fingolimod, 0.5 mg, is administered orally each day. Mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia) are more common than in controls, sometimes requiring discontinuation of the medication. First- and second-degree heart block and bradycardia can also occur when fingolimod therapy is initiated. A 6-h period of observation (including electrocardiogram monitoring) is recommended for all patients receiving their first dose. Other side effects include macular edema and, rarely, disseminated varicella-zoster virus (VZV) and cryptococcal infections; prior to initiating therapy with fingolimod, an ophthalmic examination and VZV vaccination for seronegative individuals are indicated. Fingolimod can also cause QT prolongation with the potential for drug-drug interactions with other medications that also prolong the QT interval.

Ozanimod is a S1P1- and S1P5-selective S1P inhibitor that, like fingolimod, prevents the egress of lymphocytes from secondary lymphoid organs. Ozanimod was shown to be superior to low-dose (weekly) IFN- β -1a in preventing relapses and new lesion formation on brain MRI. Because ozanimod binds only weakly to S1P3 receptors, cardiac conduction-related side effects, such as QT prolongation and secondary-degree heart block that are associated with modulation of myocardial S1P3 receptors, are not associated with ozanimod. An up-titration scheme is used when starting this medication to reduce the risk of transient decreases in heart rate and atrioventricular conduction delays that may occur after the first dose. In contrast to fingolimod, cardiovascular monitoring is not required during first-dose administration in most patients. Ozanimod was not studied in patients with severe untreated sleep apnea, class III/IV heart failure, significant cardiac conduction disorders, or in those who experienced thromboembolic events in the last 6 months, and is relatively contraindicated in these patients. Patients starting ozanimod should undergo a CBC, LFTs, ECG, and eye examination before starting therapy. Infections and hypertension should be monitored for during treatment. Live vaccines should be avoided during treatment and for 3 months after discontinuation.

Ponesimod is a S1P1-selective modulator. Ponesimod was shown to be superior to teriflunomide in preventing relapses and new MRI lesion formation. An up-titration scheme is used when starting this medication to reduce the risk of transient decreases in heart rate and atrioventricular conduction delays that may occur after the first dose.

A 4-h first-dose observation period with cardiovascular monitoring is necessary in patients whose resting heart rate is <55 beats/min. Ponesimod is contraindicated in patients who have in the prior 6 months experienced stroke, heart attack, unstable angina, class III or IV decompensated heart failure or have a Mobitz type II or greater degree of heart block without a pacemaker. Patients should undergo a CBC, LFTs, ECG, and eye examination before starting therapy, and be monitored for infections and hypertension during treatment. Live vaccines should be avoided during treatment.

■ DIMETHYL FUMARATE MODERATELY EFFECTIVE

Dimethyl fumarate (DMF) is a small-molecule and a Krebs cycle metabolite with anti-inflammatory effects. DMF is metabolized to the active compound monomethyl fumarate. Although the precise mechanisms of action are not fully understood, it seems to modulate the expression of proinflammatory and anti-inflammatory cytokines. Also, DMF inhibits the ubiquitylation and degradation of nuclear factor E2-related factor 2 (Nrf2)—a transcription factor that binds antioxidant response elements (AREs) located on DNA and induces transcription of several antioxidant proteins. DMF reduces the attack rate and significantly improves all measures of disease severity in MS patients. However, its twice-daily oral dosing schedule makes it somewhat less convenient for patients than daily oral therapies. In addition, compliance is likely to be less with a twice-daily dosing regimen—a factor that could be of concern given the observation (in a small clinical trial) that once-daily DMF lacks efficacy. A head-to-head trial provided evidence that DMF was superior to glatiramer acetate on some outcome measures. DMF, 240 mg, is administered orally twice each day. Gastrointestinal side effects (abdominal discomfort, nausea, vomiting, flushing, and diarrhea) are common at the start of therapy but generally subside with continued administration. Other adverse events include flushing, mild decreases in neutrophil and lymphocyte counts, and elevations in liver enzymes. Nevertheless, in general, treatment with DMF is well tolerated after an initial period of adjustment. Following the release of DMF, several cases of PML were reported in patients receiving products that contained DMF. Most of these patients were lymphopenic and monitoring for lymphopenia every 6 months is recommended. Patients who are persistently lymphopenic (lymphocyte count <500 cells/mL) are recommended to consider alternate treatments due to the PML risk. Clinically significant liver injury has been reported with DMF treatment. Liver function tests should be assessed before treatment and when clinically indicated. Elevations in liver function tests resolve following treatment discontinuation.

Diroximel fumarate is, like DMF, metabolized to monomethyl fumarate. The efficacy of diroximel fumarate is based upon bioavailability studies in patients with RMS and healthy subjects. The adverse event profile and monitoring requirements are the same as with DMF.

■ GLATIRAMER ACETATE MODESTLY EFFECTIVE

Glatiramer acetate is a synthetic, random polypeptide composed of four amino acids (L-glutamic acid, L-lysine, L-alanine, and L-tyrosine). Its mechanism of action may include (1) induction of antigen-specific suppressor T cells; (2) binding to MHC molecules, thereby displacing bound MBP; or (3) altering the balance between proinflammatory and regulatory cytokines. Glatiramer acetate reduces the attack rate (whether measured clinically or by MRI) in RRMS. Glatiramer acetate also benefits disease-severity measures, although, for clinical disability, this is less well established than for IFN- β . Nevertheless, two head-to-head trials demonstrated that the impact of glatiramer acetate on clinical relapse rates and disability was comparable to high-dose, high-frequency IFN- β . Therefore, glatiramer acetate should be considered as an equally effective alternative to IFN- β in RRMS patients. Its usefulness in progressive disease is unknown. Glatiramer acetate is administered by subcutaneous injection of either 20 mg every day or 40 mg thrice weekly. Injection-site reactions can occur. In addition, ~15% of patients experience one or more episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety after injection. This systemic reaction is unpredictable, brief (duration <1 h), and tends not to recur. Finally, some

patients experience lipoatrophy, which, on occasion, can be disfiguring and require cessation of treatment. Recently, glatiramer acetate was U.S. Food and Drug Administration (FDA) approved as a biosimilar medication (Glatopa) and is dosed at 20 mg every day. Although clinical trials were not performed with biosimilar glatiramer acetate, the efficacy and safety are presumed to be similar to the branded product.

■ INTERFERON β MODESTLY EFFECTIVE

Interferon β (IFN- β) is a class I interferon originally identified by its antiviral properties. Efficacy in MS probably results from immunomodulatory properties including: (1) downregulating expression of MHC molecules on antigen-presenting cells, (2) reducing proinflammatory and increasing regulatory cytokine levels, (3) inhibiting T-cell proliferation, and (4) limiting the trafficking of inflammatory cells in the CNS. IFN- β reduces the attack rate, and slows accumulation of disability and MRI-documented disease burden. IFN- β should be considered in patients with either relapsing forms of MS (either RRMS or SPMS with superimposed relapses). Head-to-head trials suggest that dosing IFN- β more frequently and at higher doses has better efficacy but is also more likely to induce neutralizing antibodies (see below). IFN- β -1a (Avonex), 30 μ g, is administered by intramuscular injection once every week. IFN- β -1a (Rebif), 44 μ g, is administered by subcutaneous injection three times per week. IFN- β -1b (Betaseron or Extavia), 250 μ g, is administered by subcutaneous injection every other day. Pegylated IFN- β -1a (Plegridy), 125 μ g, is administered by subcutaneous injection once every 14 days. Pegylated IFN- β -1a is an interferon to which a single, linear 20,000 dalton methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde molecule is covalently attached; the pegylated molecule contributes to reduced in vivo clearance allowing less frequent administration. Common side effects of IFN- β therapy include flulike symptoms (e.g., fevers, chills, and myalgias) and mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia). Rarely, more severe hepatotoxicity may occur. Subcutaneous IFN- β also causes reactions at the injection site (e.g., pain, redness, induration, or, rarely, skin necrosis). Side effects can usually be managed with concomitant nonsteroidal anti-inflammatory medications. Depression, increased spasticity, and cognitive changes have been reported, although these symptoms can also be due to the underlying disease. Side effects due to IFN- β therapy usually subside over time. Rates of serious infection are lower with IFN- β therapy than many other disease-modifying medications.

Approximately 2–10% of IFN- β -1a (Avonex) recipients, 15–25% of IFN- β -1a (Rebif) recipients, and 30–40% of IFN- β -1b (Betaseron/Extavia) recipients develop neutralizing antibodies to IFN- β , which may disappear over time. Less than 1% of patients treated with pegylated IFN- β -1a develop neutralizing antibodies. For a patient doing well on therapy, the presence of antibodies should not affect treatment. Conversely, for a patient doing poorly on therapy, alternative treatment should be considered, even if there are no detectable antibodies.

LESS COMMONLY USED AGENTS FOR RMS

■ TERIFLUNOMIDE MODESTLY EFFECTIVE

Teriflunomide inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase, which is a key part of the pathway for de novo pyrimidine biosynthesis from carbamoyl phosphate and aspartate. It is the active metabolite of the drug leflunomide (FDA-approved for rheumatoid arthritis), and it exerts its anti-inflammatory effects by limiting the proliferation of rapidly dividing T and B cells. This enzyme is not involved in the so-called salvage pathway, by which existing pyrimidine pools are recycled for DNA and RNA synthesis in resting and homeostatically proliferating cells. Consequently, teriflunomide is considered to be cytostatic rather than cytotoxic. Teriflunomide reduces the attack rate and significantly improves all measures of disease severity in MS patients. It is well tolerated, and its daily oral dosing schedule makes it very convenient for patients. A head-to-head trial suggested the equivalence, but not superiority, of teriflunomide and thrice-weekly IFN- β -1a. Teriflunomide, either 7 or 14 mg, is administered orally each day. In the pivotal clinical trials, mild hair thinning and gastrointestinal

symptoms (nausea and diarrhea) were more common than in controls, but in general, treatment with teriflunomide was well tolerated. Teriflunomide rarely causes toxic epidermal necrolysis or Stevens-Johnson syndrome. A major limitation, especially in women of childbearing age, is its possible teratogenicity (pregnancy category X); teriflunomide can remain in the bloodstream for 2 years due to hepatobiliary reabsorption. Therefore, it is recommended that exposed men and women who wish to conceive receive cholestyramine or activated charcoal to eliminate residual drug.

■ CLADRBINE MODERATELY EFFECTIVE

Cladribine is a prodrug that when phosphorylated by deoxycytidine kinase to its metabolite 2-chlorodeoxyadenosine becomes active and is incorporated into nuclear and mitochondrial DNA causing apoptosis. Because deoxycytidine kinase is expressed at high levels in lymphocytes, cladribine can be administered as a relatively specific lymphotoxic therapy. In intravenous or subcutaneously administered forms, cladribine is indicated for treatment of hairy cell leukemia. Cladribine's oral formulation is indicated for treatment of relapsing forms of MS including active SPMS. Cladribine reduces the attack rate and disability measures in RMS patients. It is well tolerated, and is dosed based on body weight (3.5 mg/kg divided into 2 yearly treatment courses). Patients are treated with 1 or 2 doses of cladribine daily for 4 or 5 consecutive days, receive a second similar cycle of treatment 23 to 27 days after the first cycle, and then are retreated after 1 year. Cladribine has beneficial effects in MS that are sustained beyond the 2-year course of administration. The basis for these benefits is poorly understood but is presumably related to immune reconstitution by nonpathogenic lymphocytes. Cladribine is associated with malignancy, including in the MS clinical trials, and for this reason is not recommended in treatment-naïve patients. Cladribine is also contraindicated in pregnant women because it is a known teratogen in animals and can cause embryolethality. Despite cladribine's relatively short terminal half-life of 1 day, women and men treated with cladribine are recommended to not plan conception for 6 months after the last dose. Prior to treatment, patients should undergo a complete blood count including lymphocyte count and liver function tests; be screened for HIV, tuberculosis, and hepatitis B and C; be vaccinated for varicella zoster virus; and undergo a brain MRI within 3 months of treatment because of a presumed risk of treatment-emergent PML.

■ ALEMKTUZUMAB HIGHLY EFFECTIVE

Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen that is expressed on both monocytes and lymphocytes. It causes lymphocyte depletion (of both B and T cells) and a change in the composition of lymphocyte subsets. Both of these changes, particularly the impact on lymphocyte subsets, are long lasting. In two phase 3 trials, which used the active comparator of thrice-weekly, high-dose IFN- β -1a, alemtuzumab markedly reduced the attack rate and significantly improved measures of disease severity in MS patients although its impact on clinical disability was found in only one of the two trials. The European and Canadian drug agencies were the first to approve this agent for use in RRMS; the FDA has also approved alemtuzumab, but only after an appeal following initial disapproval. The reasons for initial disapproval were based on a perceived lack of a convincing disability effect and concerns over potential toxicity. The toxicities of concern were the occurrence of (1) autoimmune diseases including thyroiditis, Graves' disease, thrombocytopenia, hemolytic anemia, pancytopenia, antiglomerular basement membrane disease, and membranous glomerulonephritis; (2) malignancies including thyroid cancer, melanoma, breast cancer, human papillomavirus (HPV)-related cancers, and lymphoproliferative disorders including lymphoma; (3) serious infections; and (4) infusion reactions. Because of its toxicity profile, alemtuzumab is indicated by the U.S. FDA only in patients who have tried and failed at least two other DMTs.

■ MITOXANTRONE HYDROCHLORIDE

HIGHLY EFFECTIVE

Mitoxantrone, an anthracenedione, exerts its antineoplastic action by (1) intercalating into DNA and producing both strand breaks

and interstrand cross-links, (2) interfering with RNA synthesis, and (3) inhibiting topoisomerase II (involved in DNA repair). The FDA approved mitoxantrone on the basis of a single phase 3 clinical trial in Europe, in addition to even smaller phase 2 studies. Mitoxantrone is indicated for use in patients with rapidly worsening MS (defined as patients whose neurologic status remains significantly abnormal between MS attacks). Despite this broad indication, however, data supporting its efficacy are less robust compared to other approved therapies. Mitoxantrone is cardiotoxic (e.g., cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure). As a result, a cumulative dose >140 mg/m² is not recommended. At currently approved doses (12 mg/m² every 3 months), the maximum duration of therapy can be only 2–3 years. Furthermore, >40% of women will experience amenorrhea, which may be permanent. Finally, there is risk of acute leukemia from mitoxantrone, estimated as at least a 1.4% lifetime risk. Because of these risks, and the availability of alternative therapies, mitoxantrone is now rarely used for MS.

DECISION MAKING FOR TREATMENT OF RMS

First-line therapy should be initiated in patients with a clinically isolated syndrome at high risk for MS or in patients diagnosed with RMS (according to 2017 McDonald criteria).

We favor use of the most highly effective DMTs as first-line options for most patients with active MS, rather than the more traditional “treat to target” approach in which a treatment of modest or moderate effectiveness is first used, and therapy advanced to a more effective agent when breakthrough disease (evident clinically or by MRI) occurs. As noted above, observational studies suggest that early use of high-efficacy therapy could improve long-term outcomes. For many patients, we begin with an anti-CD20 agent, either ocrelizumab or ofatumumab, or with natalizumab in JCV-negative patients. Anti-CD20 agents are attractive given their high level of efficacy, relative ease of use, favorable safety profile, and absence of rebound following discontinuation. For patients who prefer oral treatment, either an SIP modulator or fumarate is also reasonable for first-line therapy.

Switching DMTs may be required in the following situations: suboptimal response, experiencing more than one relapse with active MRI scans while on treatment, and safety issues including development of persistent high-titer neutralizing antibodies in patients receiving IFN-β. Discontinuation of DMTs is required in cases of serious adverse events that may be drug-related and for many DMTs in women who become pregnant while on treatment. Exceptions to this practice include glatiramer acetate that can be continued during pregnancy, and in some cases prior use of ocrelizumab, alemtuzumab, and cladribine that have prolonged pharmacodynamic effects that persist after the drug has been eliminated.

For patients who present with a mild initial course—e.g., normal examination or minimal impairment (EDSS ≤ 2.5) and low disease activity by MRI—either an oral (fumarates, SIP modulators, teriflunomide) or injectable (IFN-β or glatiramer acetate) agent can be considered. The injectable agents (IFN-β and glatiramer acetate) have a superb long-term track record for safety but have a high nuisance factor due to the need for frequent injections, as well as bothersome side effects that contribute to noncompliance.

The safety and value of combination therapy is also largely unknown and is generally not recommended. One clinical trial demonstrated no added benefit to the combination of glatiramer acetate with once-weekly IFN-β-1a. The optimal duration of therapy is also unknown.

The long-term impact of these treatments on the disease course remains controversial, although as noted above (“Prognosis”) several observational studies showed that these agents improve the long-term outcome of MS including a prolongation of the time to reach certain disability outcomes (e.g., SPMS and requiring assistance to ambulate) and reduction in MS-related mortality. These benefits seem most conspicuous when treatment begins early in the relapsing stage of the illness. It may be reasonable to delay initiating treatment in patients with (1) normal neurologic examinations, (2) a single attack or a low attack frequency, and (3) a low burden of disease as assessed by brain MRI. Untreated patients, however, should be followed closely with periodic brain MRI scans; the

need for therapy is reassessed if scans reveal evidence of ongoing, sub-clinical disease. Finally, vitamin D deficiency should be corrected in all patients with MS, and generally this requires oral supplementation with vitamin D3, 4000 IU daily. Several clinical trials showed that supplementation with vitamin D in relapsing MS patients reduces MRI measures of disease activity and may also reduce the relapse frequency in patients actively treated with either interferon or glatiramer acetate.

DISEASE MODIFYING THERAPIES FOR PROGRESSIVE MS

■ SPMS

Siponimod is a selective S1P1 S1P5 receptor modulator (see SIP receptor modulators above) that was shown in a single phase 3 study to be superior to placebo in reducing the risk of progression in SPMS patients. Siponimod also reduced the risk of relapse and MRI measures of the burden of disease. Subgroup analysis showed that patients with a relapse in the 2 years prior to treatment and those with contrast-enhancing lesions on brain MRI received the most therapeutic benefit. Siponimod was subsequently approved for patients with SPMS who had active disease. Siponimod is dosed based on CYP2C9 genotype. For patients with CYP2C9 1/3 or 2/3, siponimod is administered as 1 mg daily. Siponimod dosage is reduced in patients with the CYP2C9 3/3 genotype (<0.5% of the population) due to substantially elevated drug levels. Prior to treatment patients should undergo a complete blood count, ophthalmic evaluation, electrocardiogram, liver function tests, and vaccination for varicella zoster virus. Unlike fingolimod, first-dose monitoring is required only in patients with sinus bradycardia, first- or second-degree heart block, or a history of myocardial infarction or heart failure.

Ocrelizumab, cladribine, and ponesimod are also indicated in active SPMS although none of these therapies were specifically studied in this patient population. High-dose IFN-β probably has a modest beneficial effect in patients with SPMS with active disease (see above). IFN-β is probably ineffective in patients with SPMS who do not have active disease. Although mitoxantrone was approved for patients with rapidly progressive MS, this is not the population studied in the pivotal trial; therefore, no evidence-based recommendation can be made with regard to its use in this setting.

■ PPMS

Ocrelizumab (see above) was shown in a phase 3 trial to reduce progression of clinical disability in PPMS by 24%, and also to improve other clinical and MRI markers of inflammatory and degenerative disease activity. Ocrelizumab represents the first agent to convincingly modify the course of PPMS. The dosing of ocrelizumab for PPMS is identical as for RMS (above).

■ OFF LABEL TREATMENT OPTIONS FOR RMS AND SPMS

Azathioprine (2–3 mg/kg per day) has been used primarily in relapsing MS. Meta-analysis of published trials suggests that azathioprine is marginally effective at lowering relapse rates, although a benefit on disability progression has not been demonstrated.

Methotrexate (7.5–20 mg/week) was shown in one study to slow the progression of upper-extremity dysfunction in SPMS. Because of the possibility of developing irreversible liver damage, some experts recommend a blind liver biopsy after 2 years of therapy.

Cyclophosphamide (700 mg/m², every other month) may be helpful for treatment-refractory patients who are (1) otherwise in good health, (2) ambulatory, and (3) <40 years of age. Because cyclophosphamide can be used for periods in excess of 3 years, it may be preferable to mitoxantrone in these circumstances.

Intravenous immunoglobulin (IVIg), administered in monthly pulses (up to 1 g/kg) for up to 2 years, appears to reduce annual exacerbation rates. However, its use is limited because of its high cost, questions about optimal dose, and uncertainty about its having any impact on long-term disability.

Methylprednisolone in one study, administered as monthly high-dose intravenous pulses, reduced disability progression (see above).

Autologous hematopoietic stem cell transplantation appears to be highly effective in reducing the occurrence of relapses and may improve disability in relapsing MS. It appears to be ineffective for patients with progressive MS. Stem cell transplantation also carries significant risk, and randomized trials with appropriate comparators are needed in order to position this procedure with respect to available pharmacologic interventions.

PROMISING EXPERIMENTAL THERAPIES

Numerous clinical trials of promising experimental therapies are currently underway. These include studies of molecules to promote remyelination; autologous hematopoietic stem cell transplantation; higher doses of ocrelizumab; and selective kinase inhibitors including Bruton's tyrosine kinase (BTK).

OTHER THERAPEUTIC CLAIMS

Many purported treatments for MS have never been subjected to scientific scrutiny. These include dietary therapies (e.g., the Swank diet, the Paleo diet, the Wahls diet), megadose vitamins, calcium orotate, bee stings, cow colostrum, hyperbaric oxygen, procarin (a combination of histamine and caffeine), chelation, acupuncture, acupressure, various Chinese herbal remedies, and removal of mercury-amalgam tooth fillings, among many others. Patients should avoid costly or potentially hazardous unproven treatments. Many such treatments lack biologic plausibility. No reliable case of mercury poisoning resembling typical MS has ever been described, therefore challenging the notion that removal of mercury-amalgam tooth fillings would be beneficial. Although potential roles for EBV, human herpesvirus (HHV) 6, or chlamydia have been suggested for MS, treatment with antiviral agents or antibiotics is not recommended. A chronic cerebrospinal insufficiency (CCSVI) was proposed as a cause of MS with vascular-surgical intervention recommended. However, multiple independent studies have failed to even approximate the initial claims, and patients should be strongly advised to avoid diagnostic procedures and potentially dangerous surgery for this condition. A double-blind trial of high-dose biotin to improve disability in progressive forms of MS found no benefit.

SYMPTOMATIC THERAPY

For all patients, it is important to encourage attention to a healthy lifestyle, including maintaining an optimistic outlook, a healthy diet, and regular exercise as tolerated (swimming is often well-tolerated because of the cooling effect of cold water). It is reasonable also to correct vitamin D deficiency with oral vitamin D.

Ataxia/tremor is often intractable. Clonazepam, 1.5–20 mg/d; primidone, 50–250 mg/d; propranolol, 40–200 mg/d; or ondansetron, 8–16 mg/d, may help. Wrist weights occasionally reduce tremor in the arm or hand. Thalamotomy and deep-brain stimulation have been tried with mixed success.

Spasticity and *spasms* may improve with physical therapy, regular exercise, and stretching. Avoidance of triggers (e.g., infections, fecal impactions, bed sores) is extremely important. Effective medications include baclofen (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydrochloride (10–60 mg/d). For severe spasticity, a baclofen pump (delivering medication directly into the CSF) can provide substantial relief.

Weakness can sometimes be improved with the use of potassium channel blockers such as 4-aminopyridine (20 mg/d) and 3,4-di-aminopyridine (40–80 mg/d), particularly in the setting where lower-extremity weakness interferes with the patient's ability to ambulate. The FDA approved extended-release 4-aminopyridine (at 10 mg twice daily), and this can be obtained either as dalfampridine (Ampyra) or through a compounding pharmacy. The principal concern with the use of these agents is the possibility of inducing seizures at high doses.

Pain is treated with anticonvulsants (carbamazepine, 100–1000 mg/d; phenytoin, 300–600 mg/d; gabapentin, 300–3600 mg/d; or pregabalin, 50–300 mg/d), antidepressants (amitriptyline, 25–150 mg/d; nortriptyline, 25–150 mg/d; desipramine, 100–300 mg/d; or venlafaxine, 75–225 mg/d), or antiarrhythmics (mexiletine, 300–900 mg/d). If these approaches fail, patients should be referred to a comprehensive pain-management program.

Bladder dysfunction management is best guided by urodynamic testing. Evening fluid restriction or frequent voluntary voiding may help *detrusor hyperreflexia*. If these methods fail, propantheline bromide (10–15 mg/d), oxybutynin (5–15 mg/d), hyoscyamine sulfate (0.5–0.75 mg/d), tolterodine tartrate (2–4 mg/d), or solifenacina (5–10 mg/d) may help. Coadministration of pseudoephedrine (30–60 mg) is sometimes beneficial.

Detrusor/sphincter dyssynergia may respond to phenoxybenzamine (10–20 mg/d) or terazosin hydrochloride (1–20 mg/d). Loss of reflex bladder wall contraction may respond to bethanechol (30–150 mg/d). However, both conditions often require catheterization.

Urinary tract infections should be treated promptly. Patients with postvoid residual urine volumes >200 mL are predisposed to infections. Prevention by urine acidification (with cranberry juice or vitamin C) inhibits some bacteria. Prophylactic administration of antibiotics is sometimes necessary but may lead to colonization by resistant organisms. Intermittent catheterization may help to prevent recurrent infections and reduce overflow incontinence.

Treatment of *constipation* includes high-fiber diets and fluids. Natural or other laxatives may help. *Fecal incontinence* may respond to a reduction in dietary fiber.

Depression should be treated. Useful drugs include the selective serotonin reuptake inhibitors (fluoxetine, 20–80 mg/d, or sertraline, 50–200 mg/d), the tricyclic antidepressants (amitriptyline, 25–150 mg/d; nortriptyline, 25–150 mg/d; or desipramine, 100–300 mg/d), and the nontricyclic antidepressants (venlafaxine, 75–225 mg/d).

Fatigue may improve with assistive devices, help in the home, or successful management of spasticity. Patients with frequent nocturia may benefit from anticholinergic medication at bedtime. Excessive daytime somnolence caused by MS may respond to amantadine (200 mg/d), methylphenidate (5–25 mg/d), modafinil (100–400 mg/d), or armodafinil (150–250 mg/d).

Cognitive problems may respond marginally to lisdexamfetamine (40 mg/d).

Paroxysmal symptoms respond dramatically to low-dose anticonvulsants (acetazolamide, 200–600 mg/d; carbamazepine, 50–400 mg/d; phenytoin, 50–300 mg/d; or gabapentin, 600–1800 mg/d).

Heat sensitivity may respond to heat avoidance, air-conditioning, or cooling garments.

Sexual dysfunction may be helped by lubricants to aid in genital stimulation and sexual arousal. Management of pain, spasticity, fatigue, and bladder/bowel dysfunction may also help. Sildenafil (50–100 mg), tadalafil (5–20 mg), or vardenafil (5–20 mg), taken 1–2 h before sex, are standard treatments for erectile dysfunction.

CLINICAL VARIANTS OF MS

Acute MS (Marburg's variant) is a fulminant demyelinating process that in some cases progresses inexorably to death within 1–2 years. Typically, there are no remissions. Marburg's variant does not seem to follow infection or vaccination, and it is unclear whether this syndrome represents an extreme form of MS or another disease altogether. When an acute demyelinating syndrome presents as a solitary expansile lesion, a brain tumor is often suspected (Fig. 444-4). Such cases are designated tumefactive MS, and a brain biopsy may be required to establish the diagnosis.

Balo's concentric sclerosis is another fulminant demyelinating syndrome characterized by concentric brain or spinal cord lesions with alternating spheres of demyelination and remyelination (Fig. 444-4). For these fulminant demyelinating states, no controlled trials of therapy exist; high-dose glucocorticoids, plasma exchange, and cyclophosphamide have been tried, with uncertain benefit.

ACUTE DISSEMINATED ENCEPHALOMYELITIS ADEM

DEM has a monophasic course and is most frequently associated with an antecedent infection (postinfectious encephalomyelitis); ~5% of DEM cases follow immunization (postvaccinal encephalomyelitis). DEM is far more common in children than adults, and many adult cases initially thought to represent DEM subsequently experience

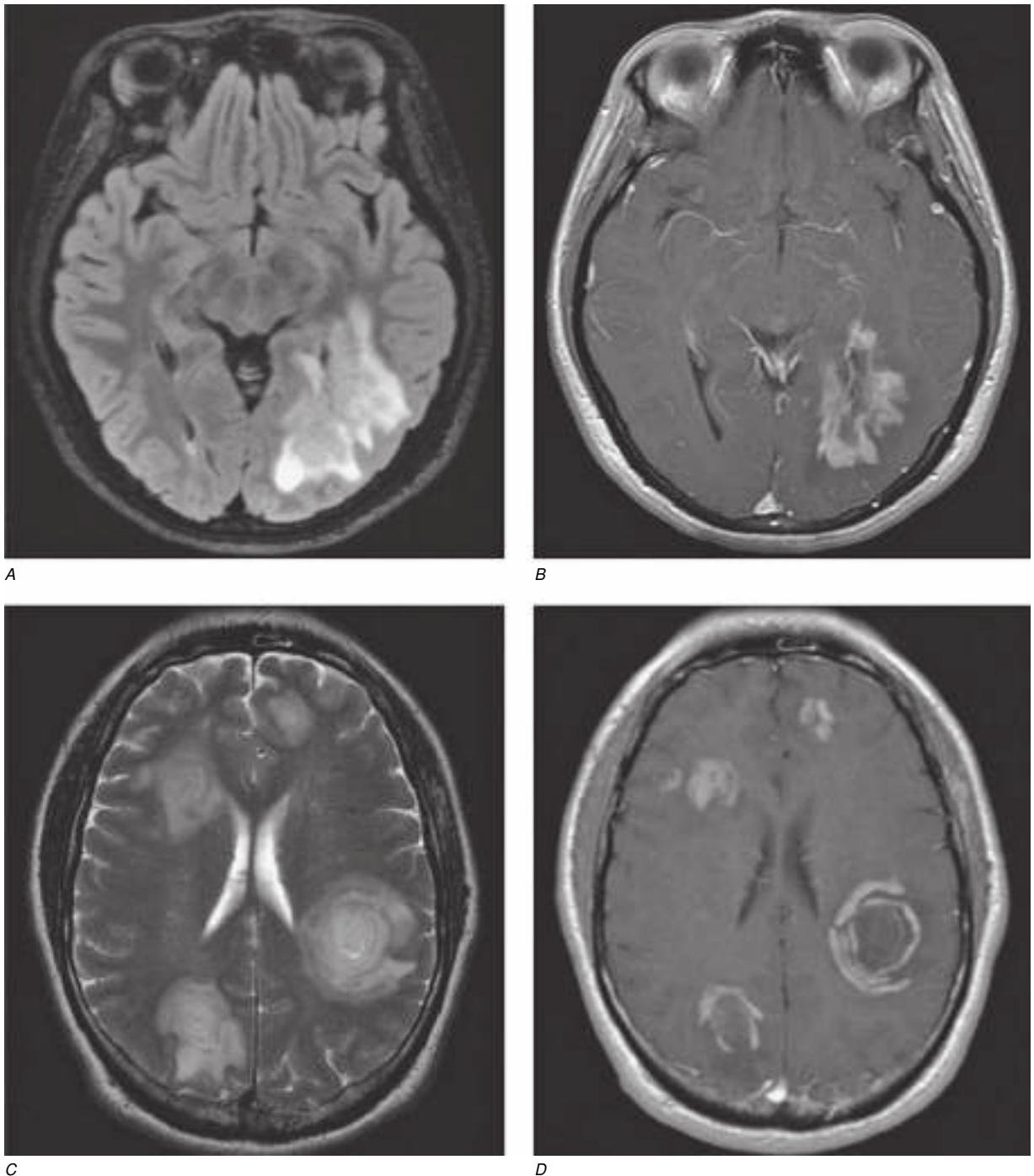


FIGURE 444-4 Magnetic resonance imaging findings in variants of MS. *A* and *B*, Acute tumefactive MS. In *A*, a sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) image of a large solitary right parieto-occipital white matter lesion is shown, with effacement of overlying cortical sulci consistent with mass effect. In *B*, T1-weighted image obtained after the intravenous administration of gadolinium DTPA reveals a large serpiginous area of blood-brain barrier disruption consistent with acute inflammation. *C* and *D*, Balo's concentric sclerosis. In *C*, an axial T2-weighted sequence shows multiple areas of abnormal ovoid bright signal in the supratentorial white matter bilaterally; some lesions reveal concentric layers, typical of Balo's concentric sclerosis. In *D*, T1-weighted MR images postgadolinium demonstrate abnormal enhancement of all lesions with some lesions demonstrating concentric ring enhancement.

late relapses qualifying as either MS or another chronic inflammatory disorder such as vasculitis, sarcoidosis, or lymphoma. The hallmark of ADEM is the presence of widely scattered foci of perivenular inflammation and demyelination that can involve both white matter and grey matter structures, in contrast to larger confluent white matter lesions typical of MS. In the most explosive form of ADEM, acute hemorrhagic

leukoencephalitis, the lesions are vasculitic and hemorrhagic, and the clinical course is devastating.

Postinfectious encephalomyelitis is most frequently associated with the viral exanthems of childhood. Infection with measles virus is the most common antecedent (1 in 1000 cases). Worldwide, measles encephalomyelitis is still common, although use of the live measles

vaccine has dramatically reduced its incidence in developed countries. An ADEM-like illness rarely follows vaccination with live measles vaccine (1–2 in 10⁶ immunizations). ADEM is now most frequently associated with varicella (chickenpox) infections (1 in 4000–10,000 cases). It may also follow infection with rubella, mumps, influenza, parainfluenza, EBV, HHV-6, HIV, dengue, Zika, other viruses, and *Mycoplasma pneumoniae*. Recently, cases have been described in association with COVID-19 infection. Some patients may have a non-specific upper respiratory infection or no known antecedent illness. In addition to measles, postvaccinal encephalomyelitis may also follow the administration of vaccines for smallpox (5 cases per million), the Semple rabies, and Japanese encephalitis. Modern vaccines that do not require viral culture in CNS tissue have reduced the ADEM risk.

All forms of ADEM presumably result from a cross-reactive immune response to the infectious agent or vaccine that then triggers an inflammatory demyelinating response. Autoantibodies to MBP and to other myelin antigens have been detected in the CSF from some patients with ADEM, and approximately half of children with ADEM have circulating and CSF antibodies against MOG (Chap. 445). Attempts to demonstrate direct viral invasion of the CNS have been unsuccessful.

CLINICAL MANIFESTATIONS

In severe cases, onset is abrupt and progression rapid (hours to days). In postinfectious ADEM, the neurologic syndrome generally begins late in the course of the viral illness as the exanthem is fading. Fever reappears, and headache, meningismus, and lethargy progressing to coma may develop. Seizures are common. Signs of disseminated neurologic disease are consistently present (e.g., hemiparesis or quadripareisis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, and brainstem involvement). In ADEM due to chickenpox, cerebellar involvement is often conspicuous. CSF protein is modestly elevated (0.5–1.5 g/L [50–150 mg/dL]). Lymphocytic pleocytosis, generally ≥200 cells/µL, occurs in 80% of patients. Occasional patients have higher counts or a mixed polymorphonuclear-lymphocytic pattern during the initial days of the illness. Transient CSF oligoclonal banding has been reported. MRI usually reveals extensive changes in the brain and spinal cord, consisting of white matter hyperintensities on T2 and fluid-attenuated inversion recovery (FLAIR) sequences with Gd enhancement on T1-weighted sequences.

DIAGNOSIS

The diagnosis is most reliably established when there is a history of recent vaccination or viral exanthematous illness. In severe cases with predominantly cerebral involvement, acute encephalitis due to infection with herpes simplex or other viruses including HIV may be difficult to exclude; other considerations include hypercoagulable states including the antiphospholipid antibody syndrome, autoimmune (paraneoplastic) limbic encephalitis, vasculitis, neurosarcoïd, primary CNS lymphoma, or metastatic cancer. An explosive presentation of MS can mimic ADEM, and, especially in adults, it may not be possible to distinguish these conditions at onset. The simultaneous onset of disseminated symptoms and signs is common in ADEM and rare in MS. Similarly, meningismus, drowsiness, coma, and seizures suggest ADEM rather than MS. Unlike MS, in ADEM, optic nerve involvement is generally bilateral and transverse myelopathy complete. MRI findings that favor ADEM include extensive and relatively symmetric white matter abnormalities, basal ganglia or cortical gray matter lesions, and Gd enhancement of all abnormal areas. By contrast, OCBs in the CSF are more common in MS. In one study of adult patients initially thought to have ADEM, 30% experienced additional relapses over a follow-up period of 3 years, and they were reclassified as having MS. Other patients initially classified as ADEM are subsequently found to have neuromyelitis optica spectrum disorder (Chap. 445). Occasional patients with “recurrent ADEM” have also been reported, especially children; however, it is not possible to distinguish this entity from atypical MS. Because of the clinical overlap at presentation between ADEM and MS, it is crucial that routine surveillance imaging be performed following recovery from ADEM so that subclinical disease activity due to MS can be recognized and treatment for MS initiated.

TREATMENT

■ ACUTE DISSEMINATED ENCEPHALOMYELITIS

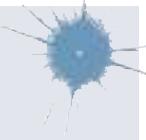
Initial treatment is with high-dose glucocorticoids; depending on the response, treatment may need to be continued for 8 weeks. Patients who fail to respond within a few days may benefit from a course of plasma exchange or intravenous immunoglobulin. The prognosis reflects the severity of the underlying acute illness. In recent case series of presumptive ADEM in adults, mortality rates of 5–20% are reported, and many survivors have permanent neurologic sequelae.

GLIAL FIBRILLARY ACIDIC PROTEIN GFAP AUTOIMMUNITY

Autoimmunity against the astrocyte protein GFAP presents with a range of symptoms referable to meningismus, encephalitis, myelitis, and optic neuritis. MRI shows characteristic patterns of gadolinium enhancement localized to GFAP-enriched CNS regions including venous structures in a periventricular radial orientation, the leptomeninges, the peri-ependymal spinal cord, and a striking serpiginous pattern involving brain parenchyma. These enhancement patterns share some similarities with patterns that can be observed in neurosarcoidosis. The presence of these patterns should prompt consideration for either condition. A lymphocytic pleocytosis is commonly present in the CSF. Antibodies against GFAP can be measured in the CSF or serum. GFAP autoimmunity is found as a paraneoplastic syndrome in 25% of cases, most commonly associated with ovarian teratoma, and can coexist with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis or neuromyelitis optica spectrum disorder (NMOSD). T cells are implicated in pathophysiology based on histopathology and association with checkpoint inhibitor treatment for cancer or in the setting of HIV. GFAP autoimmunity is generally glucocorticoid responsive. Early recognition with prompt intervention is associated with more favorable outcomes. Relapses occur in approximately 20% of patients and require use of immune suppression therapy.

■ FURTHER READING

- A M et al: Mechanisms underlying progression in multiple sclerosis. *Curr Opin Neurol* 33:277, 2020.
- B RJ et al: Meningeal inflammation and cortical demyelination in acute multiple sclerosis. *Ann Neurol* 84:829, 2018.
- B JLW et al: Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA* 321:175, 2019.
- C BAC et al: Silent progression in disease activity-free relapsing multiple sclerosis. *Ann Neurol* 85:653, 2019.
- G G et al: Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients. *Neurology* 87:1985, 2016.
- H SL et al: Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 376:221, 2017.
- H SL et al: Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med* 383:546, 2020.
- L G et al: Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. *JAMA Neurol* 77:184, 2020.
- M CB et al: Early clinical markers of aggressive multiple sclerosis. *Brain* 143:1400, 2020.
- N Y et al: Association of rituximab treatment with disability progression among patients with secondary progressive multiple sclerosis. *JAMA Neurol* 76:274, 2019.
- M X et al: Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 376:209, 2017.
- P D et al: Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. *Neurology* 87(9 Suppl 2):S38, 2016.
- S F et al: Autoimmune glial fibrillary acidic protein astrocytopathy: A review of the literature. *Front Immunol* 9:2802, 2018.
- T AJ et al: Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 17:162, 2018.
- Z SS, H SL: Antigen presentation by B cells in multiple sclerosis. [Review] *N Engl J Med* 384:378, 2021.



INTRODUCTION

Neuromyelitis optica (NMO; Devic's disease) is an aggressive inflammatory disorder characterized by recurrent attacks of optic neuritis (ON) and myelitis; the more inclusive term *NMO spectrum disorder* (NMOSD) was proposed to include individuals with partial forms, and also those with involvement of additional regions in the central nervous system (Table 445-1). NMO is more frequent in women than men (9:1), and typically begins in adulthood, with a mean age of onset of 40 years, but can arise at any age. An important consideration, especially early in its presentation, is distinguishing NMO from multiple sclerosis (MS; Chap. 444). In patients with NMO, attacks of ON can be bilateral and produce severe visual loss (uncommon in MS); myelitis can be severe and transverse (rare in MS) and is typically longitudinally extensive (Fig. 445-1), involving three or more contiguous vertebral segments. In contrast to MS, progressive symptoms typically do not occur in NMO. The brain MRI was earlier thought to be normal in NMO, but it is now recognized that in many cases brain lesions are present, including areas of nonspecific signal change as well as lesions

TABLE 445-1 Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder

Diagnostic Criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best-available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

Diagnostic Criteria for NMOSD Without AQP4-IgG or NMOSD with Unknown AQP4-IgG Status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
 - a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
 - b. Dissemination in space (2 or more different clinical characteristics)
 - c. Fulfillment of additional MRI requirements, as applicable
2. Negative test for AQP4-IgG using best-available detection method or testing unavailable
3. Exclusion of alternative diagnoses

Core Clinical Characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea or vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Additional MRI Requirements for NMOSD Without AQP4-IgG and NMOSD with Unknown AQP4-IgG Status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion of T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome requires periependymal brainstem lesions

Source: Reproduced with permission from DM Wingerchuk et al: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85:177, 2015.

associated with specific syndromes such as the hypothalamus causing an endocrinopathy; the area postrema in the lower medulla presenting as intractable hiccups or vomiting; or the cerebral hemispheres producing focal symptoms, encephalopathy, or seizures. Large MRI lesions in the cerebral hemispheres can be asymptomatic, sometimes have a "cloudlike" appearance and, unlike MS lesions, are often not destructive and can resolve completely. Spinal cord MRI lesions typically consist of focal enhancing areas of swelling and tissue destruction, extending over three or more spinal cord segments, and on axial sequences, these are centered on the grey matter of the cord. Cerebrospinal fluid (CSF) findings include pleocytosis greater than that observed in MS, with neutrophils and eosinophils present in many acute cases; oligoclonal bands (OCBs) are uncommon, occurring in <20% of NMO patients. The pathology of NMO is a distinctive astrocytopathy with inflammation, loss of astrocytes, and an absence of staining of the water channel protein AQP4 by immunohistochemistry, plus thickened blood vessel walls, demyelination, and deposition of antibody and complement.

IMMUNOLOGY

NMO is an autoimmune disease associated with a highly specific autoantibody directed against aquaporin-4 (AQP-4) that is present in the sera of ~90% of patients with a clinical diagnosis of NMO. AQP-4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces, as well as at paranodal regions near nodes of Ranvier. It is likely that AQP-4 antibodies are pathogenic because their passive transfer into laboratory animals can reproduce histologic features of the disease. Antibody-mediated complement fixation is thought to represent the primary mechanism of astrocyte injury in NMO. During acute attacks of myelitis, CSF levels of interleukin-6 (IL-6; a proinflammatory cytokine) and astrocyte-specific glial fibrillary acidic protein (GFAP) levels are markedly elevated, consistent with active inflammation and astrocyte injury. Proinflammatory T-lymphocytes of the Th17 type recognize an immunodominant epitope of AQP4 and may also contribute to pathogenesis. Because of the high specificity of the antibody, its presence is considered to be diagnostic when found in conjunction with a typical clinical presentation. Anti-AQP4 seropositive patients have a high risk for future relapses; more than half of untreated patients will relapse within 1 year.

CLINICAL COURSE

NMO is typically a recurrent disease; the course is monophasic in <10% of patients. Individuals who test negative for AQP4 antibodies are somewhat more likely to have a monophasic course. Untreated NMO is usually quite disabling over time; in one series, respiratory failure from cervical myelitis was present in one-third of patients, and 8 years after onset, 60% of patients were blind and more than half had permanent paralysis of one or more limbs. The long-term course of NMO appears to have been substantially improved with the development of therapies to treat acute attacks and prevent relapses. Estimates of the 5-year survival rate increased from 68–75% in 1999 to 91–98% in 2017, a change likely due to improved diagnosis and widespread use of immunosuppressant drugs.

GLOBAL CONSIDERATIONS

The incidence and prevalence of NMO show considerable variation between populations and geographic regions, with prevalence estimates that range from <1 to >4 per 100,000. Although NMO can occur in people of any ethnic background, individuals of Asian and African origin are disproportionately affected. The highest reported prevalence is from Martinique. Among white populations, MS (Chap. 444) is far more common than NMO.

Interestingly, when MS affects individuals of African or Asian ancestry, there is a propensity for demyelinating lesions to involve predominantly the optic nerve and spinal cord, an MS subtype termed *opticospinal MS*. Some individuals with opticospinal MS are seropositive for AQP4 antibodies, indicating that such cases represent NMOSD.

ASSOCIATED CONDITIONS

Up to 40% of NMO patients have a systemic autoimmune disorder, such as systemic lupus erythematosus, Sjögren's syndrome, perinuclear antineutrophil cytoplasmic antibody (p-ANCA)-associated vasculitis, myasthenia



FIGURE 445-1 Imaging findings in neuromyelitis optica: longitudinally extensive transverse myelitis, optic neuritis, and brainstem involvement. *A*, Sagittal fluid attenuation inversion recovery (FLAIR) cervical-spine MRI showing an area of increased signal change on T2-weighted imaging spanning >3 vertebral segments in length. *B*, Sagittal T1-weighted cervical-spine MRI following gadolinium-diethylenetriamine pentaacetic acid (DPTA) infusion showing enhancement. *C*, Coronal brain MRI shows hyperintense signal on FLAIR imaging within the left optic nerve. *D*, Coronal T1-weighted brain MRI following gadolinium-DPTA infusion shows enhancement of the left optic nerve. *E*, Axial brain MRI shows an area of hyperintense signal on T2-weighted imaging within the area postrema (arrow). *F*, Axial T1-weighted brain MRI following gadolinium-DPTA infusion shows punctate enhancement of the area postrema (arrow).

gravis, Hashimoto's thyroiditis, or mixed connective tissue disease. This is another feature distinct from MS; MS patients rarely have other comorbid autoimmune diseases with the exception of hypothyroidism. In some NMO cases, onset may be associated with acute infection with varicella zoster virus, Epstein-Barr virus, HIV, or tuberculosis. Rare cases appear to be paraneoplastic and associated with breast, lung, or other cancers.

TREATMENT

Neuromyelitis Optica

Until recently, disease-modifying therapies were not rigorously studied in NMO. Acute attacks are usually treated with high-dose glucocorticoids (e.g., methylprednisolone

1 g/d for 5–10 days followed by a prednisone taper). Plasma exchange (typically 5–7 exchanges of 1.5 plasma volumes/exchange) is used empirically for acute episodes that do not respond to glucocorticoids. Given the unfavorable natural history of untreated NMO, prophylaxis against relapses is recommended for most patients and several empiric regimens have been commonly used including: mycophenolate mofetil (1000 mg bid); the B-cell depleting anti-CD20 monoclonal antibody rituximab (2 g IV Q 6 months); or a combination of glucocorticoids (500 mg IV methylprednisolone daily for 5 days; then oral prednisone 1 mg/kg per day for 2 months, followed by slow taper) plus azathioprine (2 mg/kg per day started on week 3). Importantly, some therapies with efficacy in MS do not appear to be useful for NMO. Available evidence suggests that interferon beta is ineffective and paradoxically may increase the

TABLE 445-2 Therapeutic Trials for NMO

	RISK REDUCTION IN AQP4-SEROPOSITIVE PATIENTS
Eculizumab (add-on to immune suppression)	94%, P<0.001
Inolimomab (monotherapy)	78%, P=0.01
Satralizumab (add-on to immune suppression)	74%, P=0.001
Satralizumab (monotherapy)	77%, P<0.001

risk of NMO relapses, and based on limited data glatiramer acetate, fingolimod, natalizumab, and alemtuzumab also appear to be ineffective. These differences highlight the importance of distinguishing NMO from MS.

Three monoclonal antibody therapies have now received regulatory approval for attack prevention in NMO: eculizumab, a terminal complement inhibitor; inebilizumab, a B-cell depleter; and satralizumab, an IL-6 receptor blocker (Table 445-2).

Eculizumab is a monoclonal antibody that binds to the complement protein C5, inhibiting its cleavage into C5a and C5b and preventing generation of the terminal complement attack complex C5b-9. Investigated as add-on therapy in AQP4 seropositive NMO, eculizumab lengthened the time to first attack by 94%, reduced the attack rate by 96%, and reduced rates of hospitalization, glucocorticoid, and plasma exchange use. Eculizumab is dosed as follows: 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter.

Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Life-threatening and fatal meningococcal infections have occurred in eculizumab-treated patients (Boxed Warning). Eculizumab-treated patients should be immunized with meningococcal vaccines at least 2 weeks prior to administering the first dose unless the risk of delaying eculizumab therapy outweigh the risk of developing a meningococcal infection. Vaccination reduces, but does not eliminate, the risk of meningococcal infections. All eculizumab-treated patients must be monitored for early signs of meningococcal infections and evaluated immediately if infection is suspected.

Inebilizumab is a humanized monoclonal antibody that binds to the B-cell-specific surface antigen CD19 and depletes a wide range of B cells including some plasmablasts as well as a proportion of plasma cells in secondary lymphoid organs and bone marrow. Inebilizumab used as monotherapy reduced time to the first NMO attack by 77% compared to placebo, and also reduced hospitalizations by 78%, disability worsening by 63%, and new MRI lesions by 43%. Inebilizumab is dosed as follows: 300 mg IV infusion followed 2 weeks later by a second 300 mg IV infusion with subsequent doses of 300 mg infusions every 6 months thereafter.

Inebilizumab is associated with a dose-dependent decline in serum IgG levels and with neutropenia in some patients.

Satralizumab is a monoclonal antibody that binds to the interleukin-6 receptor, blocking engagement of IL-6. Satralizumab was investigated in NMOSD in two trials: one as monotherapy and the other as add-on therapy. Both AQP4 seropositive and AQP4 seronegative participants were enrolled. In both studies, the time to first attack was longer with satralizumab treatment compared with placebo. The risk of attack was reduced by 74% in the monotherapy study, and in the add-on study by 78%, with satralizumab. Although both studies recruited substantial numbers of AQP4 seronegative participants, there was no clinically meaningful impact of satralizumab in the seronegative participants. Satralizumab is administered as follows: a loading dosage of 120 mg by subcutaneous injection at weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks.

Screening for hepatitis B virus, tuberculosis, and liver transaminase elevations is required before starting satralizumab. Hepatic transaminases should be monitored during treatment for

transaminase elevation, and CBC should be monitored during treatment for neutropenia. Satralizumab is also associated with weight gain.

MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY ASSOCIATED DISEASE MOGAD

Although long considered to be a likely target for antibody-mediated demyelination, anti-MOG antibodies detected by a cell-based assay that enables recognition of myelin oligodendrocyte glycoprotein (MOG) epitopes in a lipid bilayer were recently found to be associated with cases of acute disseminated encephalomyelitis (ADEM) (Chap. 444) in children, and then with cases of AQP4 seronegative NMO. Further studies showed that patients who are seropositive for anti-MOG antibodies are at risk for bilateral, synchronous optic neuritis and myelitis. A clinical feature that can help distinguish ON associated with MOGAD from NMO or MS is the presence of papillitis seen by funduscopic or orbital MRI. ON associated with MOGAD is typically longitudinally extensive on MRI, and brain MRI can be normal or show fluffy areas of increased signal change in white or grey matter structures, similar to NMO. MRI lesions that are typical for MS, including finger-like lesions oriented perpendicular to the ventricular surface (Dawson fingers) and T1-hypointense lesions, are uncommon. Spinal cord lesions can be longitudinally extensive or short and sometimes involve the conus medullaris. Demyelination associated with MOGAD is sometimes monophasic, as in ADEM, but can also be recurrent. The CSF may show a pleocytosis with occasional neutrophils. Elevated intrathecal synthesis of gammaglobulins is atypical: oligoclonal bands are present in ~6–13% of cases and intrathecal synthesis of anti-MOG antibodies does not occur. The mechanism of CNS injury in MOGAD is not established. Studies in MOG-induced experimental autoimmune encephalomyelitis suggest that anti-MOG antibodies may opsonize traces of MOG protein in secondary lymphoid tissues, triggering an encephalitogenic peripheral immune response.

Acute episodes are managed with high-dose glucocorticoids followed by a prednisone taper and sometimes by plasmapheresis, as with NMO. Brain lesions associated with MOGAD often respond rapidly to treatment with glucocorticoids and may resolve entirely. Some patients experience disease recurrence following discontinuation of prednisone and can become glucocorticoid dependent. Clinical trials have not been undertaken and there is limited data on other immune-suppressing medications typically used in NMO. Off-label empiric treatments include daily prednisone, IVIg, rituximab, and mycophenolate mofetil. Anti-MOG antibody titers appear to decline either spontaneously or in the setting of treatment.

Rare cases of relapsing optic nerve and spinal cord disease resembling NMOSD have recently been recognized in patients with autoantibodies against glial fibrillary acidic protein (GFAP), an astrocyte-specific protein, although more commonly the disorder presents as a meningoencephalitis resembling acute disseminated encephalomyelitis. **GFAP astrocytopathy is discussed in Chap. 444.**

FURTHER READING

- C BAC et al: Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): A double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 394:1352, 2019.
- H SR et al: Autoimmune AQP4 channelopathies and neuromyelitis optica spectrum disorders. Handb Clin Neurol 133:377, 2016.
- M R et al: Myelin-oligodendrocyte glycoprotein antibody-associated disease. Lancet Neurol 20:762, 2021.
- P SJ et al: Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med 381:614, 2019.
- T A et al: Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol 19:402, 2020.
- W DM et al: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85:177, 2015.



Peripheral nerves are composed of sensory, motor, and autonomic elements. Diseases can affect the cell body of a neuron or its peripheral processes, namely the axons or the encasing myelin sheaths. Most peripheral nerves are mixed and contain sensory and motor as well as autonomic fibers. Nerves can be subdivided into three major classes: large myelinated, small myelinated, and small unmyelinated. Motor axons are usually large myelinated fibers that conduct rapidly (~50 m/s). Sensory fibers may be any of the three types. Large-diameter sensory fibers conduct proprioception and vibratory sensation to the brain, while the smaller-diameter myelinated and unmyelinated fibers transmit pain and temperature sensation. Autonomic nerves are also small in diameter. Thus, peripheral neuropathies can impair sensory, motor, or autonomic function, either singly or in combination. Peripheral neuropathies are further classified into those that primarily affect the cell body (e.g., neuronopathy or ganglionopathy), myelin (myelinopathy), and the axon (axonopathy). These different classes of peripheral neuropathies have distinct clinical and electrophysiologic features. This chapter discusses the clinical approach to a patient suspected of having a peripheral neuropathy, as well as specific neuropathies, including hereditary and acquired neuropathies. The inflammatory neuropathies are discussed in Chap. 447.

GENERAL APPROACH

In approaching a patient with a neuropathy, the clinician has three main goals: (1) identify where the lesion is, (2) identify the cause, and (3) determine the proper treatment. The first goal is accomplished by obtaining a thorough history, neurologic examination, and electrodiagnostic and other laboratory studies (Fig. 446-1). While gathering this information, seven key questions are asked (Table 446-1), the answers to which help identify the pattern of involvement and the cause of the neuropathy (Table 446-2). Despite an extensive evaluation, in approximately half of patients, no etiology is ever found; these patients typically have a predominantly sensory polyneuropathy and have been labeled as having idiopathic or cryptogenic sensory and sensorimotor polyneuropathy (CSPN).

INFORMATION FROM THE HISTORY AND PHYSICAL EXAMINATION: SEVEN KEY QUESTIONS TABLE 446 1

1. What Systems Are Involved? It is important to determine if the patient's symptoms and signs are motor, sensory, autonomic, or a combination of these. If the patient has only weakness without any evidence of sensory or autonomic dysfunction, a motor neuropathy, neuromuscular junction abnormality, or myopathy should be considered. Some peripheral neuropathies are associated with significant autonomic nervous system dysfunction. Symptoms of autonomic involvement include fainting spells or orthostatic lightheadedness; heat intolerance; or any bowel, bladder, or sexual dysfunction (Chap. 440). There will typically be an orthostatic fall in blood pressure without an appropriate increase in heart rate. Autonomic dysfunction in the absence of diabetes should alert the clinician to the possibility of amyloid polyneuropathy. Rarely, a pandysautonomic syndrome can be the only manifestation of a peripheral neuropathy without other motor or sensory findings. The majority of neuropathies are predominantly sensory in nature.

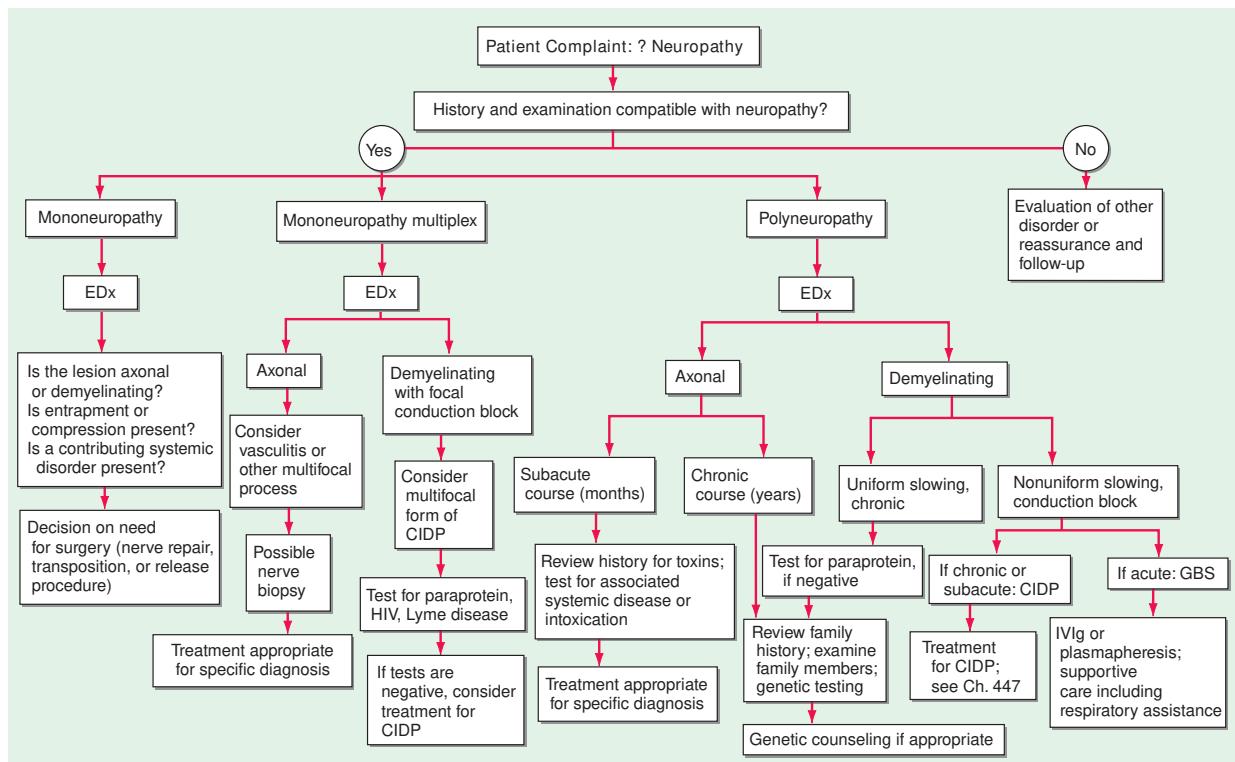


FIGURE 446-1 Approach to the evaluation of peripheral neuropathies. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EDx, electrodiagnostic; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin.

TABLE 446-1 Approach to Neuropathic Disorders: Seven Key Questions

- What systems are involved?
 - Motor, sensory, autonomic, or combinations
- What is the distribution of weakness?
 - Only distal versus proximal and distal
 - Focal/asymmetric versus symmetric
- What is the nature of the sensory involvement?
 - Temperature loss or burning or stabbing pain (e.g., small fiber)
 - Vibratory or proprioceptive loss (e.g., large fiber)
- Is there evidence of upper motor neuron involvement?
 - Without sensory loss
 - With sensory loss
- What is the temporal evolution?
 - Acute (days to 4 weeks)
 - Subacute (4–8 weeks)
 - Chronic (>8 weeks)
 - Monophasic, progressive, or relapsing-remitting
- Is there evidence for a hereditary neuropathy?
 - Family history of neuropathy
 - Lack of sensory symptoms despite sensory signs
- Are there any associated medical conditions?
 - Cancer, diabetes mellitus, connective tissue disease or other autoimmune diseases, infection (e.g., HIV, Lyme disease, leprosy)
 - Medications including over-the-counter drugs that may cause a toxic neuropathy
 - Preceding events, drugs, toxins

2. What Is the Distribution of Weakness? Delineating the pattern of weakness, if present, is essential for diagnosis, and in this regard, two additional questions should be answered: (1) Does the weakness only involve the distal extremity, or is it both proximal and distal? and (2) Is the weakness focal and asymmetric, or is it symmetric? Symmetric proximal and distal weakness is the hallmark of acquired immune demyelinating polyneuropathies, both the acute form (Guillain-Barré syndrome [GBS]) and the chronic form (chronic inflammatory demyelinating polyneuropathy [CIDP]) ([Chap. 447](#)). The importance of finding symmetric proximal and distal weakness in a patient who presents with both motor and sensory symptoms cannot be overemphasized because this identifies the important subset of patients who may have a treatable acquired demyelinating neuropathic disorder (i.e., GBS or CIDP).

Findings of an asymmetric or multifocal pattern of weakness narrow the differential diagnosis. Some neuropathic disorders may present with unilateral extremity weakness. In the absence of sensory symptoms and signs, such weakness evolving over weeks or months would be worrisome for motor neuron disease (e.g., amyotrophic lateral sclerosis [ALS]), but it would be important to exclude multifocal motor neuropathy that may be treatable ([Chap. 447](#)). In a patient presenting with asymmetric subacute or acute sensory and motor symptoms and signs, radiculopathies, plexopathies, compressive mononeuropathies, or multiple mononeuropathies (e.g., mononeuropathy multiplex) must be considered.

ALS can produce prominent neck extensor weakness (head drop), tongue and pharyngeal weakness (dysarthria and dysphagia), or shortness of breath. These focal symmetric weakness patterns can also be seen in neuromuscular junction disorders (myasthenia gravis, Lambert-Eaton myasthenic syndrome [LEMS] [[Chap. 448](#)]) and some myopathies, particularly isolated neck extensor myopathy ([Chap. 449](#)).

3. What Is the Nature of the Sensory Involvement? The patient may have loss of sensation (numbness), altered sensation to touch (hyperesthesia or allodynia), or uncomfortable spontaneous sensations (tingling, burning, or aching) ([Chap. 25](#)). Neuropathic pain can be burning, dull, and poorly localized (protopathic pain), presumably transmitted by polymodal C nociceptor fibers, or sharp and lancinating

TABLE 446-2 Patterns of Neuropathic Disorders

- Pattern 1: Symmetric proximal and distal weakness with sensory loss**
Consider: inflammatory demyelinating polyneuropathy (GBS and CIDP)
- Pattern 2: Symmetric distal sensory loss with or without distal weakness**
Consider: cryptogenic or idiopathic sensory polyneuropathy (CSPN), diabetes mellitus and other metabolic disorders, drugs, toxins, familial (HSAN), CMT, amyloidosis, and others
- Pattern 3: Asymmetric distal weakness with sensory loss**
With involvement of multiple nerves
Consider: multifocal CIDP, vasculitis, cryoglobulinemia, amyloidosis, sarcoid, infectious (leprosy, Lyme, hepatitis B, C, or E, HIV, CMV), HNPP, tumor infiltration
With involvement of single nerves/regions
Consider: may be any of the above but also could be compressive mononeuropathy, plexopathy, or radiculopathy
- Pattern 4: Asymmetric proximal and distal weakness with sensory loss**
Consider: polyradiculopathy or plexopathy due to diabetes mellitus, meningeal carcinomatosis or lymphomatosis, sarcoid, amyloid, hereditary plexopathy (HNPP, HNA), idiopathic
- Pattern 5: Asymmetric distal weakness without sensory loss**
With upper motor neuron findings
Consider: motor neuron disease
Without upper motor neuron findings
Consider: progressive muscular atrophy, juvenile monomelic amyotrophy (Hirayama's disease), multifocal motor neuropathy, multifocal acquired motor axonopathy
- Pattern 6: Symmetric sensory loss and distal areflexia with upper motor neuron findings**
Consider: vitamin B₁₂, vitamin E, and copper deficiency with combined system degeneration with peripheral neuropathy, chronic liver disease, hereditary leukodystrophies (e.g., adrenomyeloneuropathy) HSP-plus
- Pattern 7: Symmetric weakness without sensory loss**
With proximal and distal weakness
Consider: SMA
With distal weakness
Consider: hereditary motor neuropathy ("distal" SMA) or atypical CMT
- Pattern 8: Focal midline proximal symmetric weakness**
Neck extensor weakness
Consider: ALS
Bulbar weakness
Consider: ALS/PLS, isolated bulbar ALS (IBALS), Kennedy's syndrome (X-linked, bulbospinal SMA), bulbar presentation GBS
Diaphragm weakness (SOB)
Consider: ALS
- Pattern 9: Asymmetric proprioceptive sensory loss without weakness**
Consider causes of a sensory neuropathy (ganglionopathy):
Cancer (paraneoplastic)
Sjögren's syndrome
Idiopathic sensory neuropathy (possible GBS variant)
Cisplatin and other chemotherapeutic agents
Vitamin B₆ toxicity
HIV-related sensory neuropathy
- Pattern 10: Autonomic symptoms and signs**
Consider neuropathies associated with prominent autonomic dysfunction:
Hereditary sensory and autonomic neuropathy
Amyloidosis (familial and acquired)
Diabetes mellitus
GBS
Idiopathic pandysautonomia (may be a variant of GBS)
Porphyria
HIV-related autonomic neuropathy
Vincristine and other chemotherapeutic agents

Abbreviations: ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth disease; CMV, cytomegalovirus; GBS, Guillain-Barré syndrome; HIV, human immunodeficiency virus; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; HSP-plus, hereditary spastic paraparesis plus neuropathy; PLS, primary lateral sclerosis; SMA, spinal muscular atrophy; SOB, shortness of breath.

(epicritic pain), relayed by A-delta fibers. If pain and temperature perception are lost, while vibratory and position sense are preserved along with muscle strength, deep tendon reflexes, and normal nerve conduction studies (NCS), a small-fiber neuropathy is likely. The most likely causes of small-fiber neuropathies, when one is identified, are diabetes mellitus (DM) or glucose intolerance. Amyloid neuropathy should be considered as well in such cases, but most of these small-fiber neuropathies remain idiopathic despite extensive evaluation.

Severe proprioceptive loss also narrows the differential diagnosis. Affected patients will note imbalance, especially in the dark. A neurologic examination revealing a dramatic loss of proprioception with vibration loss and normal strength should alert the clinician to consider a sensory neuropathy/ganglionopathy (Pattern 9, Table 446-2). In particular, if this loss is asymmetric or affects the arms more than the legs, this pattern suggests a non-length-dependent process as seen in sensory neuropathies.

4. Is There Evidence of Upper Motor Neuron Involvement? If the patient presents with symmetric distal sensory symptoms and signs suggestive of a distal sensory neuropathy, but there is additional evidence of symmetric upper motor neuron involvement (Chap. 24), the physician should consider a combined system degeneration with neuropathy. The most common cause for this pattern is vitamin B₁₂ deficiency, but other etiologies should also be considered (e.g., copper deficiency, human immunodeficiency virus [HIV] infection, severe hepatic disease, adrenomyeloneuropathy [AMN]), and hereditary spastic paraparesis plus a neuropathy.

5. What Is the Temporal Evolution? It is important to determine the onset, duration, and evolution of symptoms and signs. Does the disease have an acute (days to 4 weeks), subacute (4–8 weeks), or chronic (>8 weeks) course? Is the course monophasic, progressive, or relapsing? Most neuropathies are insidious and slowly progressive in nature. Neuropathies with acute and subacute presentations include GBS, vasculitis, and radiculopathies related to diabetes or Lyme disease. A relapsing course can be present in CIDP and porphyria.

6. Is There Evidence for a Hereditary Neuropathy? In patients with slowly progressive distal weakness over many years with few sensory symptoms yet significant sensory deficits on clinical examination, the clinician should consider a hereditary neuropathy (e.g., Charcot-Marie-Tooth disease [CMT]). On examination, the feet may show high or flat arches or hammer toes, and scoliosis may be present. In suspected cases, it may be necessary to perform neurologic and electrophysiologic studies on family members in addition to the patient.

7. Does the Patient Have Any Other Medical Conditions? It is important to inquire about associated medical conditions (e.g., DM, systemic lupus erythematosus [SLE]); preceding or concurrent infections (e.g., diarrheal illness preceding GBS); surgeries (e.g., gastric bypass and nutritional neuropathies); medications (toxic neuropathy), including over-the-counter vitamin preparations (B₆); alcohol; dietary habits; and use of dentures (e.g., fixatives contain zinc that can lead to copper deficiency).

PATTERN RECOGNITION APPROACH TO NEUROPATHIC DISORDERS

Based on the answers to the seven key questions, neuropathic disorders can be classified into several patterns based on the distribution or pattern of sensory, motor, and autonomic involvement (Table 446-2). Each pattern has a limited differential diagnosis, and information from laboratory studies usually permits a final diagnosis to be established.

ELECTRODIAGNOSTIC STUDIES

The electrodiagnostic (EDx) evaluation of patients with a suspected peripheral neuropathy consists of NCS and needle electromyography (EMG). In addition, studies of autonomic function can be valuable. The electrophysiologic data can confirm whether the neuropathic disorder is a mononeuropathy, multiple mononeuropathy (mononeuropathy multiplex), radiculopathy, plexopathy, or generalized polyneuropathy.

TABLE 446-3 Electrophysiologic Features: Axonal Degeneration versus Segmental Demyelination

	AXONAL DEGENERATION	SEGMENTAL DEMYELINATION
Motor Nerve Conduction Studies		
CMAP amplitude	Decreased	Normal (except with CB or distal dispersion)
Distal latency	Normal	Prolonged
Conduction velocity	Normal	Slow
Conduction block	Absent	Present
Temporal dispersion	Absent	Present
Fwave	Normal or absent	Prolonged or absent
Hreflex	Normal or absent	Prolonged or absent
Sensory Nerve Conduction Studies		
SNAP amplitude	Decreased	Normal or decreased
Distal latency	Normal	Prolonged
Conduction velocity	Normal	Slow
Needle EMG		
Spontaneous activity		
Fibrillations	Present	Absent
Fasciculations	Present	Absent
Motor unit potentials		
Recruitment	Decreased	Decreased
Morphology	Long duration, large amplitude, polyphasic (if there is reinnervation)	Normal

Abbreviations: CB, conduction block; CMAP, compound motor action potential; EMG, electromyography; SNAP, sensory nerve action potential.

Similarly, EDx evaluation can ascertain whether the process involves only sensory fibers, motor fibers, autonomic fibers, or a combination of these. Finally, the electrophysiologic data can help distinguish axonopathies from myelinopathies as well as axonal degeneration secondary to ganglionopathies from the more common length-dependent axonopathies.

NCS are most helpful in classifying a neuropathy as due to axonal degeneration or segmental demyelination (Table 446-3). In general, low-amplitude potentials with relatively preserved distal latencies, conduction velocities, and late potentials, along with fibrillations on needle EMG, suggest an axonal neuropathy. On the other hand, slow conduction velocities, prolonged distal latencies and late potentials, relatively preserved amplitudes, and the absence of fibrillations on needle EMG imply a primary demyelinating neuropathy. The presence of nonuniform slowing of conduction velocity, conduction block, or temporal dispersion further suggests an acquired demyelinating neuropathy (e.g., GBS or CIDP) as opposed to a hereditary demyelinating neuropathy (e.g., CMT type 1).

Autonomic studies are used to assess small myelinated (A-delta) or unmyelinated (C) nerve fiber involvement. Such testing includes heart rate response to deep breathing, heart rate, and blood pressure response to both the Valsalva maneuver and tilt-table testing and quantitative sudomotor axon reflex testing (Chap. 440). These studies are particularly useful in patients who have pure small-fiber neuropathy or autonomic neuropathy in which routine NCS are normal.

OTHER IMPORTANT LABORATORY INFORMATION

In patients with generalized symmetric peripheral neuropathy, a standard laboratory evaluation should include a complete blood count, basic chemistries including serum electrolytes and tests of renal and hepatic function, fasting blood glucose (FBS), hemoglobin (Hb) A_{1c}, urinalysis, thyroid function tests, B₁₂, folate, erythrocyte sedimentation rate (ESR), rheumatoid factor, antinuclear antibodies (ANA), serum protein electrophoresis (SPEP) and immunoelectrophoresis or immunofixation, and urine for Bence Jones protein. Quantification of the

concentration of serum-free light chains and the kappa/lambda ratio is more sensitive than SPEP, immunoelectrophoresis, or immunofixation to detect a monoclonal gammopathy and therefore should be done if amyloidosis is suspected. A skeletal survey should be performed in patients with acquired demyelinating neuropathies and M-spikes to look for osteosclerotic or lytic lesions. Patients with monoclonal gammopathy should also be referred to a hematologist for consideration of a bone marrow biopsy. An oral glucose tolerance test is indicated in patients with painful sensory neuropathies even if FBS and HbA_{1c} are normal, as the test is abnormal in about one-third of such patients. In addition to the above tests, patients with a mononeuropathy multiplex pattern of involvement should have a vasculitis workup, including antineutrophil cytoplasmic antibodies (ANCA), cryoglobulins, hepatitis serology, Western blot for Lyme disease, HIV, and occasionally a cytomegalovirus (CMV) titer.

There are many autoantibody panels (various antiganglioside antibodies) marketed for screening routine neuropathy patients for a treatable condition. These autoantibodies have no proven clinical utility or added benefit beyond the information obtained from a complete clinical examination and detailed EDx. A heavy metal screen is also not necessary as a screening procedure, unless there is a history of possible exposure or suggestive features on examination (e.g., severe painful sensorimotor and autonomic neuropathy and alopecia—thallium; severe painful sensorimotor neuropathy with or without gastrointestinal [GI] disturbance and Mee's lines—arsenic; wrist or finger extensor weakness and anemia with basophilic stippling of red blood cells—lead).

In patients with suspected GBS or CIDP, a lumbar puncture is indicated to look for an elevated cerebrospinal fluid (CSF) protein. In idiopathic cases of GBS and CIDP, CSF pleocytosis is usually absent. If cells are present, one should consider HIV infection, Lyme disease, sarcoidosis, or lymphomatous or leukemic infiltration of nerve roots. Recently, serum IgG4 antibodies to neurofascin and contactin-2 have been discovered in CIDP with severe sensory ataxia, tremor, and distal weakness (*Chap. 447*). These cases are difficult to treat with standard immunotherapies but may respond to rituximab. Some patients with GBS and CIDP have abnormal liver function tests. In these cases, it is important to also check for hepatitis B and C, HIV, CMV, and Epstein-Barr virus (EBV) infection. In patients with an axonal GBS (by EMG/NCS) or those with a suspicious coinciding history (e.g., unexplained abdominal pain, psychiatric illness, significant autonomic dysfunction), it is reasonable to screen for porphyria.

In patients with a severe sensory ataxia, a sensory ganglionopathy or neuronopathy should be considered. The most common causes of sensory ganglionopathies are Sjögren's syndrome (*Chap. 361*) and a paraneoplastic neuropathy (*Chap. 94*). Neuropathy can be the initial manifestation of Sjögren's syndrome. Thus, one should always inquire about dry eyes and mouth in patients with sensory signs and symptoms. Further, some patients can manifest sicca complex without other manifestations of Sjögren's syndrome. Thus, patients with sensory ataxia should be tested for antibodies to SS-A/Ro and SS-B/La, in addition to the routine ANA. To evaluate a possible paraneoplastic sensory ganglionopathy, antineuronal nuclear antibodies (e.g., anti-Hu antibodies) should be obtained. These antibodies are most commonly seen in patients with small-cell carcinoma of the lung but are also present with breast, ovarian, lymphoma, and other cancers. Importantly, the paraneoplastic neuropathy can precede the detection of the cancer, and detection of these autoantibodies should lead to a search for malignancy.

■ NERVE BIOPSIES

Nerve biopsies are now rarely performed in the evaluation of neuropathies. The primary indication for nerve biopsy is suspicion for amyloid neuropathy or vasculitis. In most instances, the abnormalities present on biopsies do not help distinguish one form of peripheral neuropathy from another (beyond what is already apparent by clinical examination and the NCS). Nerve biopsies should only be performed when the NCS are abnormal. The sural nerve is most commonly biopsied because it is a pure sensory nerve and biopsy will not result in loss of motor function. In suspected vasculitis, a combination biopsy of a superficial

peroneal nerve (pure sensory) and the underlying peroneus brevis muscle obtained from a single small incision increases the diagnostic yield. Tissue can be analyzed to assess for evidence of inflammation, vasculitis, or amyloid deposition. Semithin plastic sections, teased fiber preparations, and electron microscopy are used to assess the morphology of the nerve fibers and to distinguish axonopathies from myelinopathies.

■ SKIN BIOPSIES

Skin biopsies are sometimes used to diagnose a small-fiber neuropathy. Following a punch biopsy of the skin in the distal lower extremity, immunologic staining can be used to measure the density of small unmyelinated fibers. The density of these nerve fibers is reduced in patients with small-fiber neuropathies in whom NCS and routine nerve biopsies are often normal. This technique may allow for an objective measurement in patients with mainly subjective symptoms. However, it often adds little to what one already knows from the clinical examination and EDx.

SPECIFIC DISORDERS

■ HEREDITARY NEUROPATHIES

CMT disease is the most common type of hereditary neuropathy (Pattern 2, Table 446-2). Rather than one disease, CMT is a syndrome of many genetically distinct disorders (*Table 446-4*). The various subtypes of CMT are classified according to the nerve conduction velocities (NCVs) and predominant pathology (e.g., demyelination or axonal degeneration), inheritance pattern (autosomal dominant, recessive, or X-linked), and the specific mutated genes. Type 1 CMT (or CMT1) refers to inherited demyelinating sensorimotor neuropathies, whereas the axonal sensory neuropathies are classified as CMT2. By definition, motor conduction velocities in the arms are slowed to <38 m/s in CMT1 and are >38 m/s in CMT2. However, most cases of CMT1 actually have motor NCVs between 20 and 25 m/s. CMT1 and CMT2 usually begin in childhood or early adult life; however, onset later in life can occur, particularly in CMT2. Both are inherited in an autosomal dominant fashion, with a few exceptions. CMT3 is an autosomal dominant neuropathy that appears in infancy and is associated with severe demyelination or hypomyelination. CMT4 is an autosomal recessive neuropathy that typically begins in childhood or early adult life. There are no medical therapies for any of the CMTs, but physical and occupational therapy can be beneficial, as can bracing (e.g., ankle-foot orthotics for foot drop) and other orthotic devices.

■ CMT1

CMT1 is the most common form of hereditary neuropathy. Affected individuals usually present in the first to third decade of life with distal leg weakness (e.g., foot drop), although patients may remain asymptomatic even late in life. People with CMT generally do not complain of numbness or tingling, which can be helpful in distinguishing CMT from acquired forms of neuropathy in which sensory symptoms usually predominate. Although usually asymptomatic, reduced sensation to all modalities is apparent on examination. Muscle stretch reflexes are unobtainable or reduced throughout. There is often atrophy of the muscles below the knee (particularly the anterior compartment), leading to so-called inverted champagne bottle legs.

Motor NCVs are generally in the 20–25 m/s range. Nerve biopsies usually are not performed on patients suspected of having CMT1, because the diagnosis usually can be made by less invasive testing (e.g., NCS and genetic studies). However, when done, the biopsies reveal reduced numbers of myelinated nerve fibers with a predilection for loss of large-diameter fibers and Schwann cell proliferation around thinly or demyelinated fibers, forming so-called onion bulbs.

CMT1A is the most common subtype of CMT1, representing 70% of cases, and is caused by a 1.5-megabase (Mb) duplication within chromosome 17p11.2-12 encoding the gene for peripheral myelin protein-22 (PMP-22). This results in patients having three copies of the PMP-22 gene rather than two. This protein accounts for 2–5% of myelin protein and is expressed in compact regions of the peripheral myelin sheath. Approximately 20% of patients with CMT1 have CMT1B,

TABLE 446-4 Classification of Charcot-Marie-Tooth Disease and Related Neuropathies

NAME	INHERITANCE	GENE LOCATION	GENE PRODUCT
CMT1			
CMT1A	AD	17p11.2	PMP-22 (usually duplication of gene)
CMT1B	AD	1q21-23	MPZ
CMT1C	AD	16p13.1-p12.3	LITAF
CMT1D	AD	10q21.1-22.1	ERG2
CMT1E (with deafness)	AD	17p11.2	Point mutations in <i>PMP-22</i> gene
CMT1F	AD	8p13-21	Neurofilament light chain
CMT1G	AD	8q21	PMP2
CMT1X	X-linked dominant	Xq13	Connexin-32
HNPP	AD	17p11.2 1q21-23	PMP-22 MPZ
CMT dominant-intermediate (CMTDI)			
CMT-DIA	AD	10q24.1-25.1	?
CMT-DIB	AD	19p12-13.2	Dynamin 2
CMT-DIC	AD	1p35	YARS
CMT-DID	AD	1q22	MPZ
CMT-DIE	AD	14q32.33	IFN-2
CMT-DIF	AD	3q26	GNB4
CMT-DIG	AD	8p31	NEFL
CMT recessive-intermediate (CMT-RI)			
CMT-RIA	AR	8q21.1	GDAP1
CMT-RIB	AR	6q23	KARS5
CMT-RIC	AR	1p36	PLEKHG5
CMT-RID	AR	12q24	COX6A1
CMT2			
CMT2A2 (allelic to HMSN VI with optic atrophy)	AD	1p36.2	MFN2
CMT2B	AD	3q13-q22	RAB7
CMT2B1 (allelic to LGMD 1B)	AR	1q21.2	Lamin A/C
CMT2B2	AR and AD	19q13	MED25 for AR; unknown for AD
CMT2C (with vocal cord and diaphragm paralysis)	AD	12q23-24	TRPV4
CMT2D (allelic to distal SMA5)	AD	7p14	Glycine tRNA synthetase
CMT2E (allelic to CMT 1F)	AD	8p21	Neurofilament light chain
CMT2F	AD	7q11-q21	Heat-shock 27-kDa protein-1
CMT2G	AD	9q31.3-34.2	LRSAM1
CMT2I (allelic to CMT1B)	AD	1q22	MPZ
CMT2J	AD	1q22	MPZ
CMT2H, CMT2K (allelic to CMT4A)	AD	8q13-q21	GDAP1
CMT2L (allelic to distal hereditary motor neuropathy type 2)	AD	12q24	Heat-shock protein 8
CMT2M	AD	16q22	Dynamin-2
CMT2N	AD	16q22.1	AARS
CMT2O	AD	14q32.31	DYNC1H1
CMT2P	AD	9q31.3-34.2	LRSAM1
CMT2P-Okinawa (HSMN2P)	AD	3q13-q14	TFG
CMT2Q	AD	10p14	DHTKD1
CMT2U	AD	12q13	MARS
CMT2V	AD	17q11	NAGLU
CMT2W	AD	5q31	HARS
CMT2Y	AD	9p13	VCP
CMT2Z	AD	22q12	MRC2
CMT2X	X-linked	Xq22-24	PRPS1
CMT3	AD	17p11.2	PMP-22
(Dejerine-Sottas disease, congenital hypomyelinating neuropathy)	AD	1q21-23	MPZ
	AR	10q21.1-22.1	ERG2
	AR	19q13	Periaxon

(Continued)

TABLE 446-4 Classification of Charcot-Marie-Tooth Disease and Related Neuropathies (Continued)

NAME	INHERITANCE	GENE LOCATION	GENE PRODUCT
CMT4			
CMT4A	AR	8q13-21.1	GDAP1
CMT4B1	AR	11q23	MTMR2
CMT4B2	AR	11p15	MTMR13
CMT4C	AR	5q23-33	SH3TC2
CMT4D (HMSN-Lom)	AR	8q24	NDRG1
CMT4E (congenital hypomyelinating neuropathy)	AR	Multiple	Includes PMP-22, MPZ, and ERG-2
CMT4F	AR	19q13.1-13.3	Periaxin
CMT4G	AR	10q23.2	HK1
CMT4H	AR	12q12-q13	Frabin
CMT4J	AR	6q21	FIG4
CMT4K	AR	9q34	SURF1
HNA	AD	17q24	SEPT9
HSAN1A	AD	9q22	SPTLC1
HSAN1B	AD	3q21	RAB7
HSAN1C	AD	14q24.3	SPTLC2
HSAN1D	AD	14q21.3	ATL1
HSAN1E	AD	19p13.2	DNMT1
HSAN2A	AR	12p13.33	PRKWNK1
HSAN2B	AR	5p15.1	FAM134B
HSAN2C	AR	12q13.13	KIF1A
HSAN2D	AR	2q24.3	SCN9A
HSAN3A	AR	9q21	IKAP
HSAN3B	AR	6p12.1	Dystonin
HSAN4	AR	3q	trkA/NGF receptor
HSAN5	AD or AR	1p11.2-p13.2 2q24.3 3p22.2	NGFb SCN9A SCN11A
HSAN6	AR	6p12.1	Dystonin

Abbreviations: AARS, alanyl-tRNA synthetase; AD, autosomal dominant; AR, autosomal recessive; ATL, atlastin; CMT, Charcot-Marie-Tooth; DNMT1, DNA methyltransferase 1; DYNC1HI, cytoplasmic dynein 1 heavy chain 1; ERG2, early growth response-2 protein; FAM 134B, family with sequence similarity 134, member B; FIG4, FDG1-related F actin-binding protein; GDAP1, ganglioside-induced differentiation-associated protein-1; HK1, hexokinase 1; HMSN-P, hereditary motor and sensory neuropathy proximal; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; IFN2, inverted formin-2; IKAP, β kinase complex-associated protein; LGMD, limb girdle muscular dystrophy; LITAF, lipopolysaccharide-induced tumor necrosis factor α factor; LRSAM1, E3 ubiquitin-protein ligase; MED25, mediator 25; MFN2, mitochondrial fusion protein mitofusin 2 gene; MPZ, myelin protein zero protein; MTMR2, myotubularin-related protein-2; NDRG1, N-myc downstream regulated 1; PMP-22, peripheral myelin protein-22; PRKWNK1, protein kinase, lysine deficient 1; PRPS1, phosphoribosylpyrophosphate synthetase 1; RAB7, Ras-related protein 7; SEPT9, Septin 9; SH3TC2, SH3 domain and tetratricopeptide repeats 2; SMA, spinal muscular atrophy; SPTLC, serine palmitoyltransferase long-chain base; TFG, TRK-fused gene; TrkA/NGF, tyrosine kinase A/nerve growth factor; tRNA, transfer ribonucleic acid; TRPV4, transient receptor potential cation channel, subfamily V, member 4; WNK1, WNK lysine deficient; YARS, tyrosyl-tRNA synthetase.

Source: Modified from AA Amato, J Russell: *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill, 2016, Table 11-1, pp 265–266.

caused by mutations in the myelin protein zero (MPZ). CMT1B is for the most part clinically, electrophysiologically, and histologically indistinguishable from CMT1A. MPZ is an integral myelin protein and accounts for more than half of the myelin protein in peripheral nerves. Other forms of CMT1 are much less common and also indistinguishable from one another clinically and electrophysiologically.

■ CMT2

CMT2 occurs approximately half as frequently as CMT1, and CMT2 tends to present later in life. Affected individuals usually become symptomatic in the second decade; some cases present earlier in childhood, whereas others remain asymptomatic into late adult life. Clinically, CMT2 is for the most part indistinguishable from CMT1. NCS are helpful in this regard; in contrast to CMT1, the velocities are normal or only slightly slowed. The most common cause of CMT2 is a mutation in the gene for mitofusin 2 (MFN2), which accounts for ~20–30% of CMT2 cases overall. MFN2 localizes to the outer mitochondrial membrane, where it regulates the mitochondrial network architecture by participating in mitochondrial fusion. The other genes associated with CMT2 are much less common.

■ CMTDI

In dominant-intermediate CMTs (CMTDIs), the NCVs are faster than usually seen in CMT1 (e.g., >38 m/s) but slower than in CMT2.

■ CMT3

CMT3 was originally described by Dejerine and Sottas as a hereditary demyelinating sensorimotor polyneuropathy presenting in infancy or early childhood. Affected children are severely weak. Motor NCVs are markedly slowed, typically \leq 10 m/s. Most cases of CMT3 are caused by point mutations in the genes for PMP-22, MPZ, or ERG-2, which are also the genes responsible for CMT1.

■ CMT4

CMT4 is extremely rare and is characterized by a severe, childhood-onset sensorimotor polyneuropathy that is usually inherited in an autosomal recessive fashion. Electrophysiologic and histologic evaluations can show demyelinating or axonal features. CMT4 is genetically heterogeneous (Table 446-4).

■ CMT1X

CMT1X is an X-linked dominant disorder with clinical features similar to CMT1 and CMT2, except that the neuropathy is much more severe in males than in females. CMT1X accounts for ~10–15% of CMT overall. Males usually present in the first two decades of life with atrophy and weakness of the distal arms and legs, areflexia, pes cavus, and hammer toes. Obligate female carriers are frequently asymptomatic

3486 but can develop signs and symptoms of CMT. Onset in females is usually after the second decade of life, and the neuropathy is milder in severity.

NCS reveal features of both demyelination and axonal degeneration.

In males, motor NCVs in the arms and legs are moderately slowed (in the low to mid 30-m/s range). About 50% of males with CMT1X have motor NCVs between 15 and 35 m/s with ~80% of these falling between 25 and 35 m/s (intermediate slowing). In contrast, ~80% of females with CMT1X have NCVs in the normal range and 20% have NCVs in the intermediate range. CMT1X is caused by mutations in the connexin-32 gene. Connexins are gap junction structural proteins that are important in cell-to-cell communication.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) HNPP is an autosomal dominant disorder related to CMT1A. While CMT1A is usually associated with a 1.5-Mb duplication in chromosome 17p11.2 that results in an extra copy of PMP-22 gene, HNPP is caused by inheritance of the chromosome with the corresponding 1.5-Mb deletion of this segment, and thus, affected individuals have only one copy of the PMP-22 gene. Patients usually manifest in the second or third decade of life with painless numbness and weakness in the distribution of single peripheral nerves, although multiple mononeuropathies can occur (Pattern 3, Table 446-2). Symptomatic mononeuropathy or multiple mononeuropathies are often precipitated by trivial compression of nerve(s) as can occur with wearing a backpack, leaning on the elbows, or crossing one's legs for even a short period of time. These pressure-related mononeuropathies may take weeks or months to resolve. In addition, some affected individuals manifest with a progressive or relapsing, generalized and symmetric, sensorimotor peripheral neuropathy that resembles CMT.

Hereditary Neuralgic Amyotrophy (HNA) HNA is an autosomal dominant disorder characterized by recurrent attacks of pain, weakness, and sensory loss in the distribution of the brachial plexus often beginning in childhood (Pattern 4, Table 446-2). These attacks are similar to those seen with idiopathic brachial plexitis (see below). Attacks may occur in the postpartum period, following surgery, or at other times of stress. Most patients recover over several weeks or months. Slightly dysmorphic features, including hypotelorism, epicanthal folds, cleft palate, syndactyly, micrognathia, and facial asymmetry, are evident in some individuals. EDx demonstrate an axonal process. HNA is genetically heterogeneous but can be caused by mutations in septin 9 (*SEPT9*). Septins may be important in formation of the neuronal cytoskeleton and have a role in cell division, but it is not known how mutations in *SEPT9* lead to HNA.

Hereditary Sensory and Autonomic Neuropathy (HSAN) The HSANs are a very rare group of hereditary neuropathies in which sensory and autonomic dysfunction predominates over muscle weakness, unlike CMT, in which motor findings are most prominent (Pattern 2, Table 446-2; Table 446-4). Nevertheless, affected individuals can develop motor weakness, and there can be overlap with CMT. There are no medical therapies available to treat these neuropathies, other than prevention and treatment of mutilating skin and bone lesions.

Of the HSANs, only HSAN1 typically presents in adults. HSAN1 is the most common of the HSANs and is inherited in an autosomal dominant fashion. Affected individuals usually manifest in the second through fourth decades of life. HSAN1 is associated with the degeneration of small myelinated and unmyelinated nerve fibers leading to severe loss of pain and temperature sensation, deep dermal ulcerations, recurrent osteomyelitis, Charcot joints, bone loss, gross foot and hand deformities, and amputated digits. Although most people with HSAN1 do not complain of numbness, they often describe burning, aching, or lancinating pains. Autonomic neuropathy is not a prominent feature, but bladder dysfunction and reduced sweating in the feet may occur. HSAN1A, which is most common, is caused by mutations in the serine palmitoyltransferase long-chain base 1 (*SPTLC1*) gene.

OTHER HEREDITARY NEUROPATHIES

TABLE 446-5

FABRY'S DISEASE

Fabry's disease (angiokeratoma corporis diffusum) is an X-linked dominant disorder. Although men are more commonly and severely affected, women can also manifest symptoms and signs of the disease. Angiokeratomas are reddish-purple maculopapular lesions that are usually found around the umbilicus, scrotum, inguinal region, and perineum. Burning or lancinating pain in the hands and feet often develops in males in late childhood or early adult life (Pattern 2, Table 446-2). However, the neuropathy is usually overshadowed by complications arising from an associated premature atherosclerosis (e.g., hypertension, renal failure, cardiac disease, and stroke) that often lead to death by the fifth decade of life. Some patients also manifest primarily with a dilated cardiomyopathy.

Fabry's disease is caused by mutations in the α -galactosidase gene that leads to the accumulation of ceramide trihexoside in nerves and blood vessels. A decrease in α -galactosidase activity is evident in leukocytes and cultured fibroblasts. Glycolipid granules may be appreciated in ganglion cells of the peripheral and sympathetic nervous systems and in perineurial cells. Enzyme replacement therapy with α -galactosidase B can improve the neuropathy if patients are treated early, before irreversible nerve fiber loss develops.

ADRENOLEUKODYSTROPHY/ADRENOMYELONEUROPATHY

Adrenoleukodystrophy (ALD) and AMN are allelic X-linked dominant disorders caused by mutations in the peroxisomal transmembrane adenosine triphosphate-binding cassette (ABC) transporter gene. Patients with ALD manifest with central nervous system (CNS) abnormalities. However, ~30% of patients with mutations in this gene present with the AMN phenotype that typically manifests in the third to fifth decade of life as mild to moderate peripheral neuropathy combined with

TABLE 446-5 Rare Hereditary Neuropathies

Hereditary Disorders of Lipid Metabolism

- Metachromatic leukodystrophy
- Krabbe's disease (globoid cell leukodystrophy)
- Fabry's disease
- Adrenoleukodystrophy/adrenomyeloneuropathy
- Refsum's disease
- Tangier disease
- Cerebrotendinous xanthomatosis

Hereditary Ataxias with Neuropathy

- Friedreich's ataxia
- Vitamin E deficiency
- Spinocerebellar ataxia
- Abetalipoproteinemia (Bassen-Kornzweig disease)

Disorders of Defective DNA Repair

- Ataxia-telangiectasia
- Cockayne's syndrome

Giant Axonal Neuropathy

Porphyria

- Acute intermittent porphyria (AIP)
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)

Familial Amyloid Polyneuropathy (FAP)

- Transthyretin-related
- Gelsolin-related
- Apolipoprotein A1-related

Source: Modified from AA Amato, J Russell: *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill, 2016, Table 12-1, p. 299.

progressive spastic paraparesis (Pattern 6, Table 446-2) ([Chap. 442](#)). Rare patients present with an adult-onset spinocerebellar ataxia or only with adrenal insufficiency.

EDx is suggestive of a primary axonopathy with secondary demyelination. Nerve biopsies demonstrate a loss of myelinated and unmyelinated nerve fibers with lamellar inclusions in the cytoplasm of Schwann cells. Very-long-chain fatty acid (VLCFA) levels (C24, C25, and C26) are increased in the urine. Laboratory evidence of adrenal insufficiency is evident in approximately two-thirds of patients. The diagnosis can be confirmed by genetic testing.

Adrenal insufficiency is managed by replacement therapy; however, there is no proven effective therapy for the neurologic manifestations of ALD/AMN. Diets low in VLCFAs and supplemented with Lorenzo's oil (erucic and oleic acids) reduce the levels of VLCFAs and increase the levels of C22 in serum, fibroblasts, and liver; however, several large, open-label trials of Lorenzo's oil failed to demonstrate efficacy.

REFSUM'S DISEASE

Refsum's disease can manifest in infancy to early adulthood with the classic tetrad of (1) peripheral neuropathy, (2) retinitis pigmentosa, (3) cerebellar ataxia, and (4) elevated CSF protein concentration. Most affected individuals develop progressive distal sensory loss and weakness in the legs leading to foot drop by their twenties (Pattern 2, Table 446-2). Subsequently, the proximal leg and arm muscles may become weak. Patients may also develop sensorineural hearing loss, cardiac conduction abnormalities, ichthyosis, and anosmia.

Serum phytanic acid levels are elevated. Sensory and motor NCS reveal reduced amplitudes, prolonged latencies, and slowed conduction velocities. Nerve biopsy demonstrates a loss of myelinated nerve fibers, with remaining axons often thinly myelinated and associated with onion bulb formation.

Refsum's disease is genetically heterogeneous but autosomal recessive in nature. Classical Refsum's disease with childhood or early adult onset is caused by mutations in the gene that encodes for phytanoyl-CoA α -hydroxylase (PAHX). Less commonly, mutations in the gene encoding peroxin 7 receptor protein (PRX7) are responsible. These mutations lead to the accumulation of phytanic acid in the central and peripheral nervous systems. Treatment is removal of phytanic precursors (phytols: fish oils, dairy products, and ruminant fats) from the diet.

TANGIER DISEASE

Tangier disease is a rare autosomal recessive disorder that can present as (1) asymmetric multiple mononeuropathies, (2) a slowly progressive symmetric polyneuropathy predominantly in the legs, or (3) a pseudo-syringomyelia pattern with dissociated sensory loss (i.e., abnormal pain/temperature perception but preserved position/vibration in the arms [[Chap. 442](#)]). The tonsils may appear swollen and yellowish-orange in color, and there may also be splenomegaly and lymphadenopathy.

Tangier disease is caused by mutations in the ATP-binding cassette transporter 1 (ABCI1) gene, which leads to markedly reduced levels of high-density lipoprotein (HDL) cholesterol levels, whereas triacylglycerol levels are increased. Nerve biopsies reveal axonal degeneration with demyelination and remyelination. Electron microscopy demonstrates abnormal accumulation of lipid in Schwann cells, particularly those encompassing unmyelinated and small myelinated nerves. There is no specific treatment.

PORPHYRIA

Porphyria is a group of inherited disorders caused by defects in heme biosynthesis ([Chap. 416](#)). Three forms of porphyria are associated with peripheral neuropathy: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). The acute neurologic manifestations are similar in each, with the exception that a photosensitive rash is seen with HCP and VP but not in AIP. Attacks of porphyria can be precipitated by certain drugs (usually those metabolized by the P450 system), hormonal changes (e.g., pregnancy, menstrual cycle), and dietary restrictions.

An acute attack of porphyria may begin with sharp abdominal pain. Subsequently, patients may develop agitation, hallucinations, or seizures. Several days later, back and extremity pain followed by weakness ensues, mimicking GBS (Pattern 1, Table 446-2). Weakness can involve the arms or the legs and can be asymmetric, proximal, or distal in distribution, as well as affecting the face and bulbar musculature. Dysautonomia and signs of sympathetic overactivity are common (e.g., pupillary dilation, tachycardia, and hypertension). Constipation, urinary retention, and incontinence can also be seen.

The CSF protein is typically normal or mildly elevated. Liver function tests and hematologic parameters are usually normal. Some patients are hyponatremic due to inappropriate secretion of antidiuretic hormone ([Chap. 378](#)). The urine may appear brownish in color secondary to the high concentration of porphyrin metabolites. Accumulation of intermediary precursors of heme (i.e., d-aminolevulinic acid, porphobilinogen, uroporphobilinogen, coproporphyrinogen, and protoporphyrinogen) is found in urine. Specific enzyme activities can also be measured in erythrocytes and leukocytes. The primary abnormalities on EDx are marked reductions in compound motor action potential (CMAP) amplitudes and signs of active axonal degeneration on needle EMG.

The porphyrias are inherited in an autosomal dominant fashion. AIP is associated with porphobilinogen deaminase deficiency, HCP is caused by defects in coproporphyrin oxidase, and VP is associated with protoporphyrin oxidase deficiency. The pathogenesis of the neuropathy is not completely understood. Treatment with glucose and hematin may reduce the accumulation of heme precursors. Intravenous glucose is started at a rate of 10–20 g/h. If there is no improvement within 24 h, intravenous hematin 2–5 mg/kg per day for 3–14 days should be administered.

FAMILIAL AMYLOID POLYNEUROPATHY

Familial amyloid polyneuropathy (FAP) is phenotypically and genetically heterogeneous and is caused by mutations in the genes for transthyretin (TTR), apolipoprotein A1, or gelsolin ([Chap. 112](#)). The majority of patients with FAP have mutations in the TTR gene. Amyloid deposition may be evident in abdominal fat pad, rectal, or nerve biopsies. The clinical features, histopathology, and EDx reveal abnormalities consistent with a generalized or multifocal, predominantly axonal but occasionally demyelinating, polyneuropathy.

Patients with TTR-related FAP usually develop insidious onset of numbness and painful paresthesias in the distal lower limbs in the third to fourth decade of life, although some patients develop the disorder later in life (Pattern 2, Table 446-2). Carpal tunnel syndrome (CTS) is common. Autonomic involvement can be severe, leading to postural hypotension, constipation or persistent diarrhea, erectile dysfunction, and impaired sweating (Pattern 10, Table 446-2). Amyloid deposition also occurs in the heart, kidneys, liver, and corneas. Patients usually die 10–15 years after the onset of symptoms from cardiac failure or complications from malnutrition. Because the liver produces much of the body's TTR, liver transplantation has been used to treat FAP related to TTR mutations. Serum TTR levels decrease after transplantation, and improvement in clinical and EDx features has been reported. Both tafamidis meglumine (20 mg daily) and diflunisal (250 mg twice daily), which prevent misfolding and deposition of mutated TTR, appear to slow the rate of deterioration in patients with TTR-related FAP. Recently, two different modes of gene therapy that inhibit hepatic production of TTR have been shown to improve neurologic function and quality of life compared to placebo in clinical trials. Inotersen, an antisense oligonucleotide, is given subcutaneously once a week. The main side effects are thrombocytopenia and glomerulonephritis. Patisiran, a small interfering RNA, is given at a dose of 0.3 mg/kg (up to 30 mg) every 3 weeks. Infusion reactions are common; therefore, prophylactic corticosteroids, acetaminophen, and an antihistamine should be administered.

Patients with apolipoprotein A1-related FAP (Van Allen type) usually present in the fourth decade with numbness and painful dysesthesias in the distal limbs. Gradually, the symptoms progress, leading to proximal and distal weakness and atrophy. Although autonomic neuropathy is

not severe, some patients develop diarrhea, constipation, or gastroparesis. Most patients die from systemic complications of amyloidosis (e.g., renal failure) 12–15 years after the onset of the neuropathy.

Gelsolin-related amyloidosis (Finnish type) is characterized by the combination of lattice corneal dystrophy and multiple cranial neuropathies that usually begin in the third decade of life. Over time, a mild generalized sensorimotor polyneuropathy develops. Autonomic dysfunction does not occur.

ACQUIRED NEUROPATHIES

■ PRIMARY OR AL AMYLOIDOSIS SEE CHAP. 112

Besides FAP, amyloidosis can also be acquired. In primary or AL amyloidosis, the abnormal protein deposition is composed of immunoglobulin light chains. AL amyloidosis occurs in the setting of multiple myeloma (MM), Waldenström's macroglobulinemia, lymphoma, other plasmacytomas, or lymphoproliferative disorders, or without any other identifiable disease.

Approximately 30% of patients with AL primary amyloidosis present with a polyneuropathy, most typically painful dysesthesias and burning sensations in the feet (Pattern 2, Table 446-2). However, the trunk can be involved, and some patients manifest with a mononeuropathy multiplex pattern. CTS occurs in 25% of patients and may be the initial manifestation. The neuropathy is slowly progressive, and eventually, weakness develops along with large-fiber sensory loss. Most patients develop autonomic involvement with postural hypertension, syncope, bowel and bladder incontinence, constipation, impotence, and impaired sweating (Pattern 10, Table 446-2). Patients generally die from their systemic illness (renal failure, cardiac disease).

The monoclonal protein may be composed of IgG, IgA, IgM, or only free light chain. Lambda (λ) is more common than κ light chain (>2:1) in AL amyloidosis. The CSF protein is often increased (with normal cell count), and thus, the neuropathy may be mistaken for CIDP (Chap. 447). Nerve biopsies reveal axonal degeneration and amyloid deposition in either a globular or diffuse pattern infiltrating the perineurial, epineurial, and endoneurial connective tissue and in blood vessel walls.

The median survival of patients with primary amyloidosis is <2 years, with death usually from progressive congestive heart failure or renal

failure. Chemotherapy with melphalan, prednisone, and colchicine, to reduce the concentration of monoclonal proteins, and autologous stem cell transplantation may prolong survival, but whether the neuropathy improves is controversial.

■ DIABETIC NEUROPATHY

DM is the most common cause of peripheral neuropathy in developed countries. DM is associated with several types of polyneuropathy: distal symmetric sensory or sensorimotor polyneuropathy, autonomic neuropathy, diabetic neuropathic cachexia, polyradiculoneuropathies, cranial neuropathies, and other mononeuropathies. Risk factors for the development of neuropathy include long-standing, poorly controlled DM and the presence of retinopathy and nephropathy.

Diabetic Distal Symmetric Sensory and Sensorimotor Polyneuropathy (DSPN) DSPN is the most common form of diabetic neuropathy and manifests as sensory loss beginning in the toes that gradually progresses over time up the legs and into the fingers and arms (Pattern 2, Table 446-2). When severe, a patient may develop sensory loss in the trunk (chest and abdomen), initially in the midline anteriorly and later extending laterally. Tingling, burning, deep aching pains may also be apparent. NCS usually show reduced amplitudes and mild to moderate slowing of conduction velocities. Nerve biopsy reveals axonal degeneration, endothelial hyperplasia, and, occasionally, perivascular inflammation. Tight control of glucose can reduce the risk of developing neuropathy or improve the underlying neuropathy. A variety of medications have been used with variable success to treat painful symptoms associated with DSPN, including antiepileptic medications, antidepressants, sodium channel blockers, and other analgesics (Table 446-6).

Diabetic Autonomic Neuropathy Autonomic neuropathy is typically seen in combination with DSPN. The autonomic neuropathy can manifest as abnormal sweating, dysfunctional thermoregulation, dry eyes and mouth, pupillary abnormalities, cardiac arrhythmias, postural hypotension, GI abnormalities (e.g., gastroparesis, postprandial bloating, chronic diarrhea, or constipation), and genitourinary dysfunction (e.g., impotence, retrograde ejaculation, incontinence) (Pattern 10, Table 446-2). Tests of autonomic function are generally abnormal, including sympathetic skin responses and quantitative

TABLE 446-6 Treatment of Painful Sensory Neuropathies

THERAPY	ROUTE	DOSE	SIDE EFFECTS
First-Line			
Lidoderm 5% patch	Apply to painful area	Up to 3 patches qd	Skin irritation
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)	PO	10–100 mg qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation
Gabapentin	PO	300–1200 mg tid	Cognitive changes, sedation, peripheral edema
Pregabalin	PO	50–100 mg tid	Cognitive changes, sedation, peripheral edema
Duloxetine	PO	30–60 mg qd	Cognitive changes, sedation, dry eyes, diaphoresis, nausea, diarrhea, constipation
Second-Line			
Carbamazepine	PO	200–400 mg q 6–8 h	Cognitive changes, dizziness, leukopenia, liver dysfunction
Phenytoin	PO	200–400 mg qhs	Cognitive changes, dizziness, liver dysfunction
Venlafaxine	PO	37.5–150 mg/d	Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence
Tramadol	PO	50 mg qid	Cognitive changes, gastrointestinal upset
Third-Line			
Mexitetine	PO	200–300 mg tid	Arrhythmias
Other Agents			
EMLA cream	Apply cutaneously	qid	Local erythema
2.5% lidocaine			
2.5% prilocaine			
Capsaicin 0.025–0.075% cream	Apply cutaneously	qid	Painful burning skin

Source: Modified from AA Amato, J Russell: *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill, 2016, Table 22-3, p. 485.

sudomotor axon reflex testing. Sensory and motor NCS generally demonstrate features described above with DSPN.

Diabetic Radiculoplexus Neuropathy (Diabetic Amyotrophy or Bruns-Garland Syndrome) Diabetic radiculoplexus neuropathy is the presenting manifestation of DM in approximately one-third of patients. Typically, patients present with severe pain in the low back, hip, and thigh in one leg. Rarely, the diabetic polyradiculoneuropathy begins in both legs at the same time (Pattern 4, Table 446-2). Atrophy and weakness of proximal and distal muscles in the affected leg become apparent within a few days or weeks. The neuropathy is often accompanied or heralded by severe weight loss. Weakness usually progresses over several weeks or months but can continue to progress for 18 months or more. Subsequently, there is slow recovery, but many are left with residual weakness, sensory loss, and pain. In contrast to the more typical lumbosacral radiculoplexus neuropathy, some patients develop thoracic radiculopathy or, even less commonly, a cervical polyradiculoneuropathy. CSF protein is usually elevated, while the cell count is normal. ESR is often increased. EDx reveals evidence of active denervation in affected proximal and distal muscles in the affected limbs and in paraspinal muscles. Nerve biopsies may demonstrate axonal degeneration along with perivascular inflammation. Patients with severe pain are sometimes treated in the acute period with glucocorticoids, although a randomized controlled trial has yet to be performed, and the natural history of this neuropathy is gradual improvement.

Diabetic Mononeuropathies or Multiple Mononeuropathies The most common mononeuropathies are median neuropathy at the wrist and ulnar neuropathy at the elbow, but peroneal neuropathy at the fibular head and sciatic, lateral femoral, cutaneous, or cranial neuropathies also occur (Pattern 3, Table 446-2). In regard to cranial mononeuropathies, seventh nerve palsies are relatively common but may have other, nondiabetic etiologies. In diabetes, a third nerve palsy is most common, followed by sixth nerve and, less frequently, fourth nerve palsies. Diabetic third nerve palsies are characteristically pupil-sparing (Chap. 32).

■ HYPOTHYROIDISM

Hypothyroidism is more commonly associated with a proximal myopathy, but some patients develop a neuropathy, most typically CTS. Rarely, a generalized sensory polyneuropathy characterized by painful paresthesias and numbness in both the legs and hands can occur. Treatment is correction of the hypothyroidism.

■ SJÖGREN'S SYNDROME

Sjögren's syndrome, characterized by the sicca complex of xerophthalmia, xerostomia, and dryness of other mucous membranes, can be complicated by neuropathy (Chap. 361). Most common is a length-dependent axonal sensorimotor neuropathy characterized mainly by sensory loss in the distal extremities (Pattern 2, Table 446-2). A pure small-fiber neuropathy or a cranial neuropathy, particularly involving the trigeminal nerve, can also be seen. Sjögren's syndrome is also associated with sensory neuronopathy/ganglionopathy. Patients with sensory ganglionopathies develop progressive numbness and tingling of the limbs, trunk, and face in a non-length-dependent manner such that symptoms can involve the face or arms more than the legs. The onset can be acute or insidious. Sensory examination demonstrates severe vibratory and proprioceptive loss leading to sensory ataxia.

Patients with neuropathy due to Sjögren's syndrome may have ANAs, SS-A/Ro, and SS-B/La antibodies in the serum, but most do not. NCS demonstrate reduced amplitudes of sensory studies in the affected limbs. Nerve biopsy demonstrates axonal degeneration. Nonspecific perivascular inflammation may be present, but only rarely is there necrotizing vasculitis. There is no specific treatment for neuropathies related to Sjögren's syndrome. When vasculitis is suspected, immunosuppressive agents may be beneficial. Occasionally, the sensory neuronopathy/ganglionopathy stabilizes or improves with immunotherapy, such as intravenous immunoglobulin.

■ RHEUMATOID ARTHRITIS

Peripheral neuropathy occurs in at least 50% of patients with rheumatoid arthritis (RA) and may be vasculitic in nature (Chap. 358). Vasculitic neuropathy can present with a mononeuropathy multiplex (Pattern 3, Table 446-2), a generalized symmetric pattern of involvement (Pattern 2, Table 446-2), or a combination of these patterns (Chap. 363). Neuropathies may also result from drugs used to treat RA (e.g., tumor necrosis blockers, leflunomide). Nerve biopsy often reveals thickening of the epineurial and endoneurial blood vessels as well as perivascular inflammation or vasculitis, with transmural inflammatory cell infiltration and fibrinoid necrosis of vessel walls. The neuropathy is usually responsive to immunomodulating therapies.

■ SYSTEMIC LUPUS ERYTHEMATOSUS

Between 2 and 27% of individuals with SLE develop a peripheral neuropathy (Chap. 356). Affected patients typically present with a slowly progressive sensory loss beginning in the feet. Some patients develop burning pain and paresthesias with normal reflexes, and NCS suggest a pure small-fiber neuropathy (Pattern 2, Table 446-2). Less common are multiple mononeuropathies presumably secondary to necrotizing vasculitis (Pattern 3, Table 446-2). Rarely, a generalized sensorimotor polyneuropathy meeting clinical, laboratory, electrophysiologic, and histologic criteria for either GBS or CIDP may occur. Immunosuppressive therapy may be beneficial in SLE patients with neuropathy due to vasculitis. Immunosuppressive agents are less likely to be effective in patients with a generalized sensory or sensorimotor polyneuropathy without evidence of vasculitis. Patients with a GBS or CIDP-like neuropathy should be treated accordingly (Chap. 447).

■ SYSTEMIC SCLEROSIS SCLERODERMA

A distal symmetric, mainly sensory polyneuropathy complicates 5–67% of scleroderma cases (Pattern 2, Table 446-2) (Chap. 360). Cranial mononeuropathies can also develop, most commonly of the trigeminal nerve, producing numbness and dysesthesias in the face. Multiple mononeuropathies also occur (Pattern 3, Table 446-2). The EDx and histologic features of nerve biopsy are those of an axonal sensory greater than motor polyneuropathy.

■ MIXED CONNECTIVE TISSUE DISEASE MCTD

A mild distal axonal sensorimotor polyneuropathy occurs in ~10% of patients with MCTD.

■ SARCOIDOSIS

The peripheral nervous system or CNS is involved in ~5% of patients with sarcoidosis (Chap. 367). The most common cranial nerve involved is the seventh nerve, which can be affected bilaterally. Some patients develop radiculopathy or polyradiculopathy (Pattern 4, Table 446-2). With a generalized root involvement, the clinical presentation can mimic GBS or CIDP. Patients can also present with multiple mononeuropathies (Pattern 3, Table 446-2) or a generalized, slowly progressive, sensory greater than motor polyneuropathy (Pattern 2, Table 446-2). Some have features of a pure small-fiber neuropathy. EDx reveals an axonal neuropathy. Nerve biopsy can reveal noncaseating granulomas infiltrating the endoneurium, perineurium, or epineurium along with lymphocytic necrotizing angiitis. Neurosarcoidosis may respond to treatment with glucocorticoids or other immunosuppressive agents.

■ HYPEREOSINOPHILIC SYNDROME

Hypereosinophilic syndrome is characterized by eosinophilia associated with various skin, cardiac, hematologic, and neurologic abnormalities. A generalized peripheral neuropathy or a mononeuropathy multiplex occurs in 6–14% of patients (Pattern 2, Table 446-2).

■ CELIAC DISEASE GLUTEN INDUCED ENTEROPATHY OR NONTROPICAL SPRUE

Neurologic complications, particularly ataxia and peripheral neuropathy, are estimated to occur in 10% of patients with celiac disease (Chap. 325). A generalized sensorimotor polyneuropathy, pure motor neuropathy, multiple mononeuropathies, autonomic neuropathy,

small-fiber neuropathy, and neuromyotonia have all been reported in association with celiac disease or antigliadin/antiendomysial antibodies (Patterns 2, 3, and 9; Table 446-2). Nerve biopsy may reveal a loss of large myelinated fibers. The neuropathy may be secondary to malabsorption of vitamins B₁₂ and E. However, some patients have no appreciable vitamin deficiencies. The pathogenic basis for the neuropathy in these patients is unclear but may be autoimmune in etiology. The neuropathy does not appear to respond to a gluten-free diet. In patients with vitamin B₁₂ or vitamin E deficiency, replacement therapy may improve or stabilize the neuropathy.

■ INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn's disease may be complicated by GBS, CIDP, generalized axonal sensory or sensorimotor polyneuropathy, small-fiber neuropathy, or mononeuropathy (Patterns 2 and 3, Table 446-2) (Chap. 326). These neuropathies may be autoimmune, nutritional (e.g., vitamin B₁₂ deficiency), treatment related (e.g., metronidazole), or idiopathic in nature. An acute neuropathy with demyelination resembling GBS, CIDP, or multifocal motor neuropathy may occur in patients treated with tumor necrosis factor α blockers.

■ UREMIC NEUROPATHY

Approximately 60% of patients with renal failure develop a polyneuropathy characterized by length-dependent numbness, tingling, allodynia, and mild distal weakness (Pattern 2, Table 446-2). Rarely, a rapidly progressive weakness and sensory loss very similar to GBS can occur that improves with an increase in the intensity of renal dialysis or with transplantation (Pattern 1, Table 446-2). Mononeuropathies can also occur, the most common of which is CTS. Ischemic mononeuric neuropathy (see below) can complicate arteriovenous shunts created in the arm for dialysis (Pattern 3, Table 446-2). EDx in uremic patients reveals features of a length-dependent, primarily axonal, sensorimotor polyneuropathy. Sural nerve biopsies demonstrate a loss of nerve fibers (particularly large myelinated nerve fibers), active axonal degeneration, and segmental and paranodal demyelination. The sensorimotor polyneuropathy can be stabilized by hemodialysis and improved with successful renal transplantation.

■ CHRONIC LIVER DISEASE

A generalized sensorimotor neuropathy characterized by numbness, tingling, and minor weakness in the distal aspects of primarily the lower limbs commonly occurs in patients with chronic liver failure. EDx studies are consistent with a sensory greater than motor axonopathy. Occasionally patients with severe liver disease develop a combined neuropathy and myopathy. Sural nerve biopsy reveals both segmental demyelination and axonal loss. It is not known if hepatic failure in isolation can cause peripheral neuropathy, as the majority of patients have liver disease secondary to other disorders, such as alcoholism or viral hepatitis, which can also cause neuropathy.

■ CRITICAL ILLNESS POLYNEUROPATHY

The most common causes of acute generalized weakness leading to admission to a medical intensive care unit (ICU) are GBS and myasthenia gravis (Pattern 1, Table 446-2) (Chaps. 447 and 448). However, weakness developing in critically ill patients while in the ICU is usually caused by critical illness polyneuropathy (CIP) or critical illness myopathy (CIM) or, much less commonly, by prolonged neuromuscular blockade. From a clinical and EDx standpoint, it can be quite difficult to distinguish these disorders. Most specialists believe that CIM is more common. Both CIM and CIP develop as a complication of sepsis and multiple organ failure. They usually present as an inability to wean a patient from a ventilator. A coexisting encephalopathy may limit the neurologic examination, in particular the sensory examination. Muscle stretch reflexes are absent or reduced.

Serum creatine kinase (CK) is usually normal; an elevated serum CK would point to CIM as opposed to CIP. NCS reveal absent or markedly reduced amplitudes of motor and sensory studies in CIP, whereas sensory studies are relatively preserved in CIM. Needle EMG usually reveals profuse positive sharp waves and fibrillation potentials,

and it is not unusual in patients with severe weakness to be unable to recruit motor unit action potentials. The pathogenic basis of CIP is not known. Perhaps circulating toxins and metabolic abnormalities associated with sepsis and multiorgan failure impair axonal transport or mitochondrial function, leading to axonal degeneration.

■ LEPROSY HANSEN'S DISEASE

Leprosy, caused by the acid-fast bacteria *Mycobacterium leprae*, is the most common cause of peripheral neuropathy in Southeast Asia, Africa, and South America (Chap. 179). Clinical manifestations range from tuberculoid leprosy at one end of the spectrum to lepromatous leprosy at the other end, with borderline leprosy in between. Neuropathies are most common in patients with borderline leprosy. Superficial cutaneous nerves of the ears and distal limbs are commonly affected. Mononeuropathies, multiple mononeuropathies, or a slowly progressive symmetric sensorimotor polyneuropathy may develop (Patterns 2 and 3, Table 446-2). Sensory NCS are usually absent in the lower limb and are reduced in amplitude in the arms. Motor NCS may demonstrate reduced amplitudes in affected nerves but occasionally can reveal demyelinating features. Leprosy is usually diagnosed by skin lesion biopsy. Nerve biopsy can also be diagnostic, particularly when there are no apparent skin lesions. The tuberculoid form is characterized by granulomas, and bacilli are not seen. In contrast, with lepromatous leprosy, large numbers of infiltrating bacilli, T_H2 lymphocytes, and organism-laden, foamy macrophages with minimal granulomatous infiltration are evident. The bacilli are best appreciated using the Fite stain, where they can be seen as red-staining rods often in clusters free in the endoneurium, within macrophages, or within Schwann cells.

Patients are generally treated with multiple drugs: dapsone, rifampin, and clofazimine. Other medications that are used include thalidomide, pefloxacin, ofloxacin, sparfloxacin, minocycline, and clarithromycin. Patients are generally treated for 2 years. Treatment is sometimes complicated by the so-called reversal reaction, particularly in borderline leprosy. The reversal reaction can occur at any time during treatment and develops because of a shift to the tuberculoid end of the spectrum, with an increase in cellular immunity during treatment. The cellular response is upregulated as evidenced by an increased release of tumor necrosis factor α , interferon γ , and interleukin 2, with new granuloma formation. This can result in an exacerbation of the rash and the neuropathy as well as in appearance of new lesions. High-dose glucocorticoids blunt this adverse reaction and may be used prophylactically at treatment onset in high-risk patients. Erythema nodosum leprosum (ENL) is also treated with glucocorticoids or thalidomide.

■ LYME DISEASE

Lyme disease is caused by infection with *Borrelia burgdorferi*, a spirochete usually transmitted by the deer tick *Ixodes dammini* (Chap. 186). Neurologic complications may develop during the second and third stages of infection. Facial neuropathy is most common and is bilateral in about half of cases, which is rare for idiopathic Bell's palsy. Involvement of nerves is frequently asymmetric. Some patients present with a polyradiculoneuropathy or multiple mononeuropathies (Pattern 3 or 4, Table 446-2). EDx is suggestive of a primary axonopathy. Nerve biopsies can reveal axonal degeneration with perivascular inflammation. Treatment is with antibiotics.

■ DIPHTHERITIC NEUROPATHY

Diphtheria is caused by the bacteria *Corynebacterium diphtheriae* (Chap. 150). Infected individuals present with flulike symptoms of generalized myalgias, headache, fatigue, low-grade fever, and irritability within a week to 10 days of the exposure. About 20–70% of patients develop a peripheral neuropathy caused by a toxin released by the bacteria. Three to 4 weeks after infection, patients may note decreased sensation in their throat and begin to develop dysphagia, dysarthria, hoarseness, and blurred vision due to impaired accommodation. A generalized polyneuropathy may manifest 2 or 3 months following the initial infection, characterized by numbness, paresthesias, and weakness of the arms and legs and occasionally ventilatory failure (Pattern 1, Table 446-2). CSF protein can be elevated with or without lymphocytic

pleocytosis. EDx suggests a diffuse axonal sensorimotor polyneuropathy. Antitoxin and antibiotics should be given within 48 h of symptom onset. Although early treatment reduces the incidence and severity of some complications (i.e., cardiomyopathy), it does not appear to alter the natural history of the associated peripheral neuropathy. The neuropathy usually resolves after several months.

COVID 19

GBS ([Chap. 447](#)) has been reported in the setting of acute COVID-19 infection.

HUMAN IMMUNODEFICIENCY VIRUS

HIV infection can result in a variety of neurologic complications, including peripheral neuropathies ([Chap. 202](#)). Approximately 20% of HIV-infected individuals develop a neuropathy as a direct result of the virus itself or as a result of other associated viral infections (e.g., CMV) or neurotoxicity secondary to antiviral medications (see below). The major presentations of peripheral neuropathy associated with HIV infection include (1) distal symmetric polyneuropathy (DSP), (2) inflammatory demyelinating polyneuropathy (including both GBS and CIDP), (3) multiple mononeuropathies (e.g., vasculitis, CMV-related), (4) polyradiculopathy (usually CMV-related), (5) autonomic neuropathy, and (6) sensory ganglionitis.

HIV-Related Distal Symmetric Polyneuropathy DSP is the most common form of peripheral neuropathy associated with HIV infection and usually is seen in patients with AIDS. It is characterized by numbness and painful paresthesias involving the distal extremities (Pattern 2, Table 446-2). The pathogenic basis for DSP is unknown but is not due to actual infection of the peripheral nerves. The neuropathy may be immune mediated, perhaps caused by the release of cytokines from surrounding inflammatory cells. Vitamin B₁₂ deficiency may contribute in some instances but is not a major cause of most cases of DSP. Older antiretroviral agents (e.g., dideoxycytidine, dideoxyinosine, stavudine) are also neurotoxic and can cause a painful sensory neuropathy.

HIV-Related Inflammatory Demyelinating Polyradiculoneuropathy Both acute inflammatory demyelinating polyneuropathy (AIDP) and CIDP can occur as a complication of HIV infection (Pattern 1, Table 446-2). AIDP usually develops at the time of seroconversion, whereas CIDP can occur any time in the course of the infection. Clinical and EDx features are indistinguishable from idiopathic AIDP or CIDP ([Chap. 447](#)). In addition to elevated protein levels, lymphocytic pleocytosis is evident in the CSF, a finding that helps distinguish this HIV-associated polyradiculoneuropathy from idiopathic AIDP/CIDP.

HIV-Related Progressive Polyradiculopathy An acute, progressive lumbosacral polyradiculoneuropathy usually secondary to CMV infection can develop in patients with AIDS (Pattern 4, Table 446-2). Patients present with severe radicular pain, numbness, and weakness in the legs, which is usually asymmetric. CSF is abnormal, demonstrating a high protein level, along with a reduced glucose concentration and notably a neutrophilic pleocytosis. EDx studies reveal features of active axonal degeneration. The polyradiculoneuropathy may improve with antiviral therapy.

HIV-Related Multiple Mononeuropathies Multiple mononeuropathies can also develop in patients with HIV infection, usually in the context of AIDS. Weakness, numbness, paresthesias, and pain occur in the distribution of affected nerves (Pattern 3, Table 446-2). Nerve biopsies can reveal axonal degeneration with necrotizing vasculitis or perivascular inflammation. Glucocorticoid treatment is indicated for vasculitis directly due to HIV infection.

HIV-Related Sensory Neuronopathy/ Ganglionopathy Dorsal root ganglionitis is a very rare complication of HIV infection, and neuronopathy can be the presenting manifestation. Patients develop sensory ataxia similar to idiopathic sensory neuronopathy/ganglionopathy (Pattern 9, Table 446-2). NCS reveal reduced amplitudes or absence of sensory nerve action potentials (SNAPs).

HERPES VARICELLA ZOSTER VIRUS

Peripheral neuropathy from herpes varicella-zoster (HVZ) infection results from reactivation of latent virus or from a primary infection ([Chap. 193](#)). Two-thirds of infections in adults are characterized by dermal zoster in which severe pain and paresthesias develop in a dermatomal region followed within a week or two by a vesicular rash in the same distribution (Pattern 3, Table 446-2). Weakness in muscles innervated by roots corresponding to the dermatomal distribution of skin lesions occurs in 5–30% of patients. Approximately 25% of affected patients have continued pain (postherpetic neuralgia [PHN]). A large clinical trial demonstrated that vaccination against zoster reduces the incidence of HVZ among vaccine recipients by 51% and reduces the incidence of PHN by 67%. Treatment of PHN is symptomatic (Table 446-6).

CYTOMEGALOVIRUS

CMV can cause an acute lumbosacral polyradiculopathy and multiple mononeuropathies in patients with HIV infection and in other immune deficiency conditions (Pattern 4, Table 446-2) ([Chap. 195](#)).

EPSTEIN BARR VIRUS

EBV infection has been associated with GBS, cranial neuropathies, mononeuropathy multiplex, brachial plexopathy, lumbosacral radiculoplexopathy, and sensory neuronopathies (Patterns 1, 3, 4, and 9, Table 446-2) ([Chap. 194](#)).

HEPATITIS VIRUSES

Hepatitis B and C can cause multiple mononeuropathies related to vasculitis, AIDP, or CIDP (Patterns 1 and 3, Table 446-2) ([Chap. 341](#)).

NEUROPATHIES ASSOCIATED WITH MALIGNANCY

Patients with malignancy can develop neuropathies due to (1) a direct effect of the cancer by invasion or compression of the nerves, (2) remote or paraneoplastic effect, (3) a toxic effect of treatment, or (4) as a consequence of immune compromise caused by immunosuppressive medications. The most common associated malignancy is lung cancer, but neuropathies also complicate carcinoma of the breast, ovaries, stomach, colon, rectum, and other organs, including the lymphoproliferative system.

PARANEOPLASTIC SENSORY NEURONOPATHY/GANGLIONOPATHY

Paraneoplastic encephalomyelitis/sensory neuronopathy (PEM/SN) usually complicates small-cell lung carcinoma ([Chap. 94](#)). Patients usually present with numbness and paresthesias in the distal extremities that are often asymmetric. The onset can be acute or insidiously progressive. Prominent loss of proprioception leads to sensory ataxia (Pattern 9; Table 446-2). Weakness can be present, usually secondary to an associated myelitis, motor neuronopathy, or concurrent LEMS. Many patients also develop confusion, memory loss, depression, hallucinations or seizures, or cerebellar ataxia. Polyclonal antineuronal antibodies (IgG) directed against a 35- to 40-kDa protein or complex of proteins, the so-called Hu antigen, are found in the sera or CSF in the majority of patients with paraneoplastic PEM/SN. CSF may be normal or may demonstrate mild lymphocytic pleocytosis and elevated protein. PEM/SN is probably the result of antigenic similarity between proteins expressed in the tumor cells and neuronal cells, leading to an immune response directed against both cell types. Treatment of the underlying cancer generally does not affect the course of PEM/SN. However, occasional patients may improve following treatment of the tumor. Unfortunately, plasmapheresis, intravenous immunoglobulin, and immunosuppressive agents have not shown benefit.

NEUROPATHY SECONDARY TO TUMOR INFILTRATION

Malignant cells, in particular leukemia and lymphoma, can infiltrate cranial and peripheral nerves, leading to mononeuropathy, mononeuropathy multiplex, polyradiculopathy, plexopathy, or even a generalized symmetric distal or proximal and distal polyneuropathy (Patterns 1, 2,

3492 3, and 4; Table 446-2). Neuropathy related to tumor infiltration is often painful; it can be the presenting manifestation of the cancer or the heralding symptom of a relapse. The neuropathy may improve with treatment of the underlying leukemia or lymphoma or with glucocorticoids.

■ NEUROPATHY AS A COMPLICATION OF BONE MARROW TRANSPLANTATION

Neuropathies may develop in patients who undergo bone marrow transplantation (BMT) because of the toxic effects of chemotherapy, radiation, infection, or an autoimmune response directed against the peripheral nerves. Peripheral neuropathy in BMT is often associated with graft-versus-host disease (GVHD). Chronic GVHD shares many features with a variety of autoimmune disorders, and it is possible that an immune-mediated response directed against peripheral nerves is responsible. Patients with chronic GVHD may develop cranial neuropathies, sensorimotor polyneuropathies, multiple mononeuropathies, and severe generalized peripheral neuropathies resembling AIDP or CIDP (Patterns 1, 2, and 3; Table 446-2). The neuropathy may improve by increasing the intensity of immunosuppressive or immunomodulating therapy and resolution of the GVHD.

■ LYMPHOMA

Lymphomas may cause neuropathy by infiltration or direct compression of nerves or by a paraneoplastic process. The neuropathy can be purely sensory or motor but most commonly is sensorimotor. The pattern of involvement may be symmetric, asymmetric, or multifocal, and the course may be acute, gradually progressive, or relapsing and remitting (Patterns 1, 2, and 3; Table 446-2). EDx can be compatible with either an axonal or demyelinating process. CSF may reveal lymphocytic pleocytosis and an elevated protein. Nerve biopsy may demonstrate endoneurial inflammatory cells in both the infiltrative and the paraneoplastic etiologies. A monoclonal population of cells favors lymphomatous invasion. The neuropathy may respond to treatment of the underlying lymphoma or immunomodulating therapies.

■ MULTIPLE MYELOMA

MM usually presents in the fifth to seventh decade of life with fatigue, bone pain, anemia, and hypercalcemia (*Chap. 111*). Clinical and EDx features of neuropathy occur in as many as 40% of patients. The most common pattern is that of a distal, axonal, sensory, or sensorimotor polyneuropathy (Pattern 2; Table 446-2). Less frequently, a chronic demyelinating polyradiculoneuropathy may develop (Pattern 1; Table 446-2) (see POEMS, *Chap. 447*). MM can be complicated by amyloid polyneuropathy and should be considered in patients with painful paresthesias, loss of pinprick and temperature discrimination, and autonomic dysfunction (suggestive of a small-fiber neuropathy) and CTS. Expanding plasmacytomas can compress cranial nerves and spinal roots as well. A monoclonal protein, usually composed of γ or μ heavy chains or κ light chains, may be identified in the serum or urine. EDx usually shows reduced amplitudes with normal or only mildly abnormal distal latencies and conduction velocities. A superimposed median neuropathy at the wrist is common. Abdominal fat pad, rectal, or sural nerve biopsy can be performed to look for amyloid deposition. Unfortunately, the treatment of the underlying MM does not usually affect the course of the neuropathy.

■ NEUROPATHIES ASSOCIATED WITH MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE SEE CHAP. 447

Toxic Neuropathies Secondary to Chemotherapy Many of the commonly used chemotherapy agents can cause a toxic neuropathy (Table 446-7). The mechanisms by which these agents cause toxic neuropathies vary, as does the specific type of neuropathy produced. The risk of developing a toxic neuropathy or more severe neuropathy appears to be greater in patients with a preexisting neuropathy (e.g., CMT disease, diabetic neuropathy) and those who also take other potentially neurotoxic drugs (e.g., nitrofurantoin, isoniazid, disulfiram, pyridoxine). Chemotherapeutic agents usually cause a sensory greater

than motor length-dependent axonal neuropathy or neuronopathy/ganglionopathy (Patterns 2 and 9; Table 446-2).

OTHER TOXIC NEUROPATHIES

Neuropathies can develop as complications of toxic effects of various drugs and other environmental exposures (Table 446-8). The more common neuropathies associated with these agents are discussed here.

■ CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine and hydroxychloroquine can cause a toxic myopathy characterized by slowly progressive, painless, proximal weakness and atrophy, which is worse in the legs than the arms. In addition, neuropathy can also develop with or without the myopathy leading to sensory loss and distal weakness. The "neuromyopathy" usually appears in patients taking 500 mg daily for a year or more but has been reported with doses as low as 200 mg/d. Serum CK levels are usually elevated due to the superimposed myopathy. NCS reveal mild slowing of motor and sensory NCVs with a mild to moderate reduction in the amplitudes, although NCS may be normal in patients with only the myopathy. EMG demonstrates myopathic muscle action potentials (MUAPs), increased insertional activity in the form of positive sharp waves, fibrillation potentials, and occasionally myotonic potentials, particularly in the proximal muscles. Neurogenic MUAPs and reduced recruitment are found in more distal muscles. Nerve biopsy demonstrates autophagic vacuoles within Schwann cells. Vacuoles may also be evident in muscle biopsies. The pathogenic basis of the neuropathy is not known but may be related to the amphiphilic properties of the drug. These agents contain both hydrophobic and hydrophilic regions that allow them to interact with the anionic phospholipids of cell membranes and organelles. The drug-lipid complexes may be resistant to digestion by lysosomal enzymes, leading to the formation of autophagic vacuoles filled with myeloid debris that may in turn cause degeneration of nerves and muscle fibers. The signs and symptoms of the neuropathy and myopathy are usually reversible following discontinuation of medication.

■ AMIODARONE

Amiodarone can cause a neuromyopathy similar to chloroquine and hydroxychloroquine. The neuromyopathy typically appears after patients have taken the medication for 2–3 years. Nerve biopsy demonstrates a combination of segmental demyelination and axonal loss. Electron microscopy reveals lamellar or dense inclusions in Schwann cells, pericytes, and endothelial cells. The inclusions in muscle and nerve biopsies have persisted as long as 2 years following discontinuation of the medication.

■ COLCHICINE

Colchicine can also cause a neuromyopathy. Patients usually present with proximal weakness and numbness and tingling in the distal extremities. EDx reveals features of an axonal polyneuropathy. Muscle biopsy reveals a vacuolar myopathy, whereas sensory nerves demonstrate axonal degeneration. Colchicine inhibits the polymerization of tubulin into microtubules. The disruption of the microtubules probably leads to defective intracellular movement of important proteins, nutrients, and waste products in muscle and nerves.

■ THALIDOMIDE

Thalidomide is an immunomodulating agent used to treat MM, GVHD, leprosy, and other autoimmune disorders. Thalidomide is associated with severe teratogenic effects as well as peripheral neuropathy that can be dose-limiting. Patients develop numbness, painful tingling, and burning discomfort in the feet and hands and less commonly muscle weakness and atrophy. Even after stopping the drug for 4–6 years, as many as 50% patients continue to have significant symptoms. NCS demonstrate reduced amplitudes or complete absence of SNAPs, with preserved conduction velocities when obtainable. Motor NCS are usually normal. Nerve biopsy reveals a loss of large-diameter myelinated fibers and axonal degeneration. Degeneration of dorsal root ganglion cells has been reported at autopsy.

TABLE 446-7 Toxic Neuropathies Secondary to Chemotherapy

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine)	Interfere with axonal microtubule assembly; impairs axonal transport	Symmetric, S-M, large-/small-fiber PN; autonomic symptoms common; infrequent cranial neuropathies	Axonal degeneration of myelinated and unmyelinated fibers; regenerating clusters, minimal segmental demyelination	Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception
Cisplatin	Preferential damage to dorsal root ganglia: ? binds to and cross-links DNA ? inhibits protein synthesis ? impairs axonal transport	Predominant large-fiber sensory neuropathy; sensory ataxia	Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination	Low-amplitude or unobtainable SNAPs with normal CMAPs and EMG; abnormal QST, particularly vibratory perception
Taxanes (paclitaxel, docetaxel)	Promotes axonal microtubule assembly; interferes with axonal transport	Symmetric, predominantly sensory PN; large-fiber modalities affected more than small-fiber	Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination	Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception
Suramin	Axonal PN Demyelinating PN	Unknown; ? inhibition of neurotrophic growth factor binding; ? neuronal lysosomal storage	Symmetric, length-dependent, sensory-predominant PN	None described Abnormalities consistent with an axonal S-M PN
		Unknown; ? immunomodulating effects	Subacute, S-M PN with diffuse proximal and distal weakness; areflexia; increased CSF protein	Loss of large and small myelinated fibers with primary demyelination and secondary axonal degeneration; occasional epi- and endoneurial inflammatory cell infiltrates Features suggestive of an acquired demyelinating sensorimotor PN (e.g., slow CVs, prolonged distal latencies and F-wave latencies, conduction block, temporal dispersion)
Cytarabine (ARA-C)	Unknown; ? selective Schwann cell toxicity; ? immunomodulating effects	GBS-like syndrome; pure sensory neuropathy; brachial plexopathy	Loss of myelinated nerve fibers; axonal degeneration; segmental demyelination; no inflammation	Axonal, demyelinating, or mixed S-M PN; denervation on EMG
Etoposide (VP-16)	Unknown; ? selective dorsal root ganglia toxicity	Length-dependent, sensory-predominant PN; autonomic neuropathy	None described	Abnormalities consistent with an axonal S-M PN
Bortezomib (Velcade)	Unknown	Length-dependent, sensory, predominantly small-fiber PN	Not reported	Abnormalities consistent with an axonal sensory neuropathy with early small-fiber involvement (abnormal autonomic studies)

Abbreviations: CMAP, compound motor action potential; CSF, cerebrospinal fluid; CVs, conduction velocities; EMG, electromyography; GBS, Guillain-Barré syndrome; NCS, nerve conduction studies; PN, polyneuropathy; QST, quantitative sensory testing; S-M, sensorimotor; SNAP, sensory nerve action potential.

Source: From AA Amato, JA Russell (eds): Neuromuscular Disorders, 2nd ed. McGraw-Hill Education, 2016, Table 19-3, p. 439; with permission.

■ PYRIDOXINE VITAMIN B₆ TOXICITY

Pyridoxine is an essential vitamin that serves as a coenzyme for transamination and decarboxylation. However, at high doses (116 mg/d), patients can develop a severe sensory neuropathy with dysesthesias and sensory ataxia. NCS reveal absent or markedly reduced SNAP amplitudes with relatively preserved CMAPs. Nerve biopsy reveals axonal loss of fiber at all diameters. Loss of dorsal root ganglion cells with subsequent degeneration of both the peripheral and central sensory tracts have been reported in animal models.

■ ISONIAZID

One of the most common side effects of isoniazid (INH) is peripheral neuropathy. Standard doses of INH (3–5 mg/kg per day) are associated with a 2% incidence of neuropathy, whereas neuropathy develops in at least 17% of patients taking in excess of 6 mg/kg per d. The elderly, malnourished, and “slow acetylators” are at increased risk for developing the neuropathy. INH inhibits pyridoxal phosphokinase, resulting in pyridoxine deficiency and the neuropathy. Prophylactic administration of pyridoxine 100 mg/d can prevent the neuropathy from developing.

■ ANTIRETROVIRAL AGENTS

The nucleoside analogues zalcitabine (dideoxycytidine or ddC), didanosine (dideoxyinosine or ddI), stavudine (d4T), lamivudine (3TC), and antiretroviral nucleoside reverse transcriptase inhibitor (NRTI) are used to treat HIV infection. One of the major dose-limiting side effects of these medications is a predominantly sensory, length-dependent, symmetrically painful neuropathy (Pattern 2; Table 446-2). Zalcitabine (ddC) is the most extensively studied of the nucleoside analogues, and at doses >0.18 mg/kg per d, it is associated

with a subacute onset of severe burning and lancinating pains in the feet and hands. NCS reveal decreased amplitudes of the SNAPs with normal motor studies. The nucleoside analogues inhibit mitochondrial DNA polymerase, which is the suspected pathogenic basis for the neuropathy. Because of a “coasting effect,” patients can continue to worsen even 2–3 weeks after stopping the medication. Following dose reduction, improvement in the neuropathy is seen in most patients after several months (mean time ~10 weeks).

■ HEXACARBONS n HEXANE, METHYL n BUTYL KETONE / GLUE SNIFFER'S NEUROPATHY

n-Hexane and methyl n-butyl ketone are water-insoluble industrial organic solvents that are also present in some glues. Exposure through inhalation, accidentally or intentionally (glue sniffing), or through skin absorption can lead to a profound subacute sensory and motor polyneuropathy (Pattern 2; Table 446-2). NCS demonstrate decreased amplitudes of the SNAPs and CMAPs with slightly slow CVs. Nerve biopsy reveals a loss of myelinated fibers and giant axons that are filled with 10-nm neurofilaments. Hexacarbon exposure leads to covalent cross-linking between axonal neurofilaments that results in their aggregation, impaired axonal transport, swelling of the axons, and eventual axonal degeneration.

■ LEAD

Lead neuropathy is uncommon, but it can be seen in children who accidentally ingest lead-based paints in older buildings and in industrial workers exposed to lead-containing products. The most common presentation of lead poisoning is an encephalopathy; however, symptoms and signs of a primarily motor neuropathy can also occur.

TABLE 446-8 Toxic Neuropathies

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Misonidazole	Unknown	Painful paresthesias and loss of large- and small-fiber sensory modalities and sometimes distal weakness in length-dependent pattern	Axonal degeneration of large, myelinated fibers; axonal swellings; segmental demyelination	Low-amplitude or unobtainable SNAPs with normal or only slightly reduced CMAP amplitudes
Metronidazole	Unknown	Painful paresthesias and loss of large- and small-fiber sensory modalities and sometimes distal weakness in length-dependent pattern	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal CMAPs
Chloroquine and hydroxychloroquine	Amphiphilic properties may lead to drug-lipid complexes that are indigestible and result in accumulation of autophagic vacuoles	Loss of large- and small-fiber sensory modalities and distal weakness in length-dependent pattern; superimposed myopathy may lead to proximal weakness	Axonal degeneration with autophagic vacuoles in nerves as well as muscle fibers	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; distal denervation on EMG; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy
Amiodarone	Amphiphilic properties may lead to drug-lipid complexes that are indigestible and result in accumulation of autophagic vacuoles	Paresthesias and pain with loss of large- and small-fiber sensory modalities and distal weakness in length-dependent pattern; superimposed myopathy may lead to proximal weakness	Axonal degeneration and segmental demyelination with myeloid inclusions in nerves and muscle fibers	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; can also have prominent slowing of CVs; distal denervation on EMG; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy
Colchicine	Inhibits polymerization of tubulin in microtubules and impairs axoplasmic flow	Numbness and paresthesias with loss of large-fiber modalities in a length-dependent fashion; superimposed myopathy may lead to proximal in addition to distal weakness	Nerve biopsy demonstrates axonal degeneration; muscle biopsy reveals fibers with vacuoles	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy
Podophyllin	Binds to microtubules and impairs axoplasmic flow	Sensory loss, tingling, muscle weakness, and diminished muscle stretch reflexes in length-dependent pattern; autonomic neuropathy	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Thalidomide	Unknown	Numbness, tingling, and burning pain and weakness in a length-dependent pattern	Axonal degeneration; autopsy studies reveal degeneration of dorsal root ganglia	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Disulfiram	Accumulation of neurofilaments and impaired axoplasmic flow	Numbness, tingling, and burning pain in a length-dependent pattern	Axonal degeneration with accumulation of neurofilaments in the axons	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Dapsone	Unknown	Distal weakness that may progress to proximal muscles; sensory loss	Axonal degeneration and segmental demyelination	Low-amplitude or unobtainable CMAPs with normal or reduced SNAP amplitudes
Leflunomide	Unknown	Paresthesias and numbness in a length-dependent pattern	Unknown	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Nitrofurantoin	Unknown	Numbness, painful paresthesias, and severe weakness that may resemble GBS	Axonal degeneration; autopsy studies reveal degeneration of dorsal root ganglia and anterior horn cells	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Pyridoxine (vitamin B ₆)	Unknown	Dysesthesias and sensory ataxia; impaired large-fiber sensory modalities on examination	Marked loss of sensory axons and cell bodies in dorsal root ganglia	Reduced amplitudes or absent SNAPs
Isoniazid	Inhibits pyridoxal phosphokinase leading to pyridoxine deficiency	Dysesthesias and sensory ataxia; impaired large-fiber sensory modalities on examination	Marked loss of sensory axons and cell bodies in dorsal root ganglia and degeneration of the dorsal columns	Reduced amplitudes or absent SNAPs and, to a lesser extent, CMAPs
Ethambutol	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration	Reduced amplitudes or absent SNAPs
Antinucleosides	Unknown	Dysesthesia and sensory ataxia; impaired large-fiber sensory modalities on examination	Axonal degeneration	Reduced amplitudes or absent SNAPs
Phenytoin	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration and segmental demyelination	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Lithium	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes

(Continued)

TABLE 446-8 Toxic Neuropathies (Continued)

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Acrylamide	Unknown; may be caused by impaired axonal transport	Numbness with loss of large-fiber modalities on examination; sensory ataxia; mild distal weakness	Degeneration of sensory axons in peripheral nerves and posterior columns, spinocerebellar tracts, mammillary bodies, optic tracts, and corticospinal tracts in the CNS	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Carbon disulfide	Unknown	Length-dependent numbness and tingling with mild distal weakness	Axonal swellings with accumulation of neurofilaments	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Ethylene oxide	Unknown; may act as alkylating agent and bind DNA	Length-dependent numbness and tingling; may have mild distal weakness	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Organophosphates	Bind and inhibit neuropathy target esterase	Early features are those of neuromuscular blockade with generalized weakness; later axonal sensorimotor PN ensues	Axonal degeneration along with degeneration of gracile fasciculus and corticospinal tracts	Early: repetitive firing of CMAPs and decrement with repetitive nerve stimulation; late: axonal sensorimotor PN
Hexacarbons	Unknown; may lead to covalent cross-linking between neurofilaments	Acute, severe sensorimotor PN that may resemble GBS	Axonal degeneration and giant axons swollen with neurofilaments	Features of a mixed axonal and/or demyelinating sensorimotor axonal PN—reduced amplitudes, prolonged distal latencies, conduction block, and slowing of CVs
Lead	Unknown; may interfere with mitochondria	Encephalopathy; motor neuropathy (often resembles radial neuropathy with wrist and finger drop); autonomic neuropathy; bluish-black discoloration of gums	Axonal degeneration of motor axons	Reduction of CMAP amplitudes with active denervation on EMG
Mercury	Unknown; may combine with sulphydryl groups	Abdominal pain and nephrotic syndrome; encephalopathy; ataxia; paresthesias	Axonal degeneration; degeneration of dorsal root ganglia, calcarine, and cerebellar cortex	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Thallium	Unknown	Encephalopathy; painful sensory symptoms; mild loss of vibration; distal or generalized weakness may also develop; autonomic neuropathy; alopecia	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Arsenic	Unknown; may combine with sulphydryl groups	Abdominal discomfort, burning pain, and paresthesias; generalized weakness; autonomic insufficiency; can resemble GBS	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; may have demyelinating features: prolonged distal latencies and slowing of CVs
Gold	Unknown	Distal paresthesias and reduction of all sensory modalities	Axonal degeneration	Low-amplitude or unobtainable SNAPs

Abbreviations: CMAP, compound motor action potential; CVs, conduction velocities; EMG, electromyography; GBS, Guillain-Barré syndrome; MUAP, muscle action potential; NCS, nerve conduction studies; PN, polyneuropathy; S-M, sensorimotor; SNAP, sensory nerve action potential.

Source: From AA Amato, JA Russell (eds): Neuromuscular Disorders, 2nd ed. McGraw-Hill Education, 2016, Table 20-1, p. 449-451; with permission.

The neuropathy is characterized by an insidious and progressive onset of weakness usually beginning in the arms, in particular involving the wrist and finger extensors, resembling a radial neuropathy. Sensation is generally preserved; however, the autonomic nervous system can be affected (Patterns 2, 3, and 10; Table 446-2). Laboratory investigation can reveal a microcytic hypochromic anemia with basophilic stippling of erythrocytes, an elevated serum lead level, and an elevated serum coproporphyrin level. A 24-h urine collection demonstrates elevated levels of lead excretion. The NCS may reveal reduced CMAP amplitudes, while the SNAPs are typically normal. The pathogenic basis may be related to abnormal porphyrin metabolism. The most important principle of management is to remove the source of the exposure. Chelation therapy with calcium disodium ethylene-diaminetetraacetic acid (EDTA), British anti-Lewisite (BAL), and penicillamine also demonstrates variable efficacy.

MERCURY

Mercury toxicity may occur as a result of exposure to either organic or inorganic mercurials. Mercury poisoning presents with paresthesias in hands and feet that progress proximally and may involve the face

and tongue. Motor weakness can also develop. CNS symptoms often overshadow the neuropathy. EDx shows features of a primarily axonal sensorimotor polyneuropathy. The primary site of neuromuscular pathology appears to be the dorsal root ganglia. The mainstay of treatment is removing the source of exposure.

THALLIUM

Thallium can exist in a monovalent or trivalent form and is primarily used as a rodenticide. The toxic neuropathy usually manifests as burning paresthesias of the feet, abdominal pain, and vomiting. Increased thirst, sleep disturbances, and psychotic behavior may be noted. Within the first week, patients develop pigmentation of the hair, an acne-like rash in the malar area of the face, and hyperreflexia. By the second and third weeks, autonomic instability with labile heart rate and blood pressure may be seen. Hyporeflexia and alopecia also occur but may not be evident until the third or fourth week following exposure. With severe intoxication, proximal weakness and involvement of the cranial nerves can occur. Some patients require mechanical ventilation due to respiratory muscle involvement. The lethal dose of thallium is variable, ranging from 8 to 15 mg/kg body weight. Death can result in

3496 <48 h following a particularly large dose. NCS demonstrate features of a primarily axonal sensorimotor polyneuropathy. With acute intoxication, potassium ferric ferrocyanide II may be effective in preventing absorption of thallium from the gut. However, there may be no benefit once thallium has been absorbed. Unfortunately, chelating agents are not very efficacious. Adequate diuresis is essential to help eliminate thallium from the body without increasing tissue availability from the serum.

■ ARSENIC

Arsenic is another heavy metal that can cause a toxic sensorimotor polyneuropathy. The neuropathy manifests 5–10 days after ingestion of arsenic and progresses for several weeks, sometimes mimicking GBS. The presenting symptoms are typically an abrupt onset of abdominal discomfort, nausea, vomiting, pain, and diarrhea followed within several days by burning pain in the feet and hands. Examination of the skin can be helpful in the diagnosis as the loss of the superficial epidermal layer results in patchy regions of increased or decreased pigmentation on the skin several weeks after an acute exposure or with chronic low levels of ingestion. Mee's lines, which are transverse lines at the base of the fingernails and toenails, do not become evident until 1 or 2 months after the exposure. Multiple Mee's lines may be seen in patients with long fingernails who have had chronic exposure to arsenic. Mee's lines are not specific for arsenic toxicity as they can also be seen following thallium poisoning. Because arsenic is cleared from blood rapidly, the serum concentration of arsenic is not diagnostically helpful. However, arsenic levels are increased in the urine, hair, and fingernails of patients exposed to arsenic. Anemia with stippling of erythrocytes is common, and occasionally, pancytopenia and aplastic anemia can develop. Increased CSF protein levels without pleocytosis can be seen; this can lead to misdiagnosis as GBS. NCS are usually suggestive of an axonal sensorimotor polyneuropathy; however, demyelinating features can be present. Chelation therapy with BAL has yielded inconsistent results; therefore, it is not generally recommended.

NUTRITIONAL NEUROPATHIES

■ COBALAMIN VITAMIN B₁₂

Pernicious anemia is the most common cause of cobalamin deficiency. Other causes include dietary avoidance (vegetarians), gastrectomy, gastric bypass surgery, inflammatory bowel disease, pancreatic insufficiency, bacterial overgrowth, and possibly histamine-2 blockers and proton pump inhibitors. An underappreciated cause of cobalamin deficiency is food-cobalamin malabsorption. This typically occurs in older individuals and results from an inability to adequately absorb cobalamin in food protein. No apparent cause of deficiency is identified in a significant number of patients with cobalamin deficiency. The use of nitrous oxide as an anesthetic agent or as a recreational drug can produce acute cobalamin deficiency neuropathy and subacute combined degeneration.

Complaints of numb hands typically appear before lower extremity paresthesias are noted. A preferential large-fiber sensory loss affecting proprioception and vibration with sparing of small-fiber modalities is present; an unsteady gait reflects sensory ataxia. These features, coupled with diffuse hyperreflexia and absent Achilles reflexes, should always focus attention on the possibility of cobalamin deficiency (Patterns 2 and 6; Table 446-2). Optic atrophy and, in severe cases, behavioral changes ranging from mild irritability and forgetfulness to severe dementia and frank psychosis may appear. The full clinical picture of subacute combined degeneration is uncommon. CNS manifestations, especially pyramidal tract signs, may be missing, and in fact, some patients may only exhibit symptoms of peripheral neuropathy.

EDx shows an axonal sensorimotor neuropathy. CNS involvement produces abnormal somatosensory and visual evoked potential latencies. The diagnosis is confirmed by finding reduced serum cobalamin levels. In up to 40% of patients, anemia and macrocytosis are lacking. Serum methylmalonic acid and homocysteine, the metabolites that accumulate when cobalamin-dependent reactions are blocked, are elevated. Antibodies to intrinsic factor are present in ~60% and

antiparietal cell antibodies in ~90% of individuals with pernicious anemia.

Cobalamin deficiency can be treated with various regimens of cobalamin. One typical regimen consists of 1000 µg cyanocobalamin IM weekly for 1 month and monthly thereafter. Patients with food cobalamin malabsorption can absorb free cobalamin and therefore can be treated with oral cobalamin supplementation. An oral cobalamin dose of 1000 µg/d should be sufficient. Treatment for cobalamin deficiency usually does not completely reverse the clinical manifestations, and at least 50% of patients exhibit some permanent neurologic deficit.

■ THIAMINE DEFICIENCY

Thiamine (vitamin B₁) deficiency is an uncommon cause of peripheral neuropathy in developed countries. It is now most often seen as a consequence of chronic alcohol abuse, recurrent vomiting, total parenteral nutrition, and bariatric surgery. Thiamine deficiency polyneuropathy can occur in normal, healthy young adults who do not abuse alcohol but who engage in inappropriately restrictive diets. Thiamine is water-soluble. It is present in most animal and plant tissues, but the greatest sources are unrefined cereal grains, wheat germ, yeast, soybean flour, and pork. Beriberi means "I can't, I can't" in Singhalese, the language of natives of what was once part of the Dutch East Indies (now Sri Lanka). *Dry beriberi* refers to neuropathic symptoms. The term *wet beriberi* is used when cardiac manifestations predominate (in reference to edema). Beriberi was relatively uncommon until the late 1800s when it became widespread among people for whom rice was a dietary mainstay. This epidemic was due to a new technique of processing rice that removed the germ from the rice shaft, rendering the so-called polished rice deficient in thiamine and other essential nutrients.

Symptoms of neuropathy follow prolonged deficiency. These begin with mild sensory loss and/or burning dysesthesias in the toes and feet and aching and cramping in the lower legs. Pain may be the predominant symptom. With progression, patients develop features of a nonspecific generalized polyneuropathy, with distal sensory loss in the feet and hands.

Blood and urine assays for thiamine are not reliable for diagnosis of deficiency. Erythrocyte transketolase activity and the percentage increase in activity (*in vitro*) following the addition of thiamine pyrophosphate (TPP) may be more accurate and reliable. EDx shows nonspecific findings of an axonal sensorimotor polyneuropathy. When a diagnosis of thiamine deficiency is made or suspected, thiamine replacement should be provided until proper nutrition is restored. Thiamine is usually given intravenously or intramuscularly at a dose of 100 mg/d. Although cardiac manifestations show a striking response to thiamine replacement, neurologic improvement is usually more variable and less dramatic.

■ VITAMIN E DEFICIENCY

The term *vitamin E* is usually used for α-tocopherol, the most active of the four main types of vitamin E. Because vitamin E is present in animal fat, vegetable oils, and various grains, deficiency is usually due to factors other than insufficient intake. Vitamin E deficiency usually occurs secondary to lipid malabsorption or in uncommon disorders of vitamin E transport. One hereditary disorder is abetalipoproteinemia, a rare autosomal dominant disorder characterized by steatorrhea, pigmentary retinopathy, acanthocytosis, and progressive ataxia. Patients with cystic fibrosis may also have vitamin E deficiency secondary to steatorrhea. There are genetic forms of isolated vitamin E deficiency not associated with lipid malabsorption. Vitamin E deficiency may also occur as a consequence of various cholestatic and hepatobiliary disorders as well as short-bowel syndromes resulting from the surgical treatment of intestinal disorders.

Clinical features may not appear until many years after the onset of deficiency. The onset of symptoms tends to be insidious, and progression is slow. The main clinical features are spinocerebellar ataxia and polyneuropathy, thus resembling Friedreich's ataxia or other spinocerebellar ataxias. Patients manifest progressive ataxia and signs of posterior column dysfunction, such as impaired joint position and vibratory sensation. Because of the polyneuropathy, there is hyporeflexia, but

plantar responses may be extensor as a result of the spinal cord involvement (Patterns 2 and 6; Table 446-2). Other neurologic manifestations may include ophthalmoplegia, pigmented retinopathy, night blindness, dysarthria, pseudoathetosis, dystonia, and tremor. Vitamin E deficiency may present as an isolated polyneuropathy, but this is very rare. The yield of checking serum vitamin E levels in patients with isolated polyneuropathy is extremely low, and this test should not be part of routine practice.

Diagnosis is made by measuring α -tocopherol levels in the serum. EDx shows features of an axonal neuropathy. Treatment is replacement with oral vitamin E, but high doses are not needed. For patients with isolated vitamin E deficiency, treatment consists of 1500–6000 IU/d in divided doses.

VITAMIN B₆ DEFICIENCY

Vitamin B₆, or pyridoxine, can produce neuropathic manifestations from both deficiency and toxicity. Vitamin B₆ toxicity was discussed above. Vitamin B₆ deficiency is most commonly seen in patients treated with isoniazid or hydralazine. The polyneuropathy of vitamin B₆ is nonspecific, manifesting as a generalized axonal sensorimotor polyneuropathy. Vitamin B₆ deficiency can be detected by direct assay. Vitamin B₆ supplementation with 50–100 mg/d is suggested for patients being treated with isoniazid or hydralazine. This same dose is appropriate for replacement in cases of nutritional deficiency.

PELLAGRA NIACIN DEFICIENCY

Pellagra is produced by deficiency of niacin. Although pellagra may be seen in alcoholics, this disorder has essentially been eradicated in most Western countries by means of enriching bread with niacin. Nevertheless, pellagra continues to be a problem in a number of underdeveloped regions, particularly in Asia and Africa, where corn is the main source of carbohydrate. Neurologic manifestations are variable; abnormalities can develop in the brain and spinal cord as well as peripheral nerves. When peripheral nerves are involved, the neuropathy is usually mild and resembles beriberi. Treatment is with niacin 40–250 mg/d.

COPPER DEFICIENCY

A syndrome that has only recently been described is myeloneuropathy secondary to copper deficiency. Most patients present with lower limb paresthesias, weakness, spasticity, and gait difficulties (Pattern 6; Table 446-2). Large-fiber sensory function is impaired, reflexes are brisk, and plantar responses are extensor. In some cases, light touch and pinprick sensation are affected, and NCS indicate sensorimotor axonal polyneuropathy in addition to myelopathy.

Hematologic abnormalities are a known complication of copper deficiency; these can include microcytic anemia, neutropenia, and occasionally pancytopenia. Because copper is absorbed in the stomach and proximal jejunum, many cases of copper deficiency occur in the setting of prior gastric surgery. Excess zinc is an established cause of copper deficiency. Zinc upregulates enterocyte production of metallothioneine, which results in decreased absorption of copper. Excessive dietary zinc supplements or denture cream containing zinc can produce this clinical picture. Other potential causes of copper deficiency include malnutrition, prematurity, total parenteral nutrition, and ingestion of copper-chelating agents.

Following oral or IV copper replacement, some patients show neurologic improvement, but this may take many months or not occur at all. Replacement consists of oral copper sulfate or gluconate 2 mg one to three times a day. If oral copper replacement is not effective, elemental copper in the copper sulfate or copper chloride forms can be given as 2 mg IV daily for 3–5 days, then weekly for 1–2 months until copper levels normalize. Thereafter, oral daily copper therapy can be resumed. In contrast to the neurologic manifestations, most of the hematologic indices normalize in response to copper replacement therapy.

NEUROPATHY ASSOCIATED WITH GASTRIC SURGERY

Polyneuropathy may occur following gastric surgery for ulcer, cancer, or weight reduction. This usually occurs in the context of rapid,

significant weight loss and recurrent, protracted vomiting. The clinical picture is one of acute or subacute sensory loss and weakness. Neuropathy following weight loss surgery usually occurs in the first several months after surgery. Weight reduction surgical procedures include gastrojejunostomy, gastric stapling, vertical banded gastroplasty, and gastrectomy with Roux-en-Y anastomosis. The initial manifestations are usually numbness and paresthesias in the feet (Pattern 2; Table 446-2). In many cases, no specific nutritional deficiency factor is identified.

Management consists of parenteral vitamin supplementation, especially including thiamine. Improvement has been observed following supplementation, parenteral nutritional support, and reversal of the surgical bypass. The duration and severity of deficits before identification and treatment of neuropathy are important predictors of final outcome.

CRYPTOGENIC IDIOPATHIC SENSORY AND SENSORIMOTOR POLYNEUROPATHY

Cryptogenic (idiopathic) sensory and sensorimotor polyneuropathy (CSPN) is a diagnosis of exclusion, established after a careful medical, family, and social history; neurologic examination; and directed laboratory testing. Despite extensive evaluation, the cause of polyneuropathy in as many as 50% of all patients is idiopathic. CSPN should be considered a distinct diagnostic subset of peripheral neuropathy. The onset of CSPN is predominantly in the sixth and seventh decades. Patients complain of distal numbness, tingling, and often burning pain that invariably begins in the feet and may eventually involve the fingers and hands ("burning feet syndrome"). Patients exhibit a distal sensory loss to pinprick, touch, and vibration in the toes and feet, and occasionally in the fingers (Pattern 2; Table 446-2). It is uncommon to see significant proprioception deficits, even though patients may complain of gait unsteadiness. However, tandem gait may be abnormal in a minority of cases. Neither subjective nor objective evidence of weakness is a prominent feature. Most patients have evidence of both large- and small-fiber loss on neurologic examination and EDx. Approximately 10% of patients have only evidence of small-fiber involvement. The ankle muscle stretch reflex is frequently absent, but in cases with predominantly small-fiber loss, this may be preserved. The EDx findings range from isolated SNAP abnormalities (usually with loss of amplitude), to evidence for an axonal sensorimotor neuropathy, to a completely normal study (if primarily small fibers are involved). Therapy primarily involves the control of neuropathic pain (Table 446-6) if present. Recently, a large comparative effectiveness study in CSPN showed that the drugs nortriptyline and duloxetine outperformed pregabalin and mexiletine. These drugs should not be used if the patient has only numbness and tingling but no pain.

Although no treatment is available that can reverse an idiopathic distal peripheral neuropathy, the prognosis is good. Progression often does not occur or is minimal, with sensory symptoms and signs progressing proximally up to the knees and elbows. The disorder does not lead to significant motor disability over time. The relatively benign course of this disorder should be explained to patients.

MONONEUROPATHIES/PLEXOPATHIES/RADICULOPATHIES PATTERN 3; TABLE 446 2

MEDIAN NEUROPATHY

CTS is a compression of the median nerve in the carpal tunnel at the wrist. The median nerve enters the hand through the carpal tunnel by coursing under the transverse carpal ligament. The symptoms of CTS consist of numbness and paresthesias variably in the thumb, index, middle, and half of the ring finger. At times, the paresthesias can include the entire hand and extend into the forearm or upper arm or can be isolated to one or two fingers. Pain is another common symptom and can be located in the hand and forearm and, at times, in the proximal arm. CTS is common and often misdiagnosed as thoracic outlet syndrome. The signs of CTS are decreased sensation in the median nerve distribution; reproduction of the sensation of tingling when a percussion hammer is tapped over the wrist (Tinel sign) or the

wrist is flexed for 30–60 s (Phalen sign); and weakness of thumb opposition and abduction. EDx is extremely sensitive and shows slowing of sensory and, to a lesser extent, motor median potentials across the wrist. Ultrasound can show focal swelling of the median nerve at the wrist. Treatment options consist of avoidance of precipitating activities; control of underlying systemic-associated conditions if present; nonsteroidal anti-inflammatory medications; neutral (volar) position wrist splints, especially for night use; glucocorticoid/anesthetic injection into the carpal tunnel; and surgical decompression by dividing the transverse carpal ligament. The surgical option should be considered if there is a poor response to nonsurgical treatments; if there is thenar muscle atrophy and/or weakness; and if there are significant denervation potentials on EMG.

Other proximal median neuropathies are very uncommon and include the pronator teres syndrome and anterior interosseous neuropathy. These often occur as a partial form of brachial plexitis.

■ ULNAR NEUROPATHY AT THE ELBOW “CUBITAL TUNNEL SYNDROME”

The ulnar nerve passes through the condylar groove between the medial epicondyle and the olecranon. Symptoms consist of paresthesias, tingling, and numbness in the medial hand and half of the fourth and the entire fifth fingers, pain at the elbow or forearm, and weakness. Signs consist of decreased sensation in an ulnar distribution, Tinel's sign at the elbow, and weakness and atrophy of ulnar-innervated hand muscles. The Froment sign indicates thumb adductor weakness and consists of flexion of the thumb at the interphalangeal joint when attempting to oppose the thumb against the lateral border of the second digit. EDx may show slowing of ulnar motor NCV across the elbow with prolonged ulnar sensory latencies. Ultrasound can show swelling of the ulnar nerve around the elbow as well. Treatment consists of avoiding aggravating factors, using elbow pads, and surgery to decompress the nerve in the cubital tunnel. Ulnar neuropathies can also rarely occur at the wrist in the ulnar (Guyon) canal or in the hand, usually after trauma.

■ RADIAL NEUROPATHY

The radial nerve winds around the proximal humerus in the spiral groove and proceeds down the lateral arm and enters the forearm, dividing into the posterior interosseous nerve and superficial nerve. The symptoms and signs consist of wrist drop; finger extension weakness; thumb abduction weakness; and sensory loss in the dorsal web between the thumb and index finger. Triceps and brachioradialis strength is often normal, and triceps reflex is often intact. Most cases of radial neuropathy are transient compressive (neuropraxic) injuries that recover spontaneously in 6–8 weeks. If there has been prolonged compression and severe axonal damage, it may take several months to recover. Treatment consists of cock-up wrist and finger splints, avoiding further compression, and physical therapy to avoid flexion contracture. If there is no improvement in 2–3 weeks, an EDx study is recommended to confirm the clinical diagnosis and determine the degree of severity.

■ LATERAL FEMORAL CUTANEOUS NEUROPATHY MERALGIA PARESTHETICA

The lateral femoral cutaneous nerve arises from the upper lumbar plexus (spinal levels L2/3), crosses through the inguinal ligament near its attachment to the iliac bone, and supplies sensation to the anterior lateral thigh. The neuropathy affecting this nerve is also known as meralgia paresthetica. Symptoms and signs consist of paresthesias, numbness, and occasionally pain in the lateral thigh. Symptoms are increased by standing or walking and are relieved by sitting. There is normal strength, and knee reflexes are intact. The diagnosis is clinical, and further tests usually are not performed. EDx is only needed to rule out lumbar plexopathy, radiculopathy, or femoral neuropathy. If the symptoms and signs are classic, EMG is not necessary. Symptoms often resolve spontaneously over weeks or months, but the patient may be left with permanent numbness. Treatment consists of weight loss and avoiding tight belts. Analgesics in the form of a lidocaine patch, nonsteroidal agents, and occasionally medications for neuropathic pain

can be used (Table 446-6). Rarely, locally injecting the nerve with an anesthetic can be tried. There is no role for surgery.

■ FEMORAL NEUROPATHY

Femoral neuropathies can arise as complications of retroperitoneal hematoma, lithotomy positioning, hip arthroplasty or dislocation, iliac artery occlusion, femoral arterial procedures, infiltration by hematogenous malignancy, penetrating groin trauma, pelvic surgery including hysterectomy and renal transplantation, and diabetes (a partial form of lumbosacral diabetic plexopathy); some cases are idiopathic. Patients with femoral neuropathy have difficulty extending their knee and flexing the hip. Sensory symptoms occurring either on the anterior thigh and/or medial leg occur in only half of reported cases. A prominent painful component is the exception rather than the rule, may be delayed, and is often self-limited in nature. The quadriceps (patellar) reflex is diminished.

■ SCIATIC NEUROPATHY

Sciatic neuropathies commonly complicate hip arthroplasty, pelvic procedures in which patients are placed in a prolonged lithotomy position, trauma, hematomas, tumor infiltration, and vasculitis. In addition, many sciatic neuropathies are idiopathic. Weakness may involve all motions of the ankles and toes as well as flexion of the leg at the knee; abduction and extension of the thigh at the hip are spared. Sensory loss occurs in the entire foot and the distal lateral leg. The ankle jerk and, on occasion, the internal hamstring reflex are diminished or more typically absent on the affected side. The peroneal subdivision of the sciatic nerve is typically involved disproportionately to the tibial counterpart. Thus, patients may have only ankle dorsiflexion and eversion weakness with sparing of knee flexion, ankle inversion, and plantar flexion; these features can lead to misdiagnosis of a common peroneal neuropathy.

■ PERONEAL NEUROPATHY

The sciatic nerve divides at the distal femur into the tibial and peroneal nerve. The common peroneal nerve passes posterior and laterally around the fibular head, under the fibular tunnel. It then divides into the superficial peroneal nerve, which supplies the ankle evertor muscles and sensation over the anterolateral distal leg and dorsum of the foot, and the deep peroneal nerve, which supplies ankle dorsiflexors and toe extensor muscles and a small area of sensation dorsally in the area of the first and second toes.

Symptoms and signs consist of foot drop (ankle dorsiflexion, toe extension, and ankle eversion weakness) and variable sensory loss, which may involve the superficial and deep peroneal pattern. There is usually no pain. Onset may be on awakening in the morning. Peroneal neuropathy needs to be distinguished from L5 radiculopathy. In L5 radiculopathy, ankle invertors and evertors are weak and needle EMG reveals denervation. EDx can help localize the lesion. Peroneal motor conduction velocity shows slowing and amplitude drop across the fibular head. Management consists of rapid weight loss and avoiding leg crossing. Foot drop is treated with an ankle brace. A knee pad can be worn over the lateral knee to avoid further compression. Most cases spontaneously resolve over weeks or months.

■ RADICULOPATHIES

Radiculopathies are most often due to compression from degenerative joint disease and herniated disks, but there are a number of unusual etiologies (Table 446-9). Degenerative spine disease affects a number of different structures, which narrow the diameter of the neural foramen or canal of the spinal column and compromise nerve root integrity; *these are discussed in detail in Chap. 17.*

■ PLEXOPATHIES PATTERN 4; TABLE 446 2

■ BRACHIAL PLEXUS

The brachial plexus is composed of three trunks (upper, middle, and lower), with two divisions (anterior and posterior) per trunk (Fig. 446-2). Subsequently, the trunks divide into three cords (medial, lateral, and posterior), and from these, arise the multiple terminal

TABLE 446-9 Causes of Radiculopathy

- Herniated nucleus pulposus
- Degenerative joint disease
- Rheumatoid arthritis
- Trauma
- Vertebral body compression fracture
- Pott's disease
- Compression by extradural mass (e.g., meningioma, metastatic tumor, hematoma, abscess)
- Primary nerve tumor (e.g., neurofibroma, schwannoma, neurinoma)
- Carcinomatous meningitis
- Perineurial spread of tumor (e.g., prostate cancer)
- Acute inflammatory demyelinating polyradiculopathy
- Chronic inflammatory demyelinating polyradiculopathy
- Sarcoidosis
- Amyloidoma
- Diabetic radiculopathy
- Infection (Lyme disease, herpes zoster, HIV, cytomegalovirus, syphilis, schistosomiasis, *Strongyloides*)
- Arachnoiditis (e.g., postsurgical)
- Radiation

nerves innervating the arm. The anterior primary rami of C5 and C6 fuse to form the upper trunk; the anterior primary ramus of C7 continues as the middle trunk, while the anterior rami of C8 and T1 join to form the lower trunk. There are several disorders commonly associated with brachial plexopathy.

Immune-Mediated Brachial Plexus Neuropathy Immune-mediated brachial plexus neuropathy (IBPN) goes by various terms, including *acute brachial plexitis*, *neuralgic amyotrophy*, and *Parsonage-Turner syndrome*. IBPN usually presents with an acute onset of severe pain in the shoulder region. The intense pain usually lasts several days to a few weeks, but a dull ache can persist. Individuals who are affected may not appreciate weakness of the arm early in the course because the pain limits movement. However, as the pain dissipates, weakness and often sensory loss are appreciated. Attacks can occasionally recur.

Clinical findings are dependent on the distribution of involvement (e.g., specific trunk, divisions, cords, or terminal nerves). The most common pattern of IBPN involves the upper trunk or a single or

multiple mononeuropathies primarily involving the suprascapular, long thoracic, or axillary nerves. Additionally, the phrenic and anterior interosseous nerves may be concomitantly affected. Any of these nerves may also be affected in isolation. EDx is useful to confirm and localize the site(s) of involvement. Empirical treatment of severe pain with glucocorticoids is often used in the acute period.

Brachial Plexopathies Associated with Neoplasms Neoplasms involving the brachial plexus may be primary nerve tumors, local cancers expanding into the plexus (e.g., Pancoast lung tumor or lymphoma), and metastatic tumors. Primary brachial plexus tumors are less common than the secondary tumors and include schwannomas, neurinomas, and neurofibromas. Secondary tumors affecting the brachial plexus are more common and are always malignant. These may arise from local tumors, expanding into the plexus. For example, a Pancoast tumor of the upper lobe of the lung may invade or compress the lower trunk, whereas a primary lymphoma arising from the cervical or axillary lymph nodes may also infiltrate the plexus. Pancoast tumors typically present as an insidious onset of pain in the upper arm, sensory disturbance in the medial aspect of the forearm and hand, and weakness and atrophy of the intrinsic hand muscles along with an ipsilateral Horner's syndrome. Chest computed tomography (CT) scans or magnetic resonance imaging (MRI) can demonstrate extension of the tumor into the plexus. Metastatic involvement of the brachial plexus may occur with spread of breast cancer into the axillary lymph nodes and local spread into the nearby nerves.

Perioperative Plexopathies (Median Sternotomy) The most common surgical procedures associated with brachial plexopathy as a complication are those that involve median sternotomies (e.g., open-heart surgeries and thoracotomies). Brachial plexopathies occur in as many as 5% of patients following a median sternotomy and typically affect the lower trunk. Thus, individuals manifest with sensory disturbance affecting the medial aspect of forearm and hand along with weakness of the intrinsic hand muscles. The mechanism is related to the stretch of the lower trunk, so most individuals who are affected recover within a few months.

Lumbosacral Plexus The lumbar plexus arises from the ventral primary rami of the first to the fourth lumbar spinal nerves (Fig. 446-3). These nerves pass downward and laterally from the vertebral column within the psoas major muscle. The femoral nerve derives from the dorsal branches of the second to the fourth lumbar ventral rami. The obturator nerve arises from the ventral branches

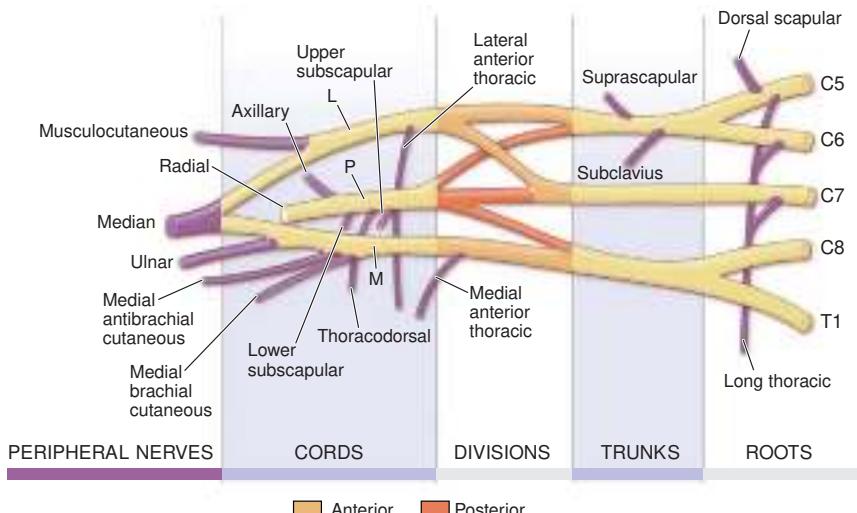


FIGURE 446-2 Brachial plexus anatomy. L, lateral; M, medial; P, posterior. (Reproduced with permission J Goodgold: Anatomical Correlates of Clinical Electromyography. Baltimore, Williams and Wilkins, 1974.)

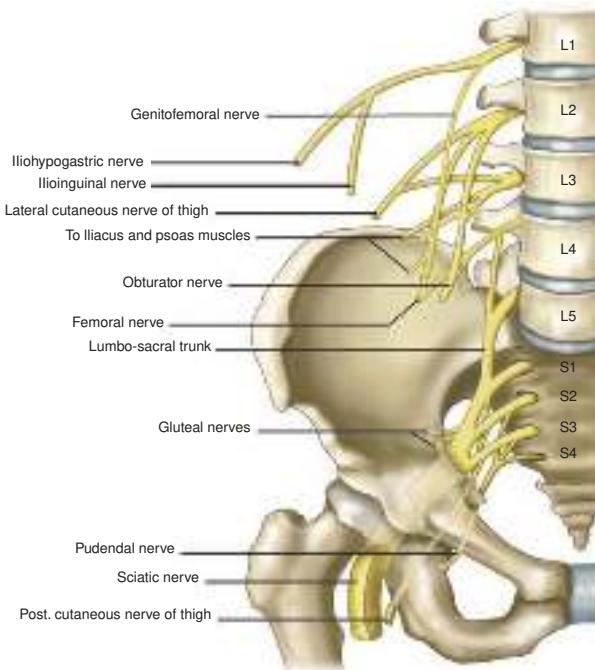


FIGURE 446-3 Lumbosacral plexus. (From AA Amato, JA Russell (eds): *Neuromuscular Disorders*, 2nd ed. McGraw-Hill Education, 2016, Figure 24-3, p. 542, with permission.)

of the same lumbar rami. The lumbar plexus communicates with the sacral plexus by the lumbosacral trunk, which contains some fibers from the fourth and all of the fibers from the fifth lumbar ventral ramus (Fig. 446-4).

The sacral plexus is the part of the lumbosacral plexus that is formed by the union of the lumbosacral trunk with the ventral rami of the first to fourth sacral nerves. The plexus lies on the posterior and posterolateral wall of the pelvis with its components converging toward the sciatic notch. The lateral trunk of the sciatic nerve (which forms the common peroneal nerve) arises from the union of the dorsal branches of the lumbosacral trunk (L4, L5) and the dorsal branches of the S1 and S2 spinal nerve ventral rami. The medial trunk of the sciatic nerve (which forms the tibial nerve) derives from the ventral branches of the same ventral rami (L4–S2).

LUMBOSACRAL PLEXOPATHIES

Plexopathies are typically recognized when motor, sensory, and if applicable, reflex deficits occur in multiple nerve and segmental distributions confined to one extremity. If localization within the lumbosacral plexus can be accomplished, designation as a lumbar plexopathy, a sacral plexopathy, a lumbosacral trunk lesion, or a panplexopathy is the best localization that can be expected. Although lumbar plexopathies may be bilateral, usually occurring in a stepwise and chronologically dissociated manner, sacral plexopathies are more likely to behave in this manner due to their closer anatomic proximity. The differential diagnosis of plexopathy includes disorders of the conus medullaris and cauda equina (polyradiculopathy). If there is a paucity of pain and sensory involvement, motor neuron disease should be considered as well.

The causes of lumbosacral plexopathies are listed in Table 446-10. Diabetic radiculopathy (discussed above) is a fairly common cause of painful leg weakness. Lumbosacral plexopathies are a well-recognized complication of retroperitoneal hemorrhage. Various primary and metastatic malignancies can affect the lumbosacral plexus as well; these include carcinoma of the cervix, endometrium, and ovary; osteosarcoma; testicular cancer; MM; lymphoma; acute myelogenous leukemia; colon cancer; squamous cell carcinoma of the

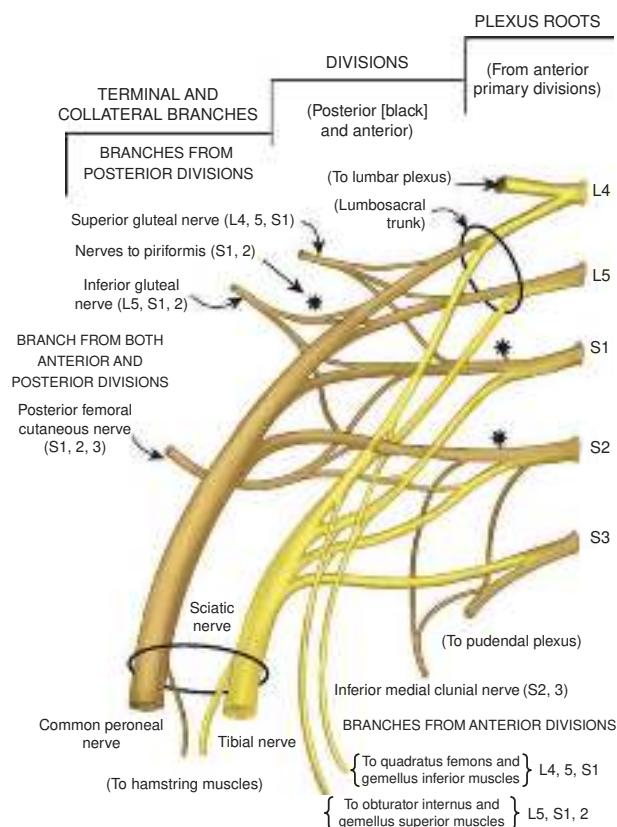


FIGURE 446-4 Lumbosacral trunk sacral plexus and sciatic nerve. (From AA Amato, JA Russell (eds): *Neuromuscular Disorders*, 2nd ed. McGraw-Hill Education, 2016, Figure 24-4, p. 542, with permission.)

rectum; adenocarcinoma of unknown origin; and intraneuronal spread of prostate cancer.

RECURRENT NEOPLASTIC DISEASE OR RADIATION INDUCED PLEXOPATHY

The treatment for various malignancies is often radiation therapy, the field of which may include parts of the brachial plexus. It can be difficult in such situations to determine if a new brachial or lumbosacral plexopathy is related to tumor within the plexus or from radiation-induced nerve damage. Radiation can be associated with microvascular abnormalities and fibrosis of surrounding tissues, which can damage the axons and the Schwann cells. Radiation-induced plexopathy can develop months or years following therapy and is dose dependent.

TABLE 446-10 Lumbosacral Plexopathies: Etiologies

- Retroperitoneal hematoma
- Psoas abscess
- Malignant neoplasm
- Benign neoplasm
- Radiation
- Amyloid
- Diabetic radiculoplexus neuropathy
- Idiopathic radiculoplexus neuropathy
- Sarcoidosis
- Aortic occlusion/surgery
- Lithotomy positioning
- Hip arthroplasty
- Pelvic fracture
- Obstetric injury

Tumor invasion is usually painful and more commonly affects the lower trunk, whereas radiation injury is often painless and affects the upper trunk. Imaging studies such as MRI and CT scans are useful but can be misleading, especially when there is small microscopic invasion of the plexus. EMG can be informative if myokymic discharges are appreciated, as this finding strongly suggests radiation-induced damage.

EVALUATION AND TREATMENT OF PLEXOPATHIES

Most patients with plexopathies will undergo both imaging with MRI and EDx evaluations. Severe pain from acute idiopathic lumbosacral plexopathy may respond to a short course of glucocorticoids.

FURTHER READING

- A D et al: Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med* 379:11, 2018.
- A AA, R AH: Sensory ganglionopathy. *N Engl J Med* 383:1657, 2020.
- A AA, R J: *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill, 2016.
- B RJ, A AA: Pattern-recognition approach to neuropathy and neuronopathy. *Neurol Clin* 31:343, 2013.
- B RJ et al: Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTROLS) Bayesian adaptive comparative effectiveness randomized trial. *JAMA Neurol* 78:68, 2021.
- B M et al: Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med* 379:22, 2018.
- C AS et al: Inherited neuropathies. *Semin Neurol* 39:620, 2019.
- E JD et al: Evaluation of distal symmetric polyneuropathy: The role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). *Muscle Nerve* 39:106, 2009.
- E JD et al: Evaluation of distal symmetric polyneuropathy: The role of laboratory and genetic testing (an evidence-based review). *Muscle Nerve* 39:116, 2009.
- F EL et al: Diabetic neuropathy. *Nat Rev Dis Primers* 5:41, 2019.
- H -W LD, J VC: Common entrapment neuropathies. *Continuum (Minneapolis Minn)* 23:487, 2017.
- J PH, S SC: Neuropathy of connective tissue diseases and other systemic diseases. *Semin Neurol* 39:651, 2019.
- W JM et al: Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. *Neurology* 87:978, 2016.

rubbery legs. Weakness typically evolves over hours to a few days and is frequently accompanied by tingling dysesthesias in the extremities. The legs are usually more affected than the arms, and facial diparesis is present in 50% of affected individuals. The lower cranial nerves are also frequently involved, causing bulbar weakness with difficulty handling secretions and maintaining an airway; the diagnosis in these patients may initially be mistaken for brainstem ischemia. Pain in the neck, shoulder, back, or diffusely over the spine is also common in the early stages of GBS, occurring in ~50% of patients. Most patients require hospitalization, and in different series, up to 30% require ventilatory assistance at some time during the illness. The need for mechanical ventilation is associated with more severe weakness on admission, a rapid tempo of progression, and the presence of facial and/or bulbar weakness during the first week of symptoms. Fever and constitutional symptoms are absent at the onset and, if present, cast doubt on the diagnosis. Deep tendon reflexes attenuate or disappear within the first few days of onset. Cutaneous sensory deficits (e.g., loss of pain and temperature sensation) are usually relatively mild, but functions subserved by large sensory fibers, such as deep tendon reflexes and proprioception, are more severely affected. Bladder dysfunction may occur in severe cases but is usually transient. If bladder dysfunction is a prominent feature and comes early in the course or there is a sensory level on examination, diagnostic possibilities other than GBS should be considered, particularly spinal cord disease (Chap. 442). Once clinical worsening stops and the patient reaches a plateau (almost always within 4 weeks of onset), further progression is unlikely.

Autonomic involvement is common and may occur even in patients whose GBS is otherwise mild. The usual manifestations are loss of vasomotor control with wide fluctuations in blood pressure, postural hypotension, and cardiac dysrhythmias. These features require close monitoring and management and can be fatal. Pain is another common feature of GBS; in addition to the acute pain described above, a deep aching pain may be present in weakened muscles that patients liken to having overexercised the previous day. Other pains in GBS include dysesthetic pain in the extremities as a manifestation of sensory nerve fiber involvement. These pains are self-limited and often respond to standard analgesics (Chap. 13).

Several subtypes of GBS are recognized, as determined primarily by electrodiagnostic (EDx) and pathologic distinctions (Table 447-1). The most common variant is acute inflammatory demyelinating polyneuropathy (AIDP). Additionally, there are two “axonal” or “nodal/paranodal” variants, which are often clinically severe: the acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN) subtypes. In addition, a range of limited or regional GBS syndromes are also encountered. Notable among these is the Miller Fisher syndrome (MFS), which presents as rapidly evolving ataxia and areflexia of limbs without weakness, and ophthalmoplegia, often with pupillary paralysis. The MFS variant accounts for ~5% of all cases and is strongly associated with antibodies to the ganglioside GQ1b (see “Immunopathogenesis,” below). Other regional variants of GBS include (1) pure sensory forms; (2) ophthalmoplegia with anti-GQ1b antibodies as part of severe motor-sensory GBS; (3) GBS with severe bulbar and facial paralysis, sometimes associated with antecedent cytomegalovirus (CMV) infection and anti-GM2 antibodies; and (4) acute pandysautonomia (Chap. 440).

Antecedent Events Approximately 70% of cases of GBS occur 1–3 weeks after an acute infectious process, usually respiratory or gastrointestinal. Culture and seroepidemiologic techniques show that 20–30% of all cases occurring in North America, Europe, and Australia are preceded by infection or reinfection with *Campylobacter jejuni*. A similar proportion is preceded by a human herpes virus infection, often CMV or Epstein-Barr virus. Other viruses (e.g., HIV, hepatitis E, Zika) and also *Mycoplasma pneumoniae* have been identified as agents involved in antecedent infections, as have recent immunizations. The swine influenza vaccine, administered widely in the United States in 1976, is the most notable example. Influenza vaccines in use from 1992 to 1994, however, resulted in only one additional case of GBS per million persons vaccinated, and the more recent seasonal influenza

447

Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies

Stephen L. Hauser, Anthony A. Amato

GUILLAIN BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature. It occurs year-round at a rate of between 10 to 20 cases per million annually; in the United States, ~5000–6000 cases occur per year. Males are at slightly higher risk for GBS than females, and in Western countries, adults are more frequently affected than children.

Clinical Manifestations GBS manifests as a rapidly evolving areflexic motor paralysis with or without sensory disturbance. The usual pattern is an ascending paralysis that may be first noticed as

TABLE 447-1 Subtypes of Guillain-Barré Syndrome (GBS)

Subtype	Features	Electrodiagnosis	Pathology
Acute inflammatory demyelinating polyneuropathy (AIDP)	Adults affected more than children; 90% of cases in Western world; recovery rapid; anti-GM1 antibodies (<50%)	Demyelinating	First attack on Schwann cell surface; widespread myelin damage, macrophage activation, and lymphocytic infiltration; variable secondary axonal damage
Acute motor axonal neuropathy (AMAN)	Children and young adults; prevalent in China and Mexico; may be seasonal; recovery rapid; anti-GD1a antibodies	Axonal	First attack at motor nodes of Ranvier; macrophage activation, few lymphocytes, frequent periaxonal macrophages; extent of axonal damage highly variable
Acute motor sensory axonal neuropathy (AMSAN)	Mostly adults; uncommon; recovery slow, often incomplete; closely related to AMAN	Axonal	Same as AMAN, but also affects sensory nerves and roots; axonal damage usually severe
Miller Fisher syndrome (MFS)	Adults and children; ophthalmoplegia, ataxia, and areflexia; anti-GQ1b antibodies (90%)	Axonal or demyelinating	Few cases examined; resembles AIDP

vaccines appear to confer a GBS risk of <1 per million. Epidemiologic studies looking at H1N1 vaccination demonstrated at most only a slight increased risk of GBS. Meningococcal vaccinations (Menactra) do not appear to carry an increased risk. Older-type rabies vaccine, prepared in nervous system tissue, is implicated as a trigger of GBS in developing countries where it is still used; the mechanism is presumably immunization against neural antigens. GBS also occurs more frequently than can be attributed to chance alone in patients with lymphoma (including Hodgkin's disease), in HIV-seropositive individuals, and in patients with systemic lupus erythematosus (SLE). GBS, other inflammatory neuropathies, and myositis can also occur as a complication of immune checkpoint inhibitors used to treat various cancers.

C. jejuni has also been implicated in summer outbreaks of AMAN among children and young adults exposed to chickens in rural China. Infection by Zika virus recently has been implicated in the increased incidence of GBS in Brazil and other endemic regions. Recently, GBS has been reported with SARS-CoV-2 infection during the COVID-19 pandemic, but a causal relationship has not been established. There appears to be an increased risk of GBS with SARS-CoV-2 vaccines using adenovirus vectors, but not the messenger RNA vaccines.

Immunopathogenesis Several lines of evidence support an autoimmune basis for acute inflammatory demyelinating polyneuropathy (AIDP), the most common and best-studied type of GBS; the concept extends to all of the subtypes of GBS (Table 447-1).

It is likely that both cellular and humoral immune mechanisms contribute to tissue damage in AIDP. T-cell activation is suggested by the finding that elevated levels of cytokines and cytokine receptors are present in serum (interleukin [IL] 2, soluble IL-2 receptor) and in cerebrospinal fluid (CSF) (IL-6, tumor necrosis factor α , interferon γ). AIDP is also closely analogous to an experimental T cell-mediated immunopathy designated *experimental allergic neuritis* (EAN). EAN is induced in laboratory animals by immune sensitization against protein fragments derived from peripheral nerve proteins and, in particular, against the P2 protein. Based on analogy to EAN, it was initially thought that AIDP was likely to be primarily a T cell-mediated disorder; however, abundant data now suggest that autoantibodies directed against T cell-independent nonprotein determinants may be central to many cases.

Circumstantial evidence suggests that all GBS results from immune responses to nonself antigens (infectious agents, vaccines) that misdirect to host nerve tissue through a resemblance-of-epitope (molecular mimicry) mechanism (Fig. 447-1). The neural targets are likely to be glycoconjugates, specifically gangliosides (Table 447-2; Fig. 447-2). Gangliosides are complex glycosphingolipids that contain one or more sialic acid residues; various gangliosides participate in cell-cell interactions (including those between axons and glia), modulation of receptors, and regulation of growth. They are typically exposed on the plasma membrane of cells, rendering them susceptible to an antibody-mediated attack. Gangliosides and other glycoconjugates are present in large quantity in human nervous tissues and in key sites, such as nodes of Ranvier. Antiganglioside antibodies, most frequently to GM1, are common in GBS (20–50%

of cases), particularly in AMAN and AMSAN, and in those cases, they are preceded by *C. jejuni* infection. Some AIDP autoantibodies may recognize glycolipid heterocomplexes, rather than single species, present on cell membranes. Furthermore, isolates of *C. jejuni* from stool cultures of patients with GBS have surface glycolipid structures that antigenically cross react with gangliosides, including GM1, concentrated in human nerves. Sialic acid residues from pathogenic *C. jejuni* strains can also trigger activation of dendritic cells via signaling through Toll-like receptor 4 (TLR4), promoting B-cell differentiation and further amplifying humoral autoimmunity. Another line of evidence implicating humoral autoimmunity is derived from cases of GBS that followed intravenous administration of bovine brain gangliosides for treatment of various neuropathies; 5–15 days after injection, some recipients developed AMAN with high titers of anti-GM1 antibodies that recognized epitopes at nodes of Ranvier and motor endplates. Experimentally, anti-GM1 antibodies can trigger complement-mediated injury at paranodal axon-glial junctions, disrupting the clustering of sodium channels and likely contributing to conduction block (see "Pathophysiology" below).

Anti-GQ1b IgG antibodies are found in >90% of patients with MFS (Table 447-2; Fig. 447-2), and titers of IgG are highest early in the course. Anti-GQ1b antibodies are not found in other forms of GBS unless there is extraocular motor nerve involvement. A possible explanation for this association is that extraocular motor nerves are enriched in GQ1b gangliosides in comparison to limb nerves. In addition, a monoclonal anti-GQ1b antibody raised against *C. jejuni* isolated from a patient with MFS blocked neuromuscular transmission experimentally.

Taken together, these observations provide strong but still inconclusive evidence that autoantibodies play an important pathogenic role in GBS. Although antiganglioside antibodies have been studied most intensively, other antigenic targets may also be important. Proof that these antibodies are pathogenic requires that they be capable of mediating disease following direct passive transfer to naïve hosts; this has not yet been demonstrated, although one case of possible maternal-fetal transplacental transfer of GBS has been described.

In AIDP, an early step in the induction of tissue damage appears to be complement deposition along the outer surface of the Schwann cell. Activation of complement initiates a characteristic vesicular disintegration of the myelin sheath and also leads to recruitment of activated macrophages, which participate in damage to myelin and axons. In AMAN, the pattern is different in that complement is deposited along with IgG at the nodes of Ranvier along large motor axons. Interestingly, in cases of AMAN, antibodies against GD1a appear to have a fine specificity that favors binding to motor rather than sensory nerve roots, even though this ganglioside is expressed on both fiber types.

Pathophysiology In the demyelinating forms of GBS, the basis for flaccid paralysis and sensory disturbance is conduction block. This finding, demonstrable electrophysiologically, implies that the axonal connections remain intact. Hence, recovery can take place rapidly as remyelination occurs. In severe cases of demyelinating GBS, secondary

Subtypes and variants	IgG autoantibodies to
Guillain-Barré syndrome	
Acute inflammatory demyelinating polyneuropathy	None
Facial variant: Facial diplegia and paresthesia	None
Acute motor axonal neuropathy	GM1, GD1a
More and less extensive forms	
Acute motor-sensory axonal neuropathy	GM1, GD1a
Acute motor-conduction-block neuropathy	GM1, GD1a
Pharyngeal-cervical-brachial weakness	GT1a>GQ1b>>GD1a
Miller Fisher syndrome	GQ1b, GT1a
Incomplete forms	
Acute ophthalmoparesis (without ataxia)	GQ1b, GT1a
Acute ataxic neuropathy (without ophthalmoplegia)	GQ1b, GT1a
CNS variant: Bickerstaff's brainstem encephalitis	GQ1b, GT1a

KEY

- ◆ Galactose
- ◆ Glucose
- ◆ N-Acetylgalactosamine
- ◆ N-Acetylneuramini acid
- Cer Ceramide

FIGURE 447-1 Spectrum of disorders in Guillain-Barré syndrome and associated antiganglioside antibodies. IgG autoantibodies against GM1 or GD1a are strongly associated with acute motor axonal neuropathy (AMAN), as well as the more extensive acute motor-sensory axonal neuropathy (AMSAN), and the less extensive acute motor-conduction-block neuropathy. IgG anti-GQ1b antibodies, which cross-react with GT1a, are strongly associated with Miller Fisher syndrome, its incomplete forms (acute ophthalmoparesis [without ataxia] and acute ataxic neuropathy [without ophthalmoplegia]), and its more extensive form, Bickerstaff's brainstem encephalitis. Pharyngeal-cervical-brachial weakness is categorized as a localized form of acute motor axonal neuropathy or an extensive form of Miller Fisher syndrome. Half of patients with pharyngeal-cervical-brachial weakness have IgG anti-GT1a antibodies, which often cross-react with GQ1b. IgG anti-GD1a antibodies have also been detected in a small percentage of patients. The anti-GQ1b antibody syndrome includes Miller Fisher syndrome, acute ophthalmoparesis, acute ataxic neuropathy, Bickerstaff's brainstem encephalitis, and pharyngeal-cervical-brachial weakness. The presence of clinical overlap also indicates that Miller Fisher syndrome is part of a continuous spectrum with these conditions. Patients who have had Guillain-Barré syndrome overlapped with Miller Fisher syndrome or with its related conditions have IgG antibodies against GM1 or GD1a as well as against GQ1b or GT1a, supporting a link between AMAN and anti-GQ1b syndrome. (From N Yuki, H-P Hartung: Guillain-Barré syndrome. *N Engl J Med* 366:2294, 2012. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

axonal degeneration usually occurs; its extent can be estimated electrophysiologically. More secondary axonal degeneration correlates with a slower rate of recovery and a greater degree of residual disability. With AMAN and AMSAN, a primary axonal pattern is encountered electrophysiologically (low-amplitude compound muscle action potentials). The implication has been that axons have degenerated and become disconnected from their targets, specifically the neuromuscular junctions, and must therefore regenerate for recovery to take place. However, the rapid recover in many cases suggests the low amplitudes are often from reversible conduction block due to binding of antibodies to ion channel proteins in the nodes and paranodes. In severe cases, axonal degeneration can occur, and it is in these cases that recovery is much slower.

Laboratory Features CSF findings are distinctive, consisting of an elevated CSF protein level (1–10 g/L [100–1000 mg/dL]) without accompanying pleocytosis. The CSF is often normal when symptoms have been present for ≤ 48 h; by the end of the first week, the level of protein is usually elevated. A transient increase in the CSF white cell count (10–100/ μ L) occurs on occasion in otherwise typical GBS; however, a sustained CSF pleocytosis suggests an alternative diagnosis (viral myelitis) or a concurrent diagnosis such as unrecognized HIV infection, leukemia or lymphoma with infiltration of nerves, or neurosarcoidosis. EDx features are mild or absent in the early stages of GBS and lag behind the clinical evolution. In AIDP, the earliest features are prolonged F-wave latencies, prolonged distal latencies, and reduced amplitudes of compound muscle action potentials (CMAPs), probably owing to the predilection for involvement of nerve roots and distal motor nerve terminals early in the course. Later, slowing of conduction velocity, conduction block, and temporal dispersion may be appreciated (Table 447-1). Occasionally, sensory nerve action

potentials (SNAPs) may be normal in the feet (e.g., sural nerve) when abnormal in the arms. This is also a sign that the patient does not have one of the more typical “length-dependent” polyneuropathies. As mentioned, in AMAN and AMSAN, the principal EDx finding is reduced amplitude of CMAPs (and also SNAPs with AMSAN) without conduction slowing or prolongation of distal latencies, which early on is caused by conduction block but later can be due to axonal degeneration.

Diagnosis GBS is a descriptive entity. The diagnosis of AIDP is made by recognizing the pattern of rapidly evolving paralysis with areflexia, absence of fever or other systemic symptoms, and characteristic antecedent events. In 2011, the Brighton Collaboration developed a new set of case definitions for GBS in response to needs of epidemiologic studies of vaccination and assessing risks of GBS (Table 447-3). These criteria have subsequently been validated. Other disorders that may enter into the differential diagnosis include acute myelopathies (especially with prolonged back pain and sphincter disturbances); diphtheria (early oropharyngeal disturbances); Lyme polyradiculitis and other tick-borne paralyses; porphyria (abdominal pain, seizures, psychosis); vasculitic neuropathy (check erythrocyte sedimentation rate, described below); poliomylitis and acute flaccid myelitis (wild-type poliovirus, West Nile virus, enterovirus D68, enterovirus A71, Japanese encephalitis virus, and the wild-type poliovirus); CMV polyradiculitis (in immunocompromised patients); critical illness neuropathy or myopathy; neuromuscular junction disorders such as myasthenia gravis and botulism (pupillary reactivity lost early); poisonings with organophosphates, thallium, or arsenic; paralytic shellfish poisoning; or severe hypophosphatemia (rare). Cases of acute flaccid myelitis may pose particular challenges

TABLE 447-2 Principal Antiglycolipid Antibodies Implicated in Immune Neuropathies

CLINICAL PRESENTATION	ANTIBODY TARGET	USUAL ISOTYPE
Acute Immune Neuropathies (Guillain-Barré Syndrome)		
Acute inflammatory demyelinating polyneuropathy (AIDP)	No clear patterns GM1 most common	IgG (polyclonal)
Acute motor axonal neuropathy (AMAN)	GD1a, GM1, GM 1b, GalNAc–GD1a (<50% for any)	IgG (polyclonal)
Miller Fisher syndrome (MFS)	GQ1b (>90%)	IgG (polyclonal)
Acute pharyngeal cervicobrachial neuropathy (APCBN)	GT1a (? most)	IgG (polyclonal)
Chronic Immune Neuropathies		
Chronic inflammatory demyelinating polyneuropathy (CIDP) (75%)	Approximately 10% to CNTN1 or NF155, less often to NF140/186 and Caspr1, and even more rarely to P0, myelin P2 protein, or PMP22	IgG4 with CNTN1, NF155, NF140/186, Caspr1 Rare IgM with NF155
CIDP-M (MGUS associated) (25%)	Neural binding sites	IgG, IgA (monoclonal)
Chronic sensory > motor neuropathy	SGPG, SGLPG (on MAG) (50%)	IgM (monoclonal)
	Uncertain (50%)	IgM (monoclonal)
Multifocal motor neuropathy (MMN)	GM1, GalNAc–GD1a, others (25–50%)	IgM (polyclonal, monoclonal)
Chronic sensory ataxic neuropathy	GD1b, GQ1b, and other b-series gangliosides	IgM (monoclonal)

Abbreviations: CIDP-M, CIDP with a monoclonal gammopathy; Caspr1, contactin associated protein-1; CNTN1, contactin-1; MAG, myelin-associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance; NF140/186, neurofascin 140/186; NF155, neurofascin 155; SGPG, sulfoglucuronyl paragloboside; SGLPG, sulfoglucuronyl lactosaminyl paragloboside.

Source: Reproduced with permission from HJ Willison, N Yuki: Peripheral neuropathies and anti-glycolipid antibodies. *Brain* 125:2591, 2002.

in distinguishing these from GBS because sphincter disturbances are often absent.

Laboratory tests are helpful primarily to exclude mimics of GBS. CSF pleocytosis is seen with poliomyelitis, acute flaccid myelitis, and Lyme and CMV polyradiculitis. EDx features may be minimal early in GBS, and the CSF protein level may not rise until the end of the first week. If the diagnosis is strongly suspected, treatment should be initiated without waiting for evolution of the characteristic EDx and CSF findings to occur. GBS patients with risk factors for HIV or with CSF pleocytosis should have a serologic test for HIV.

TREATMENT

Guillain-Barré Syndrome

In the vast majority of patients with GBS, treatment should be initiated as soon after diagnosis as possible. Each day counts; ~2 weeks after the first motor symptoms, it is not known whether immunotherapy is still effective. If the patient has already reached the plateau stage, then treatment probably is no longer indicated, unless the patient has severe motor weakness and one cannot exclude the possibility that an immunologic attack is still ongoing. Either high-dose intravenous immune globulin (IVIg) or plasmapheresis (PLEX) can be initiated, as they are equally effective for typical GBS. A combination of the two therapies is not significantly better than either alone. IVIg is often the initial therapy chosen because of its ease of administration and good safety record. IVIg is usually administered as five daily infusions for a total dose of

2 g/kg body weight. There is some evidence that GBS autoantibodies are neutralized by anti-idiotypic antibodies present in IVIg preparations, perhaps accounting for the therapeutic effect. A course of PLEX usually consists of ~40–50 mL/kg plasma exchange (PE) 4–5 times over 7–10 days. Meta-analysis of randomized clinical trials indicates that treatment reduces the need for mechanical ventilation by nearly half (from 27 to 14% with PLEX) and increases the likelihood of full recovery at 1 year (from 55 to 68%). Functionally significant improvement may occur toward the end of the first week of treatment or may be delayed for several weeks. The lack of noticeable improvement following a course of IVIg or PLEX is not an indication to treat with the alternate treatment. However, there are occasional patients who are treated early in the course of GBS and improve, who then relapse within a month. Brief retreatment with the original therapy is usually effective in such cases. Glucocorticoids have not been found to be effective in GBS. Occasional patients with very mild forms of GBS, especially those who appear to have already reached a plateau when initially seen, may be managed conservatively without IVIg or PLEX.

In the worsening phase of GBS, most patients require monitoring in a critical care setting, with particular attention to vital capacity, heart rhythm, blood pressure, nutrition, deep-vein thrombosis prophylaxis, cardiovascular status, early consideration (after 2 weeks of intubation) of tracheotomy, and chest physiotherapy. As noted, ~30% of patients with GBS require ventilatory assistance, sometimes for prolonged periods of time (several weeks or longer). Frequent turning and assiduous skin care are important, as are daily range-of-motion exercises to avoid joint contractures and daily reassurance as to the generally good outlook for recovery.

Prognosis and Recovery Approximately 85% of patients with GBS achieve a full functional recovery within several months to a year, although minor findings on examination (such as areflexia) may persist and patients often complain of continued symptoms, including fatigue. The mortality rate is <5% in optimal settings; death usually results from secondary pulmonary complications. The outlook is worst in patients with severe proximal motor and sensory axonal damage. Such axonal damage may be either primary or secondary in nature (see “Pathophysiology,” above), but in either case, successful regeneration cannot occur. Other factors that worsen the outlook for recovery are advanced age, a fulminant or severe attack, and a delay in the onset of treatment. Between 5 and 10% of patients with typical GBS have one or more late relapses; many of these cases are then classified as chronic inflammatory demyelinating polyneuropathy (CIDP).

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

CIDP is distinguished from GBS by its chronic course. In other respects, this neuropathy shares many features with the common demyelinating form of GBS, including elevated CSF protein levels and the EDx findings of acquired demyelination. Most cases occur in adults, and males are affected slightly more often than females. The incidence of CIDP is lower than that of GBS, but due to the protracted course, the prevalence is greater. As with GBS, CIDP and its variants can be triggered by use of immune checkpoint inhibitors used to treat various cancers.

Clinical Manifestations Onset is usually gradual over a few months or longer, but in a few cases, the initial attack is indistinguishable from that of GBS. An acute-onset form of CIDP may mimic GBS but should be considered if it deteriorates >9 weeks after onset or relapses at least three times. Symptoms are both motor and sensory in most cases. Weakness of the limbs is usually symmetric but can be strikingly asymmetric in multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy variant (Lewis-Sumner syndrome) in which discrete peripheral nerves are involved. There is considerable

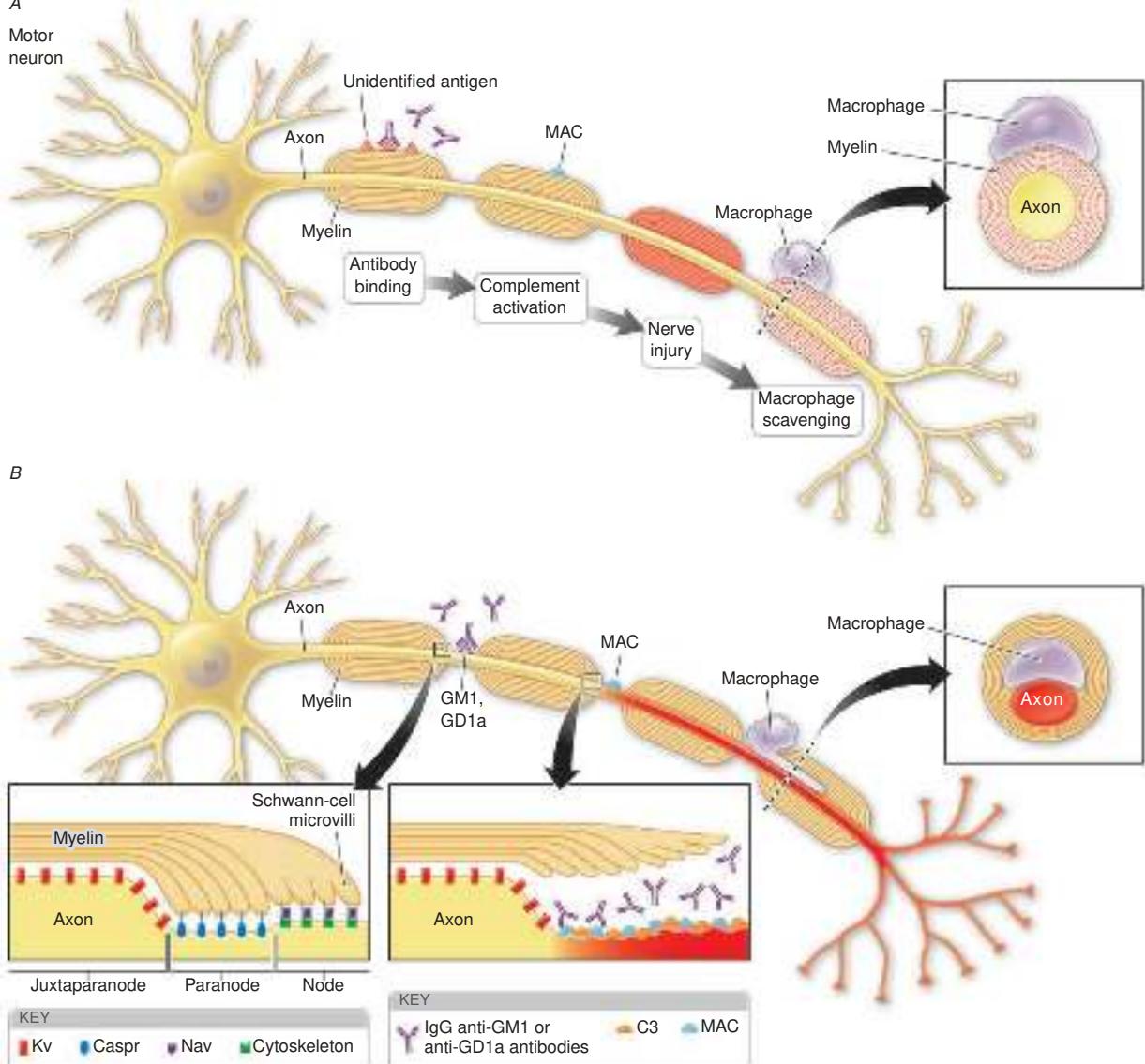


FIGURE 447-2 Possible immune mechanisms in Guillain-Barré syndrome (GBS). Panel A shows the immunopathogenesis of AIDP. Although autoantigens have yet to be unequivocally identified, autoantibodies may bind to myelin antigens and activate complement. This is followed by the formation of membrane-attack complex (MAC) on the outer surface of Schwann cells and the initiation of vesicular degeneration. Macrophages subsequently invade myelin and act as scavengers to remove myelin debris. Panel B shows the immunopathogenesis of acute axonal forms of GBS (acute motor axonal neuropathy [AMAN] and acute motor-sensory axonal neuropathy [AMSAN]). Myelinated axons are divided into four functional regions: the nodes of Ranvier, paranodes, juxtaparanodes, and internodes. Gangliosides GM1 and GD1a are strongly expressed at the nodes of Ranvier, where the voltage-gated sodium (Nav) channels are localized. Contactin-associated protein (Caspr) and voltage-gated potassium (Kv) channels are respectively present at the paranodes and juxtaparanodes. IgG anti-GM1 or anti-GD1a autoantibodies bind to the nodal axolemma, leading to MAC formation. This results in the disappearance of Nav clusters and the detachment of paranodal myelin, which can lead to nerve-conduction failure and muscle weakness. Axonal degeneration may follow at a later stage. Macrophages subsequently invade from the nodes into the periaxonal space, scavenging the injured axons. (From N Yuki, H-P Hartung: Guillain-Barré syndrome. *N Engl J Med* 366:2294, 2012. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

variability from case to case. Some patients experience a chronic progressive course, whereas others, usually younger patients, have a relapsing and remitting course. A small proportion have cranial nerve findings, including external ophthalmoplegia. Some have only motor findings, and a small proportion present with a relatively pure syndrome of sensory ataxia. The latter can be seen in the chronic inflammatory sensory polyradiculopathy (CISP) variant of CIDP in which demyelination predominantly occurs at the sensory roots or with the distal acquired demyelinating symmetric (DADS) variant.

Approximately, 10% of cases are associated with IgG4 isotype antibodies directed against contactin-1 (CNTN1) or neurofascin 155 (NF155), with early axonal damage, severe distal motor involvement,

or sensory ataxia with tremor. Less commonly, IgM anti-NF140/186 CIDP associated with sensory ataxia but without tremor, low-amplitude CMAPs (conduction block or axonal degeneration), and nephrotic syndrome have also been reported. Anti-contactin associated protein-1 (Caspr1) antibodies occur in CIDP associated with severe neuropathic pain.

CIDP tends to ameliorate over time with treatment; the result is that many years after onset, nearly 75% of patients have reasonable functional status. Death from CIDP is uncommon.

Diagnosis The diagnosis rests on characteristic clinical, CSF, and electrophysiologic findings. The CSF is usually acellular with an

TABLE 447-3 Brighton Criteria for Diagnosis of Guillain-Barré Syndrome (GBS) and Miller Fisher Syndrome

Clinical case definitions for diagnosis of GBS	Absence of limb weakness
<i>Level 1 of diagnostic certainty</i>	<i>AND</i>
Bilateral AND flaccid weakness of the limbs	Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND	AND
Decreased or absent deep tendon reflexes in weak limbs	Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/ μ L)
AND	AND
Electrophysiologic findings consistent with GBS	Nerve conduction studies are normal, OR indicate involvement of sensory nerves only
AND	AND
Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/ μ L)	No alterations in consciousness or corticospinal tract signs
AND	AND
Absence of an identified alternative diagnosis for weakness	Absence of identified alternative diagnosis
<i>Level 2 of diagnostic certainty</i>	<i>Level 2 of diagnostic certainty</i>
Bilateral AND flaccid weakness of the limbs	Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
AND	AND
Decreased or absent deep tendon reflexes in weak limbs	Absence of limb weakness
AND	AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau	Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND	AND
CSF total white cell count <50 cells/ μ L (with or without CSF protein elevation above laboratory normal value)	CSF with a total white cell count <50 cells/ μ L (with or without CSF protein elevation above laboratory normal value)
OR	OR
If CSF not collected or results not available, electrophysiologic studies consistent with GBS	Nerve conduction studies are normal, OR indicate involvement of sensory nerves only
AND	AND
Absence of identified alternative diagnosis for weakness	No alterations in consciousness or corticospinal tract signs
<i>Level 3 of diagnostic certainty</i>	<i>Level 3 of diagnostic certainty</i>
Bilateral and flaccid weakness of the limbs	Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
AND	AND
Decreased or absent deep tendon reflexes in weak limbs	Absence of limb weakness
AND	AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau	Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND	AND
Absence of identified alternative diagnosis for weakness	No alterations in consciousness or corticospinal tract signs
Clinical case definitions for diagnosis of Miller Fisher syndrome	Absence of identified alternative diagnosis
<i>Level 1 of diagnostic certainty</i>	
Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes, and ataxia	
AND	

Abbreviation: CSF, cerebrospinal fluid.

Source: From JJ Sejvar et al: Guillain-Barré syndrome and Fisher syndrome: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 29:599, 2011. Validation study published by C Fokke et al: Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain 137:33, 2014.

elevated protein level, sometimes several times normal. As with GBS, a CSF pleocytosis should lead to the consideration of HIV infection, leukemia or lymphoma, and sarcoidosis. EDx findings reveal variable degrees of conduction slowing, prolonged distal latencies, distal and temporal dispersion of CMAPs, and conduction block as the principal features. In particular, the presence of conduction block is a certain sign of an acquired demyelinating process. Evidence of axonal loss, presumably secondary to demyelination, is present in >50% of patients. Serum protein electrophoresis with immunofixation is indicated to search for monoclonal gammopathy and associated conditions (see “Monoclonal Gammopathy of Undetermined Significance,” below). MRI can demonstrate enlarged nerves, clumping of cauda equina, and enhancement. Ultrasound is cheaper and often more readily available and can likewise show enlargement of nerves at the roots or more distally. Studies have shown that imaging complements

EDx findings and increases sensitivity. In all patients with presumptive CIDP, it is also reasonable to exclude vasculitis, collagen vascular disease (especially SLE), chronic hepatitis, HIV infection, amyloidosis, and diabetes mellitus. Other associated conditions include inflammatory bowel disease and lymphoma.

Pathogenesis Biopsy in typical CIDP reveals little inflammation and onion-bulb changes (imbricated layers of attenuated Schwann cell processes surrounding an axon) that result from recurrent demyelination and remyelination (Fig. 447-1). The response to therapy suggests that CIDP is immune-mediated; CIDP responds to glucocorticoids, whereas GBS does not. Passive transfer of demyelination into experimental animals has been accomplished using IgG purified from the serum of some patients with CIDP, lending support for a humoral autoimmune pathogenesis. A minority of patients have serum antibodies

against P0, myelin P2 protein, or PMP22 (proteins whose genes are mutated in certain forms of hereditary Charcot-Marie-Tooth neuropathy). As previously mentioned, antibodies of IgG4 isotype directed against CNTN1, NF155, NF140/186, and Caspr1 have been associated with early nodal and paranodal damage with a poor response to IVIg. CNTN1 and its partner Caspr1 interact with NF155 at paranodal axoglial junctions. Passive transfer of IgG4 CNTN1 antibodies produces paranodal damage and ataxia in rodents. It is also of interest that a CIDP-like illness developed spontaneously in the nonobese diabetic (NOD) mouse when the immune co-stimulatory molecule B7-2 (CD86) was genetically deleted; this suggests that CIDP can result from altered triggering of T cells by antigen-presenting cells.

As many as 25% of patients with clinical features of CIDP also have a monoclonal gammopathy of undetermined significance (MGUS), discussed below. Cases associated with monoclonal IgA or IgG kappa usually respond to treatment as favorably as cases without a monoclonal gammopathy. Patients with IgM-kappa monoclonal gammopathy and antibodies directed against myelin-associated glycoprotein (MAG) have a distinct demyelinating polyneuropathy with more sensory findings, usually only distal weakness, and a poor response to immunotherapy.

TREATMENT

Chronic Inflammatory Demyelinating Polyneuropathy

Most authorities initiate treatment for CIDP when progression is rapid or walking is compromised. If the disorder is mild, management can be expectant, awaiting spontaneous remission. Controlled studies have shown that high-dose IVIg, subcutaneous Ig (scIg), PLEX, and glucocorticoids are all more effective than placebo. Initial therapy is usually with IVIg, administered as 2.0 g/kg body weight given in divided doses over 2–5 days; three monthly courses are generally recommended before concluding a patient has failed treatment. If the patient responds, the infusion intervals can be gradually increased or the dosage decreased (e.g., starting at 1 g/kg every 3–4 weeks). Patients who require more frequent IVIg, experience side effects with IVIg (headaches), have poor venous access, or find it more convenient are treated with scIg (2–3 times a week such that the total dosage per month is the same or slightly higher than the monthly dosage of IVIg). PLEX, which appears to be as effective as IVIg, is initiated at 2–3 treatments per week for 6 weeks; periodic retreatment may also be required. Treatment with glucocorticoids is another option (60–80 mg prednisone PO daily for 1–2 months, followed by a gradual dose reduction of 10 mg per month as tolerated), but long-term adverse effects including bone demineralization, gastrointestinal bleeding, and cushingoid changes are problematic. As many as one-third of patients with CIDP fail to respond adequately to the initial therapy chosen; a different treatment should then be tried. Patients who fail therapy with IVIg, scIg, PLEX, and glucocorticoids may benefit from treatment with immunosuppressive agents such as azathioprine, methotrexate, cyclosporine, and cyclophosphamide, either alone or as adjunctive therapy. CIDP associated with anti-CNTN1, NF155, NF140/186, and Caspr1 antibodies (IgG4 subclass antibodies) is typically refractory to IVIg, but several studies suggest a response to rituximab. Use of these therapies requires periodic reassessment of their risks and benefits. In patients with a CIDP-like neuropathy who fail to respond to treatment, it is important to evaluate for POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; see below).

MULTIFOCAL MOTOR NEUROPATHY

Multifocal motor neuropathy (MMN) is a distinctive but uncommon neuropathy that presents as slowly progressive motor weakness and atrophy evolving over years in the distribution of selected nerve trunks,

associated with sites of persistent focal motor conduction block in the same nerve trunks. Sensory fibers are relatively spared. The arms are affected more frequently than the legs, and >75% of all patients are male. Some cases have been confused with lower motor neuron forms of amyotrophic lateral sclerosis (*Chap. 437*). Less than 50% of patients present with high titers of polyclonal IgM antibody to the ganglioside GM1. It is uncertain how this finding relates to the discrete foci of persistent motor conduction block, but high concentrations of GM1 gangliosides are normal constituents of nodes of Ranvier in peripheral nerve fibers. Pathology reveals demyelination and mild inflammatory changes at the sites of conduction block.

Most patients with MMN respond to high-dose IVIg or scIg (doses as for CIDP, above); periodic retreatment is required (usually at least monthly) to maintain the benefit. Some refractory patients have responded to rituximab or cyclophosphamide. Glucocorticoids and PE are not effective.

NEUROPATHIES WITH MONOCLONAL GAMMOPATHY

MULTIPLE MYELOMA

Clinically overt polyneuropathy occurs in ~5% of patients with the commonly encountered type of multiple myeloma, which exhibits either lytic or diffuse osteoporotic bone lesions. These neuropathies are sensorimotor, are usually mild and slowly progressive but may be severe, and generally do not reverse with successful suppression of the myeloma. In most cases, EDx and pathologic features are consistent with a process of axonal degeneration.

In contrast, myeloma with osteosclerotic features, although representing only 3% of all myelomas, is associated with polyneuropathy in one-half of cases. These neuropathies, which may also occur with solitary plasmacytoma, are distinct because they (1) are demyelinating or mixed axonal and demyelinating by EDx, have elevated CSF protein, and clinically resemble CIDP; (2) often respond to radiation therapy or removal of the primary lesion; (3) are associated with different monoclonal proteins and light chains (almost always lambda as opposed to primarily kappa in the lytic type of multiple myeloma); (4) are typically refractory to standard treatments of CIDP; and (5) may occur in association with other systemic findings including thickening of the skin, hyperpigmentation, hypertrichosis, organomegaly, endocrinopathy, anasarca, and clubbing of fingers. These are features of POEMS syndrome. Levels of vascular endothelial growth factor (VEGF) are increased in the serum, and this factor is thought to somehow play a pathogenic role in this syndrome. Treatment of the neuropathy is best directed at the osteosclerotic myeloma using surgery, radiotherapy, chemotherapy, or autologous peripheral blood stem cell transplantation.

Neuropathies are also encountered in other systemic conditions with gammopathy, including Waldenström macroglobulinemia, primary systemic amyloidosis, and cryoglobulinemic states (mixed essential cryoglobulinemia, some cases of hepatitis C).

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Chronic polyneuropathies occurring in association with MGUS are usually associated with the immunoglobulin isotypes IgG, IgA, and IgM. Most patients present with isolated sensory symptoms in their distal extremities and have EDx features of an axonal sensory or sensorimotor polyneuropathy. These patients otherwise resemble idiopathic sensory polyneuropathy, and the MGUS might just be coincidental. They usually do not respond to immunotherapies designed to reduce the concentration of the monoclonal protein. Some patients, however, present with generalized weakness and sensory loss and EDx studies indistinguishable from CIDP without monoclonal gammopathy (see “Chronic Inflammatory Demyelinating Polyneuropathy,” above), and their response to immunosuppressive agents is also similar. An exception is the syndrome of IgM-kappa monoclonal gammopathy associated with an indolent, long-standing, sometimes static

sensory neuropathy, frequently with tremor and sensory ataxia. Most patients are men and aged >50 years. In the majority, the monoclonal IgM immunoglobulin binds to a normal peripheral nerve constituent, MAG, found in the paranodal regions of Schwann cells. Binding appears to be specific for a polysaccharide epitope that is also found in other normal peripheral nerve myelin glycoproteins, P0 and PMP22, and also in other normal nerve-related glycosphingolipids (Fig. 447-1). In the MAG-positive cases, IgM paraprotein is incorporated into the myelin sheaths of affected patients and widens the spacing of the myelin lamellae, thus producing a distinctive ultrastructural pattern. Demyelination and remyelination are the hallmarks of the lesions, but axonal loss develops over time. These anti-MAG polyneuropathies are typical refractory to immunotherapy. In a small proportion of patients (30% at 10 years), MGUS will in time evolve into frankly malignant conditions such as multiple myeloma or lymphoma.

VASCULITIC NEUROPATHY

Peripheral nerve involvement is common in polyarteritis nodosa (PAN), appearing in half of all cases clinically and in 100% of cases at postmortem studies (Chap. 363). The most common pattern is multifocal (asymmetric) motor-sensory neuropathy (mononeuropathy multiplex) due to ischemic lesions of nerve trunks and roots; however, some cases of vasculitic neuropathy present as a distal, symmetric sensorimotor polyneuropathy. Symptoms of neuropathy are a common presenting complaint in patients with PAN. The EDx findings are those of an axonal process. Small- to medium-sized arteries of the vasa nervorum, particularly the epineurial vessels, are affected in PAN, resulting in a widespread ischemic neuropathy. A high frequency of neuropathy occurs in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome [CSS]).

Systemic vasculitis should always be considered when a subacute or chronically evolving mononeuropathy multiplex occurs in conjunction with constitutional symptoms (fever, anorexia, weight loss, loss of energy, malaise, and nonspecific pains). Diagnosis of suspected vasculitic neuropathy is made by a combined nerve and muscle biopsy, with serial section or skip-serial techniques.

Approximately one-third of biopsy-proven cases of vasculitic neuropathy are “nonsystemic” in that the vasculitis appears to affect only peripheral nerves. Constitutional symptoms are absent, and the course is more indolent than that of PAN. The erythrocyte sedimentation rate may be elevated, but other tests for systemic disease are negative. Nevertheless, clinically silent involvement of other organs is likely, and vasculitis is frequently found in muscle biopsied at the same time as nerve.

Vasculitic neuropathy may also be seen as part of the vasculitis syndrome occurring in the course of other connective tissue disorders. The most frequent is rheumatoid arthritis, but ischemic neuropathy due to involvement of vasa nervorum may also occur in mixed cryoglobulinemia, Sjögren's syndrome, granulomatosis with polyangiitis (formerly known as Wegener's), hypersensitivity angiitis, SLE, and progressive systemic sclerosis.

Some vasculitides are associated with antineutrophil cytoplasmic antibodies (ANCAs), which in turn are subclassified as cytoplasmic (cANCA) or perinuclear (pANCA). cANCAs are directed against proteinase 3 (PR3), whereas pANCAs target myeloperoxidase (MPO). PR3/cANCAs are associated with eosinophilic granulomatosis with polyangiitis, whereas MPO/pANCAs are typically associated with microscopic polyangiitis, CSS, and less commonly PAN. Of note, MPO/pANCA has also been seen in minocycline-induced vasculitis.

Management of these neuropathies, including the “nonsystemic” vasculitic neuropathy, consists of treatment of the underlying condition as well as the aggressive use of glucocorticoids and cyclophosphamide. Use of these immunosuppressive agents has resulted in dramatic improvements in outcome, with 5-year survival rates now

>80%. Clinical trials found that the combination of rituximab and glucocorticoids is not inferior to cyclophosphamide and glucocorticoids. Thus, combination therapy with glucocorticoids and rituximab is recommended as the standard initial treatment, particularly for ANCA-associated vasculitis. Mepolizumab, an anti-IL-5 monoclonal antibody, when added to standard care, is also effective for treatment of eosinophilic granulomatosis with polyangiitis.

ANTI Hu PARANEOPLASTIC NEUROPATHY CHAP. 94

This uncommon immune-mediated disorder manifests as a sensory neuronopathy (i.e., selective damage to sensory nerve bodies in dorsal root ganglia). The onset is often asymmetric with dysesthesias and sensory loss in the limbs that soon progress to affect all limbs, the torso, and the face. Marked sensory ataxia, pseudoathetosis, and inability to walk, stand, or even sit unsupported are frequent features and are secondary to the extensive deafferentation. Subacute sensory neuronopathy may be idiopathic, but more than half of cases are paraneoplastic, primarily related to lung cancer, and most of those are small-cell lung cancer (SCLC). Diagnosis of the underlying SCLC requires awareness of the association, testing for the paraneoplastic antibody, and often positron emission tomography (PET) scanning for the tumor. The target antigens are a family of RNA-binding proteins (HuD, HuC, and Hel-N1) that in normal tissues are only expressed by neurons. The same proteins are usually expressed by SCLC, triggering in some patients an immune response characterized by antibodies and cytotoxic T cells that cross-react with the Hu proteins of the dorsal root ganglion neurons, resulting in immune-mediated neuronal destruction. An encephalomyelitis may accompany the sensory neuronopathy and presumably has the same pathogenesis. Neurologic symptoms usually precede, by ≤6 months, the identification of SCLC. The sensory neuronopathy runs its course in a few weeks or months and stabilizes, leaving the patient disabled. Most cases are unresponsive to treatment with glucocorticoids, IVIg, PE, or immunosuppressant drugs.

FURTHER READING

- A AA, R AH: Sensory ganglionopathy. *N Engl J Med* 383:1657, 2020.
- A AA, R JA (eds): *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill, 2016, pp 320–383.
- B N et al: Vasculitic neuropathies. *Semin Neurol* 39:608, 2009.
- B C et al: Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *Lancet Neurol* 18:784, 2019.
- F Y et al: Acute flaccid myelitis: A clinical overview for 2019. *Mayo Clin Proc* 94:875, 2019.
- G AC, A AA: COVID-19 and neuromuscular disorders. *Neurology* 94:959, 2020.
- L SE et al: Diagnosis and management of Guillain-Barré syndrome in ten steps. *Nat Rev Neurol* 15:671, 2019.
- M BV et al: Guillain-Barre Syndrome following ChAdOx1-S/nCoV-19 vaccine. *Ann Neurol* 90:312, 2021.
- P A et al: Clinical spectrum of neuromuscular complications after immune checkpoint inhibition. *Neuromuscul Disord* 29:127, 2019.
- T G et al: Guillain-Barré syndrome associated with SARS-CoV-2. *N Engl J Med* 382:2574, 2020.
- U A, V J-M: Autoimmune nodo-paranodopathies of peripheral nerve: The concept is gaining ground. *J Neurol Neurosurg Psychiatry* 89:627, 2018.
- W EF, K CJ: Guillain-Barré syndrome. *Mayo Clin Proc* 92:467, 2017.



Anthony A. Amato

Myasthenia gravis (MG) is a neuromuscular junction (NMJ) disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is a decrease in the number of available acetylcholine receptors (AChRs) at NMJs due to an antibody-mediated autoimmune attack. Treatment now available for MG is highly effective, although a specific cure has remained elusive.

■ PATHOPHYSIOLOGY

At the NMJ (Fig. 448-1, Video 448-1), acetylcholine (ACh) is synthesized in the motor nerve terminal and stored in vesicles (quanta). When an action potential travels down a motor nerve and reaches the

nerve terminal, ACh from 150 to 200 vesicles is released and combines with AChRs that are densely packed at the peaks of postsynaptic folds. The AChR consists of five subunits (2α , 1β , 1δ , 1γ , or ϵ) arranged around a central pore. When ACh combines with the binding sites on the α subunits of the AChR, the channel in the AChR opens, permitting the rapid entry of cations, chiefly sodium, which produces depolarization at the end-plate region of the muscle fiber. If the depolarization is sufficiently large, it initiates an action potential that is propagated along the muscle fiber, triggering muscle contraction. This process is rapidly terminated by hydrolysis of ACh by acetylcholinesterase (AChE), which is present within the synaptic folds, and by diffusion of ACh away from the receptor.

In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane. In addition, the postsynaptic folds are flattened, or “simplified.” These changes result in decreased efficiency of neuromuscular transmission. Therefore, although ACh is released normally, it produces small end-plate potentials that may fail to trigger muscle action potentials. Failure of transmission results in weakness of muscle contraction.

The amount of ACh released per impulse normally declines on repeated activity (termed *presynaptic rundown*). In the myasthenic

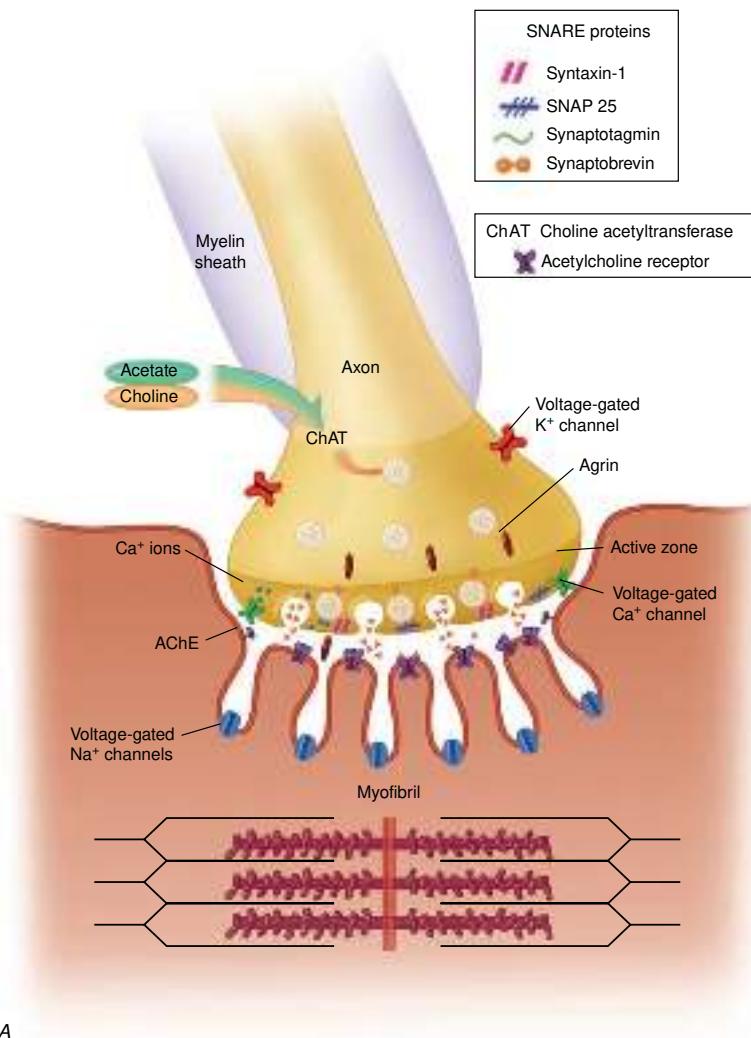


FIGURE 448-1 Illustrations of (A) a normal presynaptic neuromuscular junction, (B) a normal postsynaptic terminal, and (C) a myasthenic neuromuscular junction. ACh, acetylcholinesterase. See text for description of normal neuromuscular transmission. The myasthenia gravis (MG) junction demonstrates a reduced number of acetylcholine receptors (AChRs); flattened, simplified postsynaptic folds; and a widened synaptic space. See Video 448-1 also. (From AA Amato, J Russell: *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill, 2016, Figures 25-3 [p 588], 25-4 [p 589], and 25-5 [p 590]; with permission.)

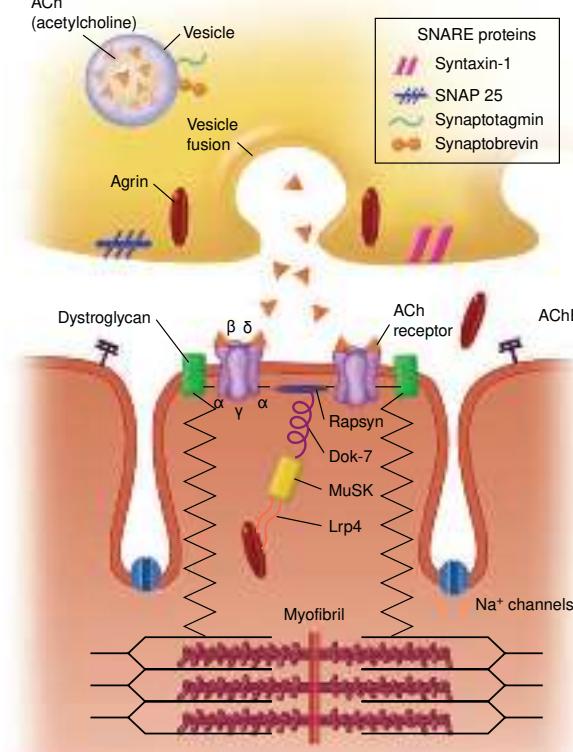
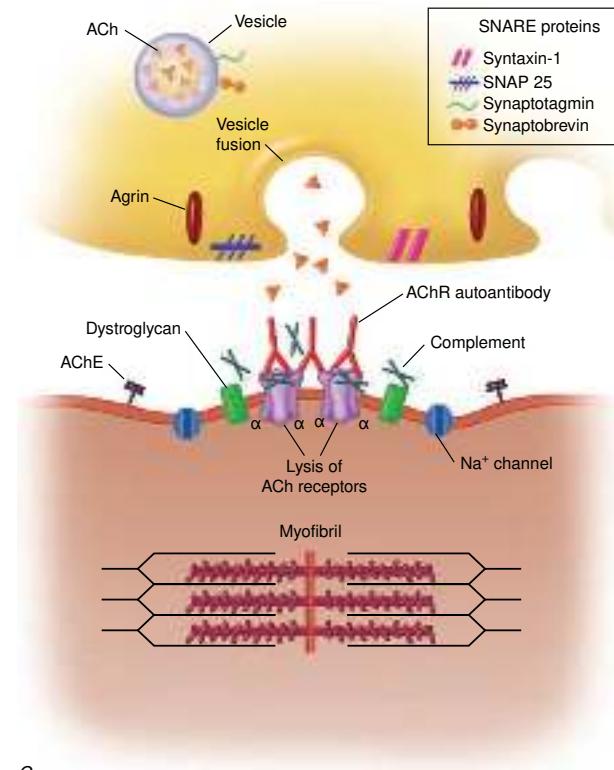
**B**

FIGURE 448-1 (Continued)

**C**

patient, the decreased efficiency of neuromuscular transmission combined with the normal rundown results in the activation of fewer and fewer muscle fibers by successive nerve impulses and hence increasing weakness, or *myasthenic fatigue*. This mechanism also accounts for the decremental response to repetitive nerve stimulation seen on electrodiagnostic testing.

MG is an autoimmune disorder most commonly caused by anti-AChR antibodies. The anti-AChR antibodies reduce the number of available AChRs at NMJs by three distinct mechanisms: (1) accelerated turnover of AChRs by a mechanism involving cross-linking and rapid endocytosis of the receptors; (2) damage to the post-synaptic muscle membrane by the antibody in collaboration with complement; and (3) blockade of the active site of the AChR (i.e., the site that normally binds Ach). An immune response to muscle-specific kinase (MuSK), a protein involved in AChR clustering at the NMJ, can also result in MG, with reduction of AChRs demonstrated experimentally. Anti-MuSK antibody occurs in ~10% of patients (~40% of AChR antibody-negative patients), whereas 1–3% have antibodies to another protein at the NMJ—low-density lipoprotein receptor-related protein 4 (LRP4)—that is also important for clustering of AChRs. The pathogenic antibodies are IgG and are T-cell dependent. Thus, immunotherapeutic strategies directed against either the antibody-producing B cells or helper T cells are effective in this antibody-mediated disease.

How the autoimmune response is initiated and maintained in MG is not completely understood, but the thymus appears to play a role in this process. The thymus is abnormal in ~75% of patients with AChR antibody-positive MG; in ~65%, the thymus is “hyperplastic,” with the presence of active germinal centers detected histologically, although the hyperplastic thymus is not necessarily enlarged. An additional 10% of patients have thymic tumors (thymomas). Muscle-like cells within the thymus (myoid cells), which express AChRs on

their surface, may serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland.

■ CLINICAL FEATURES

MG has a prevalence as high as 200 in 100,000. It affects individuals in all age groups, but peak incidences occur in women in their twenties and thirties and in men in their fifties and sixties. Overall, women are affected more frequently than men, in a ratio of ~3:2. The cardinal features are *weakness* and *fatigability* of muscles. The weakness increases during repeated use (fatigue) or late in the day and may improve following rest or sleep. The course of MG is often variable. Exacerbations and remissions may occur, particularly during the first few years after the onset of the disease. Unrelated infections or systemic disorders can lead to increased myasthenic weakness and may precipitate “crisis” (see below).

The distribution of muscle weakness often has a characteristic pattern. The cranial muscles, particularly the lids and extraocular muscles (EOMs), are typically involved early in the course of MG; diplopia and ptosis are common initial complaints. Facial weakness produces a “snarling” expression when the patient attempts to smile. Weakness in chewing is most noticeable after prolonged effort, as in chewing meat. Speech may have a nasal timbre caused by weakness of the palate or a dysarthric “mushy” quality due to tongue weakness. Difficulty in swallowing may occur as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food. Bulbar weakness and more frequent episodes of respiratory depression can be especially prominent in MuSK antibody-positive MG. In ~85% of patients, the weakness becomes generalized, affecting the limb muscles as well. If weakness remains restricted to the EOMs for 3 years, it is likely that it will not become generalized, and these patients are said to have *ocular MG*. The limb weakness in MG is often proximal and may be asymmetric. Despite the muscle weakness, deep

TABLE 448-1 Diagnosis of Myasthenia Gravis (MG)**History**

Diplopia, ptosis, dysarthria, dysphagia, dyspnea

Weakness in characteristic distribution: proximal limbs, neck extensors, generalized

Fluctuation and fatigue: worse with repeated activity, improved by rest

Effects of previous treatments

Physical examination

Evaluation for ptosis at rest and following 1 min of exercise, extraocular muscles and subjective diplopia, orbicularis oculi and oris strength, jaw opening and closure

Assessment of muscle strength in neck and extremities

Weakness following repeated shoulder abduction

Vital capacity measurement

Absence of other neurologic signs

Laboratory testing

Anti-AChR radioimmunoassay: ~85% positive in generalized MG; 50% in ocular MG; definite diagnosis if positive; negative result does not exclude MG; ~40% of AChR antibody-negative patients with generalized MG have anti-MuSK antibodies and ~2% have LRP-4 antibodies

Repetitive nerve stimulation: decrement of >10% at 3 Hz: highly probable

Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific

Edrophonium chloride (Enlon®) 2 mg + 8 mg IV; highly probable diagnosis if unequivocally positive

Ice-pack test looking for improvement in ptosis is very sensitive

For ocular or cranial MG: exclude intracranial lesions by CT or MRI

Abbreviations: AChR, acetylcholine receptor; CT, computed tomography; LRP4, lipoprotein receptor-related protein 4; MRI, magnetic resonance imaging; MuSK, muscle-specific tyrosine kinase.

tendon reflexes are preserved. If ventilatory weakness becomes requires respiratory assistance, the patient is said to be in *crisis*.

■ DIAGNOSIS AND EVALUATION TABLE 448 1

The diagnosis is suspected on the basis of weakness and fatigability in the typical distribution described above, without loss of reflexes or impairment of sensation or other neurologic function. The suspected diagnosis should always be confirmed definitively before treatment is undertaken; this is essential because (1) other treatable conditions may closely resemble MG and (2) the treatment of MG may involve surgery and the prolonged use of drugs with potentially adverse side effects.

Ice-Pack Test If a patient has ptosis, application of a pack of ice over a ptotic eye often results in improvement if the ptosis is due to an NMJ defect. This is hypothesized to be due to less depletion of quanta of AChR in the cold and reduced activity of AChE at the NMJ. It is a quick and easy test to do in the clinic or at the bedside of a hospitalized patient.

Autoantibodies Associated with MG As previously mentioned, anti-AChR antibodies are detectable in the serum of ~85% of all myasthenic patients but in only ~50% of patients with weakness confined to the ocular muscles. The presence of anti-AChR antibodies is virtually diagnostic of MG, but a negative test does not exclude the disease. The measured level of anti-AChR antibody does not correspond well with the severity of MG in different patients. Antibodies to MuSK are present in ~40% of AChR antibody-negative patients with generalized MG. MuSK antibodies are rarely present in AChR antibody-positive patients or in patients with MG limited to ocular muscles. These antibodies may interfere with clustering of AChRs at NMJs. A small proportion of MG patients without antibodies to AChR or MuSK have antibodies to LRP4. Interestingly, antibodies against agrin also have been found in rare patients with MG. Agrin is a protein derived from motor nerves that normally binds to LRP4 and is important for normal clustering of AChRs at NMJ. Additionally, anti-striated muscle antibodies directed against titin and other skeletal muscle components are found in ~30% of myasthenics without thymoma, 24% of thymoma

patients without myasthenia, and 70–80% of patients with both myasthenia and thymoma. Furthermore, antibodies directed against Netrin-1 receptors and Caspr2 (contactin-associated protein-like 2) often coexist and are associated in patients with thymoma who have MG and neuromyotonia or Morvan's syndrome.

Electrodiagnostic Testing Repetitive nerve stimulation may provide helpful diagnostic evidence of MG. Anti-AChE medication should be stopped 6–12 h before testing. It is best to test weak muscles or proximal muscle groups. Electrical stimulation is delivered at a rate of two or three per second to the appropriate nerves, and action potentials are recorded from the muscles. In normal individuals, the amplitude of the evoked muscle action potentials does not change by >10% at these rates of stimulation. However, in myasthenic patients, there is a rapid reduction of >10% in the amplitude of the evoked responses.

Anticholinesterase Test Drugs that inhibit the enzyme AChE allow ACh to interact repeatedly with the limited number of AChRs in MG, producing improvement in muscle strength. Edrophonium is used most commonly for diagnostic testing because of the rapid onset (30 s) and short duration (~5 min) of its effect. An objective end point must be selected to evaluate the effect of edrophonium, such as weakness of EOMs, impairment of speech, or the length of time that the patient can maintain the arms in forward. An initial IV dose of 2 mg of edrophonium is given. If definite improvement occurs, the test is considered positive and is terminated. If there is no change, the patient is given an additional 8 mg IV. The dose is administered in two parts because some patients react to edrophonium with side effects such as nausea, diarrhea, salivation, fasciculations, and rarely with severe symptoms of syncope or bradycardia. Atropine (0.6 mg) should be drawn up in a syringe and ready for IV administration if these symptoms become troublesome. The edrophonium test is now reserved for patients with clinical findings that are suggestive of MG but who have negative antibody, electrodiagnostic testing, or ice-pack test. False-positive tests occur in occasional patients with other neurologic disorders, such as amyotrophic lateral sclerosis (Chap. 437), and in placebo-reactors. False-negative or equivocal tests may also occur.

Pulmonary Function Tests (Chap. 284) Measurements of ventilatory function are valuable because of the frequency and seriousness of respiratory impairment in myasthenic patients.

Differential Diagnosis Other conditions that cause weakness of the cranial and/or somatic musculature include the nonautoimmune congenital myasthenia, drug-induced myasthenia, Lambert-Eaton myasthenic syndrome (LEMS), neurasthenia, hyperthyroidism (Graves' disease), botulism, intracranial mass lesions, oculopharyngeal dystrophy, and mitochondrial myopathy (Kearns-Sayre syndrome, progressive external ophthalmoplegia). Treatment with immune checkpoint inhibitors for cancer may also result in autoimmune MG. Myositis and myocarditis are also often found in combination with MG as a complication of checkpoint inhibitors (Chap. 365). Symptoms typically begin after the first or second cycle of treatment, with ptosis, diplopia, and bulbar and occasionally extremity weakness. Patients usually improve when the immune checkpoint inhibitor is discontinued and a short course of glucocorticoids or intravenous immunoglobulin (IVIg) is administered. Treatment with penicillamine (used for scleroderma or rheumatoid arthritis) has also been associated with MG. Aminoglycoside antibiotics or procainamide can cause exacerbation of weakness in myasthenic patients; very large doses can cause neuromuscular weakness in normal individuals.

The *congenital myasthenic syndromes (CMS)* comprise a rare heterogeneous group of disorders of the NMJ that are not autoimmune but rather are due to genetic mutations in which virtually any component of the NMJ may be affected. Alterations in function of the presynaptic nerve terminal, in the various subunits of the AChR, AChE, or the other molecules involved in end-plate development or maintenance, have been identified in the different forms of CMS. These disorders share many of the clinical features of autoimmune MG, including weakness and fatigability of proximal or distal extremity muscles

TABLE 448-2 Congenital Myasthenic Syndromes (CMS)

CMS SUBTYPE	GENE	CLINICAL FEATURES	ELECTROPHYSIOLOGIC FEATURES	RESPONSE TO AChE INHIBITORS	TREATMENT
Presynaptic Disorders					
CMS with paucity of ACh release	<i>CHAT; CHT</i>	AR; early onset, respiratory failure at birth, episodic apnea, improvement with age	Decremental response to RNS	Improve	AChEinhibitors; 3,4-DAP
Synaptic Disorders					
AChE deficiency	<i>COLQ</i>	AR; early onset; variable severity; axial weakness with scoliosis; apnea; +/- EOM involvement, slow or absent pupillary responses	After discharges on nerve stimulation and decrement on RNS	Worsen	Albuterol; ephedrine; 3,4-DAP; avoid AChEinhibitors
Postsynaptic Disorders Involving AChR Deficiency or Kinetics					
Primary AChR deficiency	AChR subunit genes	AR; early onset; variable severity; fatigue; typical MG features	Decremental response to RNS	Improve	AChEinhibitors; 3,4-DAP
AChR kinetic disorder: slow channel syndrome	AChR subunit genes	AD; onset childhood to early adult; weak forearm extensors and neck; respiratory weakness; variable severity	After discharges on nerve stimulation and decrement on RNS	Worsen	Fluoxetine and quinidine; avoid AChEinhibitors
AChR kinetic disorder: fast channel syndrome	AChR subunit genes	AR; early onset; mild to severe; ptosis, EOM involvement; weakness and fatigue	Decremental response to RNS	Improve	AChEinhibitors; caution with 3,4-DAP
Postsynaptic Disorders Involving Abnormal Clustering/Function of AChR					
	<i>DOK7</i>	AR; limb girdle weakness with ptosis but no EOM involvement	Decremental response to RNS	Variable	Albuterol; ephedrine; may worsen with AChEinhibitors
	<i>Rapsyn</i>	AR; early onset with hypotonia, respiratory failure, and arthrogryposis at birth to early adult onset resembling MG	Decremental response to RNS	Variable	Albuterol
	<i>Agrin</i>	AR; limb girdle or distal weakness, apnea	Decremental response to RNS	Variable	Albuterol; may worsen with AChEinhibitors
	<i>MuSK</i>	AR; congenital or childhood onset of ptosis, EOM and progressive limb girdle weakness	Decremental response to RNS	Variable	Variable response to AChE inhibitors and 3,4-DAP Positive response to albuterol
	<i>LRP4</i>	AR; congenital onset with hypotonia; ventilatory failure, mild ptosis, and EOM weakness	Decremental response to RNS	Worsen	Worsen with AChEinhibitors
Other Postsynaptic Disorders					
Limb-girdle CMS with tubular aggregates	<i>GFPT1; DPAGT1; ALG2; ALG14; DPAGT1</i>	AR; limb-girdle weakness usually without ptosis or EOM weakness; onset in infancy or early adult	Decremental response to RNS	Variable	Albuterol; ephedrine; variable response to AChE inhibitors and 3,4-DAP; albuterol
Congenital muscular dystrophy with myasthenia	<i>Plectin</i>	AR; infantile or childhood onset of generalized weakness including ptosis and EOM; epidermolysis bullosa simplex; elevated CK	Decremental response to RNS	Variable	No response to AChE and 3,4-DAP

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; AChR, acetylcholine receptor; AD, autosomal dominant; AR, autosomal recessive; CHAT, choline acetyl transferase; CHT, sodium-dependent high-affinity choline transport 1; CK, creatine kinase; CMA, congenital myasthenic syndrome; COLQ, collagenic tail of endplate acetylcholinesterase; 3,4-DAP, 3,4-diaminopyridine; Dok7, downstream of tyrosine kinase 7; DPAGT1, UDP-N-acetylgalactosamine-6-sulfatase; MuSK, muscle specific kinase; FNS, repetitive nerve stimulation.

Source: From AA Amato, J Russell: *Neuromuscular Disorders*, 2nd ed. McGraw-Hill, 2016, Table 26-2, p. 627; with permission.

and often involving EOMs and the eyelids similar to the distribution in autoimmune MG. CMS should be suspected when symptoms of myasthenia have begun in infancy or childhood, but they can present in early adulthood. As in acquired autoimmune MG, repetitive nerve stimulation is associated with a decremental response. Some forms (e.g., AChE deficiency, prolonged open channel syndrome) have a feature of after-discharges that are not seen in MG. An additional clue is the absence of AChR and MuSK antibodies, although these are absent in ~10% of generalized MG patients (so-called double seronegative MG).

The prevalence of CMS is estimated at ~3.8 per 100,000. The most common genetic defects occur in the ϵ subunit of the AChR, accounting for ~50% of CMS cases, with mutations in the genes encoding for rapsin, COLQ, DOK7, agrin, and GFPT together accounting for ~40%. In most of the recessively inherited forms of CMS, the mutations are

heteroallelic; that is, different mutations affecting each of the two alleles are present. Features of the most common forms of CMS are summarized in Table 448-2. Molecular analysis is required for precise elucidation of the defect; this may lead to helpful treatment as well as genetic counseling. Some forms of CMS improve with AChE inhibitors, while others (e.g., slow channel syndrome, AChE deficiency, DOK7-related CMS) actually worsen. Fluoxetine and quinidine can be useful for slow channel syndrome, and albuterol for mutations affecting AChE, DOK7, rapsin, and agrin. Additionally, ephedrine and 3,4-diaminopyridine (3,4-DAP) may be of benefit in some forms of CMS.

LEMS is a presynaptic disorder of the NMJ that can cause weakness similar to that of MG. The proximal muscles of the lower limbs are most commonly affected, but other muscles may be involved as well. Cranial nerve findings, including ptosis of the eyelids and diplopia, occur in up to 70% of patients and resemble features of MG. However,

the two conditions are usually readily distinguished because patients with LEMS have depressed or absent reflexes and experience autonomic changes such as dry mouth and impotence. Nerve stimulation produces an initial low-amplitude compound muscle action potential and, at low rates of repetitive stimulation (2–3 Hz), a decremental response as seen in MG; however, at high rates (20–50 Hz) or following brief exercise, incremental responses occur. LEMS is caused by autoantibodies directed against P/Q-type calcium channels at the motor nerve terminals detected in ~85% of LEMS patients. These autoantibodies impair the release of ACh from nerve terminals. In young adults, particularly women, LEMS is not associated with an underlying cancer. However, in older adults, most LEMS is associated with malignancy, most commonly small-cell lung cancer (SCLC). The tumor cells may express calcium channels that stimulate the autoimmune response. Treatment of LEMS involves plasmapheresis and immunotherapy, as for MG. 3,4-DAP and pyridostigmine can also help with symptoms. 3,4-DAP acts by blocking potassium channels, which results in prolonged depolarization of the motor nerve terminals and thus enhances ACh release. Pyridostigmine prolongs the action of ACh, allowing repeated interactions with AChRs.

Botulism (Chap. 153) is due to potent bacterial toxins produced by any of eight different strains of *Clostridium botulinum*. The toxins enzymatically cleave specific proteins essential for the release of ACh from the motor nerve terminal, thereby interfering with neuromuscular transmission. Most commonly, botulism is caused by ingestion of improperly prepared food containing toxin. Rarely, the nearly ubiquitous spores of *C. botulinum* may germinate in wounds. In infants, the spores may germinate in the gastrointestinal (GI) tract and release toxin, causing muscle weakness. Patients present with myasthenia-like bulbar weakness (e.g., diplopia, dysarthria, dysphagia) and lack sensory symptoms and signs. Weakness may generalize to the limbs and may result in respiratory failure. Reflexes are present early, but they may be diminished as the disease progresses. Mental status is normal. Autonomic findings include paralytic ileus, constipation, urinary retention, dilated or poorly reactive pupils, and dry mouth. The demonstration of toxin in serum by bioassay is definitive, but the results usually take a relatively long time to be completed and may be negative. Nerve stimulation studies reveal reduced compound muscle action potential (CMAP) amplitudes that increase following high-frequency repetitive stimulation. Treatment includes ventilatory support and aggressive inpatient supportive care (e.g., nutrition, deep-vein thrombosis prophylaxis) as needed. Antitoxin should be given as early as possible to be effective and can be obtained through the Centers for Disease Control and Prevention. A preventive vaccine is available for laboratory workers or other highly exposed individuals.

Neurasthenia is the historic term for a myasthenia-like fatigue syndrome without an organic basis. These patients may present with subjective symptoms of weakness and fatigue, but muscle testing usually reveals the “give-away weakness” characteristic of nonorganic disorders; the complaint of fatigue in these patients means tiredness or apathy rather than decreasing muscle power on repeated effort. **Hypothyroidism** is readily diagnosed or excluded by tests of thyroid function, which should be carried out routinely in patients with suspected MG. Abnormalities of thyroid function (hyper- or hypothyroidism) may increase myasthenic weakness. Diplopia resembling that in MG may occasionally be due to an intracranial mass lesion that compresses nerves to the EOMs (e.g., sphenoid ridge meningioma), but magnetic resonance imaging (MRI) of the head and orbits usually reveals the lesion.

Progressive external ophthalmoplegia is a rare condition resulting in weakness of the EOMs, which may be accompanied by weakness of the proximal muscles of the limbs and other systemic features. Most patients with this condition have mitochondrial disorders that can be detected by genetic testing or with muscle biopsy (Chap. 449).

Search for Associated Conditions (Table 448-3) Myasthenic patients have an increased incidence of several associated disorders. Thymic abnormalities occur in ~75% of AChR antibody-positive patients, as noted above. Neoplastic change (thymoma) may produce

TABLE 448-3 Disorders Associated with Myasthenia Gravis and Recommended Laboratory Tests

Associated disorders

Disorders of the thymus: thymoma, hyperplasia

Other autoimmune neurologic disorders: chronic inflammatory demyelinating polyneuropathy, neuromyelitis optica

Other autoimmune disorders: Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis, systemic lupus erythematosus, skin disorders, family history of autoimmune disorder

Disorders or circumstances that may exacerbate myasthenia gravis: hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (see Table 448-4)

Disorders that may interfere with therapy: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis, obesity

Recommended laboratory tests or procedures

CT or MRI of chest

Tests for antinuclear antibodies, rheumatoid factor

Thyroid function tests

Testing for tuberculosis

Fasting blood glucose, hemoglobin A_{1c}

Pulmonary function tests

Bone densitometry

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

enlargement of the thymus, which is detected by chest computed tomography (CT). A thymic shadow on CT scan may normally be present through young adulthood, but enlargement of the thymus in a patient age >40 years is highly suspicious of thymoma. Hyperthyroidism occurs in 3–8% of patients and may aggravate the myasthenic weakness. Thyroid function tests should be obtained in all patients with suspected MG. Other autoimmune disorders, most commonly systemic lupus erythematosus and rheumatoid arthritis, can coexist with MG; associations also occur with neuromyelitis optica, neuromyotonia, Morvan's syndrome (encephalitis, insomnia, confusion, hallucinations, autonomic dysfunction, and neuromyotonia), rippling muscle disease, granulomatous myositis/myocarditis, and chronic inflammatory demyelinating polyneuropathy.

An infection of any kind can exacerbate typical MG and should be sought carefully in patients with relapses. Because of the side effects of glucocorticoids and other immunotherapies used in the treatment of MG, a thorough medical investigation should be undertaken, searching specifically for evidence of chronic or latent infection (such as tuberculosis or hepatitis), hypertension, diabetes, renal disease, and glaucoma.

TREATMENT

Myasthenia Gravis

The prognosis has improved strikingly as a result of advances in treatment. Nearly all myasthenic patients can be returned to full productive lives with proper therapy. The most useful treatments for MG include anticholinesterase medications, glucocorticoids and other immunosuppressive agents, thymectomy, plasmapheresis, IVIg, rituximab, and complement inhibitors (eculizumab) (Fig. 448-2).

ANTICHOLINESTERASE MEDICATIONS

Anticholinesterase medication produces at least partial improvement in most myasthenic patients, although improvement is complete in only a few. Patients with anti-MuSK MG generally obtain less benefit from anticholinesterase agents than those with AChR antibodies and may actually worsen. Pyridostigmine is the most widely used anticholinesterase drug and is initiated at a dosage of 30–60 mg three to four times daily. The beneficial action of oral pyridostigmine begins within 15–30 min and lasts for 3–4 h, but individual responses vary. The frequency and amount of the dose should be tailored to the patient's individual requirements

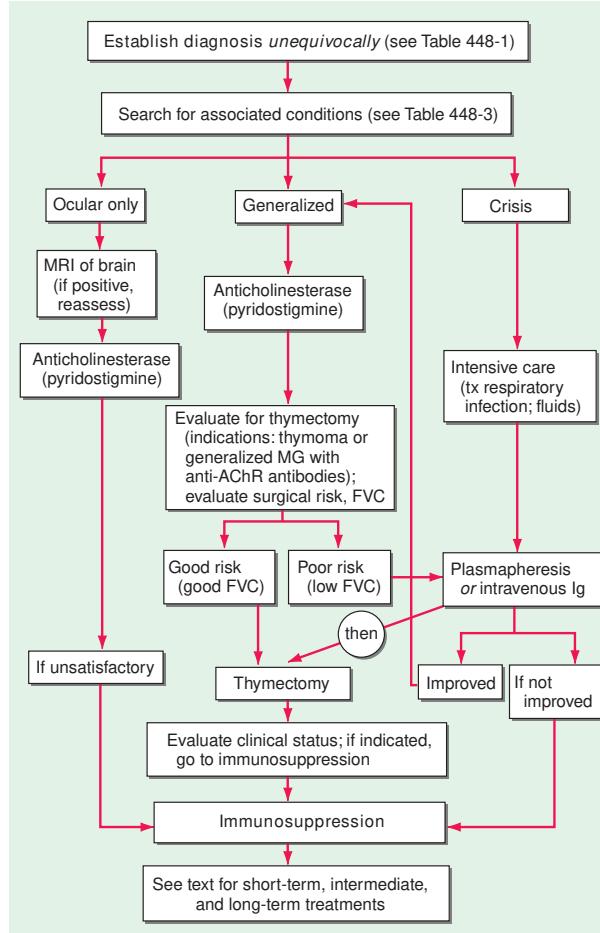


FIGURE 448-2 Algorithm for the management of myasthenia gravis. FVC, forced vital capacity; MRI, magnetic resonance imaging.

throughout the day. For example, patients with weakness in chewing and swallowing may benefit by taking the medication before meals so that peak strength coincides with mealtimes. Long-acting pyridostigmine may occasionally be useful to get the patient through the night but should not be used for daytime medication because of variable absorption. The maximum useful dose of pyridostigmine rarely exceeds 300 mg daily. Overdosage with anticholinesterase medication may cause increased weakness and other side effects. In some patients, muscarinic side effects of the anticholinesterase medication (diarrhea, abdominal cramps, salivation, nausea) may limit the dose tolerated. Atropine/diphenoxylate or loperamide is useful for the treatment of GI symptoms.

THYMECTOMY

Two separate issues should be distinguished: (1) surgical removal of thymoma, and (2) thymectomy as a treatment for MG. Surgical removal of a thymoma is necessary because of the possibility of local tumor spread, although most thymomas are histologically benign. A large international trial of extended transternal thymectomy in nonthymomatous, AChR antibody-positive, generalized MG demonstrated that participants who underwent thymectomy had improved strength and function, required less prednisone and fewer additions of second-line agents (e.g., azathioprine), and fewer hospitalizations for exacerbations lasting at least 5 years. Whether or not less invasive thymectomy may be beneficial is unknown. Also, patients with ocular myasthenia, MuSK-positive, and seronegative MG were excluded from the study; retrospective

and anecdotal evidence suggests that these patients may not benefit from thymectomy. Thymectomy should never be carried out as an emergency procedure, but only when the patient is adequately prepared. If necessary, treatment with IVIg or plasmapheresis may be used before surgery to maximize strength in weak patients.

IMMUNOTHERAPY

The choice of immunotherapy should be guided by the relative benefits and risks for the individual patient and the urgency of treatment. It is helpful to develop a treatment plan based on short-term, intermediate-term, and long-term objectives. For example, if immediate improvement is essential either because of the severity of weakness or because of the patient's need to return to activity as soon as possible, IVIg should be administered or plasmapheresis should be undertaken. For the intermediate term, glucocorticoids and cyclosporine or tacrolimus generally produce clinical improvement within a period of 1–3 months. The beneficial effects of azathioprine and mycophenolate mofetil usually begin after many months (as long as a year), but these drugs have advantages for the long-term treatment of patients with MG. There is a growing body of evidence that rituximab is effective in patients with MuSK antibody. Complement inhibition with intravenous eculizumab can improve MG within 1–3 months but is expensive and requires a loading dose of 4 weekly infusions followed by every-other-week infusions for maintenance.

Glucocorticoid Therapy Glucocorticoids, when used properly, produce improvement in myasthenic weakness in the great majority of patients. To minimize adverse side effects, prednisone should be given in a single dose rather than in divided doses throughout the day. In patients with only mild or moderate weakness, the initial dose should be relatively low (15–25 mg/d) to avoid the early weakening that occurs in 10–15% of patients treated initially with a high-dose regimen. The dose is increased stepwise, as tolerated by the patient (usually by 5 mg/d at 2- to 3-day intervals), until there is marked clinical improvement or a dose of 50–60 mg/d is reached. In patients with more severe weakness and those already in the hospital, starting at a high dose is reasonable. Patients are maintained on the dose that controls their symptoms for about a month, and then the dosage is slowly tapered (no faster than 10 mg a month until on 20 mg daily and then by 2.5–5 mg a month) to determine the minimum effective dose, and close monitoring is required. Some patients can be managed without the addition of other immunotherapies. Patients on long-term glucocorticoid therapy must be followed carefully to prevent or treat adverse side effects. The most common errors in glucocorticoid treatment of myasthenic patients include (1) insufficient persistence—improvement may be delayed and gradual; (2) tapering the dosage too early, too rapidly, or excessively; and (3) lack of attention to prevention and treatment of side effects.

The management of patients treated with glucocorticoids is discussed in Chap. 386.

Other Immunotherapies Mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, rituximab, eculizumab, and occasionally cyclophosphamide are effective in many patients, either alone or in various combinations.

Mycophenolate mofetil is widely used because of its presumed effectiveness and relative lack of side effects. A dose of 1–1.5 g bid is recommended. Its mechanism of action involves inhibition of purine synthesis by the de novo pathway. Since lymphocytes have only the de novo pathway, but lack the alternative salvage pathway that is present in all other cells, mycophenolate inhibits proliferation of lymphocytes but not proliferation of other cells. It does not kill or eliminate preexisting autoreactive lymphocytes, and therefore, clinical improvement may be delayed for many months to a year, until the preexisting autoreactive lymphocytes die spontaneously. The advantage of mycophenolate lies in its relative lack of adverse side effects, with only occasional production of GI symptoms, rare development of leukopenia, and very small risks of malignancy or

progressive multifocal leukoencephalopathy inherent in nearly all immunosuppressive treatments. Although two published studies did not show positive outcomes, most experts attribute the negative results to flaws in the trial designs, and mycophenolate is widely used for long-term treatment of myasthenic patients.

Azathioprine has long been used for MG, and a randomized, clinical trial demonstrated that it was effective in reducing the dosage of prednisone necessary to control symptoms. However, the beneficial effect can take a year or more to become evident. Approximately 10–15% of patients are unable to tolerate azathioprine because of idiosyncratic reactions consisting of flulike symptoms of fever and malaise, bone marrow suppression, or abnormalities of liver function. An initial dose of 50 mg/d is given for about a week to test for these side effects. If this dose is tolerated, it is increased gradually to ~2–3 mg/kg of total body weight or until the white blood count falls to 3000–4000/ μ L. Allopurinol should never be used in combination with azathioprine because the two drugs share a common degradation pathway; the result may be severe bone marrow suppression due to increased effects of the azathioprine.

The calcineurin inhibitors cyclosporine and tacrolimus seem to be effective in MG and appear to work more rapidly than azathioprine and mycophenolate. However, they are associated with more frequent severe side effects including hypertension and nephrotoxicity. The usual dose of cyclosporine is 4–5 mg/kg per d, and the average dose of tacrolimus is 0.07–0.1 mg/kg per d, given in two equally divided doses. “Trough” blood levels are measured 12 h after the evening dose. The therapeutic range for the trough level of cyclosporine is 150–200 ng/L, and for tacrolimus, it is 5–15 ng/L.

Rituximab (Rituxan) is a monoclonal antibody that binds to the CD20 molecule on B lymphocytes. It is widely used for the treatment of B-cell lymphomas and has also proven successful in the treatment of several autoimmune diseases including rheumatoid arthritis, pemphigus, and some IgM-related neuropathies. There is a growing literature on the benefit of rituximab in MuSK antibody-positive MG, which was previously more difficult to treat than anti-AChR-positive MG. A large, randomized trial of AChR antibody-positive generalized MG failed to demonstrate efficacy. The usual dose is 1 g IV on two occasions 2 weeks apart. Periodically, a repeat course needs to be administered; some MuSK patients go 2–3 years between infusions.

Eculizumab, a monoclonal antibody that binds to the terminal complement component 5 (C5), demonstrated efficacy in a large phase 3 clinical trial. The drug is administered intravenously every 2 weeks. Complement inhibition increases the risk of meningococcal infection, so ideally, a first series of vaccinations is given prior to initiation, and many recommend antibiotic prophylaxis (penicillin) while patients receive therapy. A benefit of eculizumab is that it works within 1–3 months and patients can often wean down on other immunotherapies. There are promising early results from other complement inhibitors, including subcutaneously administered drugs. For the rare refractory MG patient, a course of high-dose cyclophosphamide may induce long-lasting benefit. At high doses, cyclophosphamide eliminates mature lymphocytes but spares hematopoietic precursors (stem cells), because they express the enzyme aldehyde dehydrogenase, which hydrolyzes cyclophosphamide. This procedure is reserved for refractory patients and should be administered only in a facility fully familiar with this approach. Maintenance immunotherapy after treatment is usually required to sustain the beneficial effect.

PLASMAPHERESIS AND INTRAVENOUS IMMUNOGLOBULIN

Plasmapheresis has been used therapeutically in MG. Plasma, which contains the pathogenic antibodies, is mechanically separated from the blood cells, which are returned to the patient. A course of five exchanges (3–4 L per exchange) is generally administered over a 10- to 14-day period. Plasmapheresis produces a short-term reduction in anti-AChR antibodies, with clinical improvement in many patients. It is useful as a temporary expedient in seriously affected

patients or to improve the patient's condition prior to surgery (e.g., thymectomy).

The indications for the use of IVIg are the same as those for plasma exchange: to produce rapid improvement to help the patient through a difficult period of myasthenic weakness or prior to surgery. This treatment has the advantages of not requiring special equipment or large-bore venous access. The usual dose is 2 g/kg, which is typically administered over 2–5 days. Improvement occurs in ~70% of patients, beginning during treatment or within a week and continuing for weeks to months. The mechanism of action of IVIg is not known; the treatment has no consistent long-term effect on the measurable amount of circulating AChR antibody. Adverse reactions are generally not serious but may include headache, fluid overload, and rarely aseptic meningitis or renal failure. IVIg or plasma exchange is occasionally used in combination with other immunosuppressive therapy for maintenance treatment of difficult MG.

INVESTIGATIONAL TREATMENTS

Early results of fragment crystallized neonatal receptor (FcRn) blockers also appear promising. FcRn bind immunoglobulins, thereby rescuing them from lysosomal destruction. Blocking this receptor allows for degradation of anti-AChR, anti-MuSK, anti-LR4, and other antibodies, reducing their levels to 60–85% within 1–2 months. Several trials of different FcRn blockers are underway.

MANAGEMENT OF MYASTHENIC CRISIS

Myasthenic crisis is defined as an exacerbation of weakness sufficient to endanger life; it usually includes ventilatory failure caused by diaphragmatic and intercostal muscle weakness. Treatment should be carried out in intensive care units staffed with teams experienced in the management of MG. The possibility that deterioration could be due to excessive anticholinesterase medication (“cholinergic crisis”) is best excluded by temporarily stopping anticholinesterase drugs. The most common cause of crisis is intercurrent infection. This should be treated immediately because the mechanical and immunologic defenses of the patient can be assumed to be compromised. The myasthenic patient with fever and early infection should be treated like other immunocompromised patients. Early and effective antibiotic therapy, ventilatory assistance, and pulmonary physiotherapy are essentials of the treatment program. As discussed above, plasmapheresis or IVIg is frequently helpful in hastening recovery.

DRUGS TO AVOID IN MYASTHENIC PATIENTS

Many drugs can potentially exacerbate weakness in patients with MG (Table 448-4). As a rule, the listed drugs should be avoided whenever possible.

■ PATIENT ASSESSMENT

To evaluate the effectiveness of treatment as well as drug-induced side effects, it is important to assess the patient's clinical status systematically at baseline and on repeated interval examinations. Following the patient with spirometry with determination of forced vital capacity and mean inspiratory and expiratory pressures is important.

PROGNOSIS

Approximately 20% of patients with MG achieve a sustained remission and can be tapered off all immunotherapies. There does not appear to be a correlation between disease severity and likelihood of remission. Thymectomy may increase the chance of achieving remission in anti-AChR MG, but the large randomized trial was too short in duration to examine this endpoint; rather, the results revealed only that thymectomy was efficacious and led to less use of glucocorticoids and second-line agents. Mortality from MG diminished greatly during the twentieth century, changing from a “grave” illness with mortality of nearly 70% a century ago, to 2–30% by the 1950s, with contemporary estimates in the 1–2% range. Anti-MuSK patients generally were more difficult to treat than anti-AChR MG in the past. However, recent series

TABLE 448-4 Drugs with Interactions in Myasthenia Gravis (MG)

Drugs That May Exacerbate MG

Antibiotics	
Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin	
Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin	
Macrolides: e.g., erythromycin, azithromycin	
Nondepolarizing muscle relaxants for surgery	
D-Tubocurarine (curare), pancuronium, vecuronium, atracurium	
Beta-blocking agents	
Propranolol, atenolol, metoprolol	
Local anesthetics and related agents	
Procaine, Xylocaine in large amounts	
Procainamide (for arrhythmias)	
Botulinum toxin	
Botox exacerbates weakness	
Quinine derivatives	
Quinine, quinidine, chloroquine, mefloquine (Lariam)	
Magnesium	
Decreases acetylcholine release	
Penicillamine	
May cause MG	
Check point inhibitors	
May cause MG and other autoimmune neuromuscular disorders (e.g., myositis, inflammatory neuropathy)	
Drugs with Important Interactions in MG	
Cyclosporine and tacrolimus	
Broad range of drug interactions, which may raise or lower levels.	
Azathioprine	
Avoid allopurinol—combination may result in myelosuppression.	

suggest that rituximab is effective in this subgroup, thereby reducing these risks and improving the prognosis. Nonparaneoplastic LEMS is usually responsive to immunotherapy and symptomatic treatment with pyridostigmine and 3,4-DAP. In older adults, LEMS is most often paraneoplastic, and screening for an underlying tumor is indicated (Chap. 94). Recent studies suggest that survival in patients with LEMS has improved, for uncertain reasons and likely not due to earlier diagnosis and treatment of the tumor. There is wide variability in age of onset, severity, and prognosis of the many types of CMS.

GLOBAL ISSUES

The incidence of MG and its subtypes varies in different populations, for example, occurring in ~2–10/10⁶ individuals in the United States and the Netherlands and up to 20/10⁶ individuals in Spain. Estimates of prevalence in different parts of the world range widely from 2–200/10⁶. The age of onset may also be influenced by geographic and/or ethnic differences. Juvenile-onset MG is uncommon in Western populations but may represent more than half of cases in Asians. MuSK MG appears to be more common in the Mediterranean area of Europe than in northern Europe and is also more common in the northern regions of East Asia than in the southern regions. A concern during the COVID-19 pandemic is whether MG patients on immunosuppressive therapies might be at increased risk of infection or developing a more severe course. Furthermore, flares of MG can be triggered by infection, and contracting COVID-19 may lead to an exacerbation, including MG crisis. I have not reduced the dosage of immunosuppressive medications in MG patients who are doing well but have been more likely to manage worsening disease by treating with IVIg rather than increasing the dosage of, or adding new, immunosuppressive agents. Patients are strongly advised to wear masks and maintain social distancing. An international panel has published guidelines for management of MG patients during this crisis.

FURTHER READING

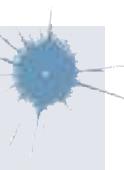
- A AA, R JA: *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill, 2016, pp. 581–655.
- C E: Myasthenia gravis and congenital myasthenic syndromes. *Continuum (Minneapolis Minn)* 25:1767, 2009.
- E A et al: Myasthenia gravis with antibodies to MuSK: An update. *Ann NY Acad Sci* 1412:82, 2018.
- G N et al: Late presentations of congenital myasthenic syndromes: How many do we miss? *Muscle Nerve* 54:721, 2016.
- G NE: Myasthenia gravis. *N Engl J Med* 375:2570, 2016.
- G AC: Lambert-Eaton myasthenic syndrome, botulism, and immune checkpoint inhibitor-related myasthenia gravis. *Continuum (Minneapolis Minn)* 25:1785, 2019.
- H JF J et al: Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): A phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol* 16:976, 2017.
- H JF J et al: Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology* 92:e2661, 2019.
- I MG/COVID-19 W G et al: Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci* 412:116803, 2020.
- T R et al: Rituximab treatment of myasthenia gravis: A systematic review. *Muscle Nerve* 56:185, 2017.
- W GI et al: Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 375:511, 2016.
- W GI et al: Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. *Lancet Neurol* 18:259, 2019.

VIDEO 448-1 Myasthenia gravis and other diseases of the neuromuscular junction.

449

Muscular Dystrophies and Other Muscle Diseases

Anthony A. Amato, Robert H. Brown, Jr.



Myopathies are disorders with structural changes or functional impairment of muscle and can be differentiated from other diseases of the motor unit (e.g., lower motor neuron or neuromuscular junction pathologies) by characteristic clinical and laboratory findings. [Myasthenia gravis and related disorders are discussed in Chap. 448; inflammatory myopathies are discussed in Chap. 365.](#)

CLINICAL FEATURES

The most important aspect of assessing individuals with neuromuscular disorders is taking a thorough history of the patient's symptoms, disease progression, and past medical and family history, as well as performing a detailed neurologic examination. Based on this and additional laboratory workup (e.g., serum creatine kinase [CK], electromyography [EMG]), one can usually localize the site of the lesion to muscle (as opposed to motor neurons, peripheral nerves, or neuromuscular junction) and the pattern of muscle involvement. It is this pattern of muscle involvement that is most useful in narrowing the differential diagnosis ([Table 449-1](#)). Most myopathies present with proximal, symmetric limb weakness with preserved reflexes and sensation. However, asymmetric and predominantly distal weakness can be seen in some myopathies. An associated sensory loss suggests a peripheral neuropathy or a central nervous system (CNS) abnormality

TABLE 449-1 Myopathies by Pattern of Weakness/Muscle Involvement

Proximal (Limb-Girdle) Weakness	Late-onset central core (<i>RYR1</i> mutations) Sporadic late-onset nemaline rod with or without a monoclonal gammopathy Metabolic (late-onset Pompe, McArdle disease, lipid storage, mitochondrial) Hyperparathyroidism/osteomalacia/vitamin D deficiency Myasthenia gravis
Most dystrophies (e.g., dystrophinopathies, limb-girdle, myofibrillar myopathy, myotonic dystrophy type 2, rare FSHD)	
Congenital myopathies (e.g., central core, multimimicore, centronuclear, nemaline rod)	
Metabolic myopathies (e.g., glycogen and lipid storage diseases)	
Mitochondrial myopathies	
Inflammatory myopathies (DM, PM, IMNM, anti-synthetase syndrome)	
Toxic myopathies (see Table 449-6)	
Endocrine myopathies	
Neuromuscular junction disorders (myasthenia gravis, LEMS, congenital myasthenia, botulism, see Chap. 448)	
Distal Weakness	
Distal muscular dystrophies/myofibrillar myopathy (see Table 449-5)	
Congenital myopathies (e.g., late-onset centronuclear and nemaline rod myopathies)	
Metabolic	
Glycogen storage disease (e.g., brancher and debrancher deficiency, rarely McArdle disease)	
Lipid storage disease (e.g., neutral lipid storage myopathy, multiacyldehydrogenase deficiency)	
NMJ disorders (e.g., rare myasthenia gravis and congenital myasthenia)	
Proximal Arm/Distal Leg Weakness (Scapuloperoneal or Humeroperonal) Weakness	
Facioscapulohumeral muscular dystrophy (FSHD)	
Scapuloperoneal myopathy and neuropathy	
Myofibrillar myopathies	
Emery-Dreifuss muscular dystrophy (EDMD)	
Bethlem myopathy	
Distal Arm/Proximal Leg Weakness	
Inclusion body myositis (usually wrist and finger flexors in arms, hip flexors and knee extensors in legs, and asymmetric)	
Myotonic dystrophy (uncommon presentation)	
Axial Muscle Weakness	
Inflammatory (cervicobrachial myositis)	
sIBM and hIBM	
Myotonic dystrophy 2	
Isolated neck extensor myopathy/bent spine syndrome	
FSHD	
	Eye Muscle Weakness (Ptosis/Ophthalmoparesis)
	Ptosis without ophthalmoparesis
	Myotonic dystrophy
	Congenital myopathies
	Neuromuscular junction disorders
	Ptosis with ophthalmoparesis
	Oculopharyngeal dystrophy
	Mitochondrial myopathy
	hIBM type 3
	Neuromuscular junction disorders
	Episodic Weakness or Myoglobinuria
	Related to exercise
	Glycogenoses (e.g., McArdle disease, etc.)
	Lipid disorders (e.g., CPT2 deficiency)
	Mitochondrial myopathies (e.g., cytochrome B deficiency)
	Not related to exercise
	<i>RYR1</i> mutations can cause malignant hyperthermia, episodic rhabdomyolysis/ myoglobinuria, and atypical periodic paralysis
	Other causes of malignant hyperthermia
	Drugs/toxins (e.g., statins)
	Prolonged/intensive eccentric exercise
	Inflammatory (e.g., PM/DM—rare, viral/bacterial infections)
	Delayed or unrelated to exercise
	Periodic paralysis (e.g., hereditary hyper- or hypokalemic, thyrotoxic, associated renal tubular acidosis, acquired electrolyte imbalance)
	NMJ disorders
	Muscle Stiffness/Decreased Ability to Relax
	Myotonic dystrophy 1 and 2
	Myotonia congenita
	Paramyotonia congenita
	Hyperkalemic periodic paralysis with myotonia
	Potassium aggravated myotonia
	Schwartz-Jampel syndrome
	Other: rippling muscle disease (acquired and hereditary), acquired neuromyotonia (Isaacs' syndrome), stiff-person syndrome, Brody's disease

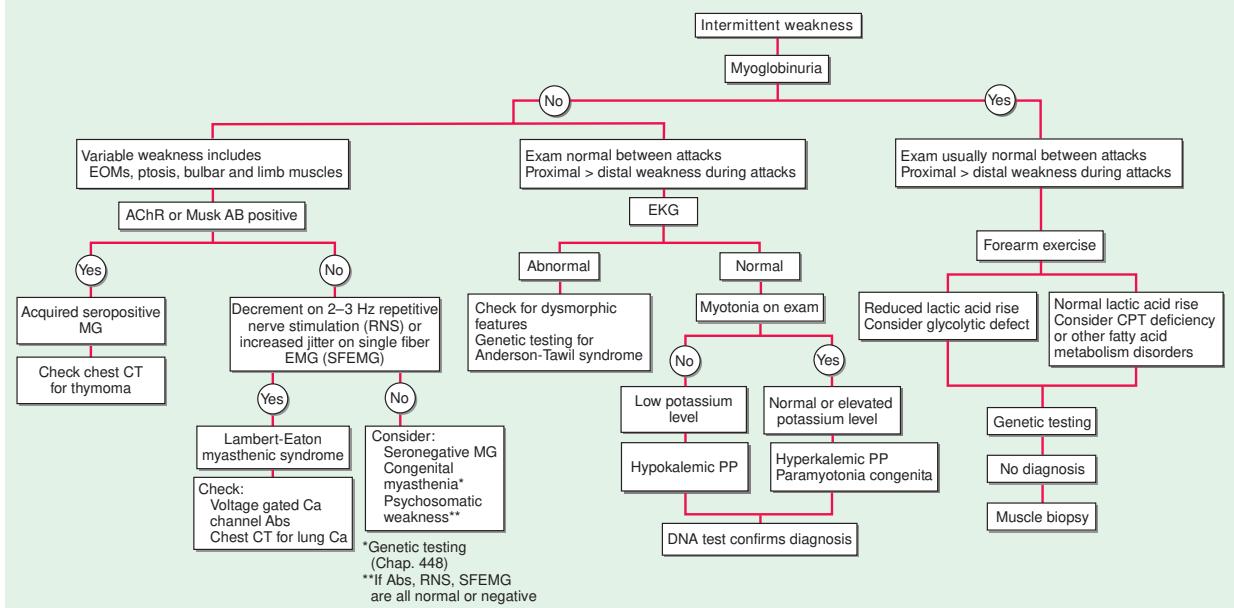
Abbreviations: DM, dermatomyositis; hIBM, hereditary inclusion body myopathy; IMNM, immune-mediated necrotizing myopathy; LEMS, Lambert-Eaton myasthenic syndrome; NMJ, neuromuscular junction; PM, polymyositis; sIBM, sporadic inclusion body myositis.

(e.g., myelopathy) rather than a myopathy. On occasion, disorders affecting the motor nerve cell bodies in the spinal cord (anterior horn cell disease), the neuromuscular junction, or peripheral nerves can mimic findings of myopathy.

Muscle Weakness Symptoms of muscle weakness can be either intermittent or persistent. Disorders causing *intermittent weakness* (Table 449-1 and Fig. 449-1) include myasthenia gravis, periodic paralyses (hypokalemic or hyperkalemic), and metabolic energy deficiencies of glycolysis (especially myophosphorylase deficiency), fatty acid utilization (carnitine palmitoyltransferase [CPT] deficiency), and some mitochondrial myopathies. The states of energy deficiency cause activity-related muscle breakdown accompanied by myoglobinuria.

Most muscle disorders cause *persistent weakness* (Table 449-1 and Fig. 449-2). In the majority of these, including most types of muscular dystrophy and inflammatory myopathies, the proximal muscles are weaker than the distal and are symmetrically affected, and the facial muscles are spared, a pattern referred to as *limb-girdle weakness*. The

differential diagnosis is more restricted for other patterns of weakness. Facial weakness (difficulty with eye closure and impaired smile) and scapular winging (Fig. 449-3) are characteristic of facioscapulohumeral dystrophy (FSHD). Facial and distal limb weakness associated with hand grip myotonia is virtually diagnostic of myotonic dystrophy type 1. When other cranial nerve muscles are weak, causing ptosis or extraocular muscle weakness, the most important disorders to consider include neuromuscular junction disorders, oculopharyngeal muscular dystrophy, mitochondrial myopathies, or some of the congenital myopathies (Table 449-1). A pathognomonic pattern characteristic of inclusion body myositis is atrophy and weakness of the flexor forearm (e.g., wrist and finger flexors) and quadriceps muscles that is often asymmetric. Less frequently seen, but important diagnostically, are the axial myopathies that predominantly affect the paraspinal muscles and include dropped head syndrome indicative of selective neck extensor muscle weakness. The most important neuromuscular diseases associated with this axial muscle weakness include myasthenia gravis, amyotrophic lateral sclerosis, late-onset core or nemaline rod myopathy,



hyperparathyroidism, focal myositis, and some forms of inclusion body myopathy. A final pattern, recognized because of preferential distal extremity weakness, is seen in the distal myopathies.

It is important to examine functional capabilities to help disclose certain patterns of weakness (Table 449-1 and Table 449-2). The Gower sign (Fig. 449-4) is particularly useful. Observing the gait of an individual may disclose a lordotic posture caused by combined trunk and hip weakness, frequently exaggerated by toe walking (Fig. 449-5). A waddling gait is caused by the inability of weak hip muscles to prevent hip drop or hip dip. Hyperextension of the knee

(genu recurvatum or back-kneeling) is characteristic of quadriceps muscle weakness; and a steppage gait, due to foot drop, accompanies distal weakness.

Any disorder causing muscle weakness may be accompanied by *fatigue*, referring to an inability to maintain or sustain a force (pathologic fatigability). This condition must be differentiated from asthenia, a type of fatigue caused by excess tiredness or lack of energy. Associated symptoms may help differentiate asthenia and pathologic fatigability. Asthenia is often accompanied by a tendency to avoid physical activities, complaints of daytime sleepiness, necessity for frequent naps, and

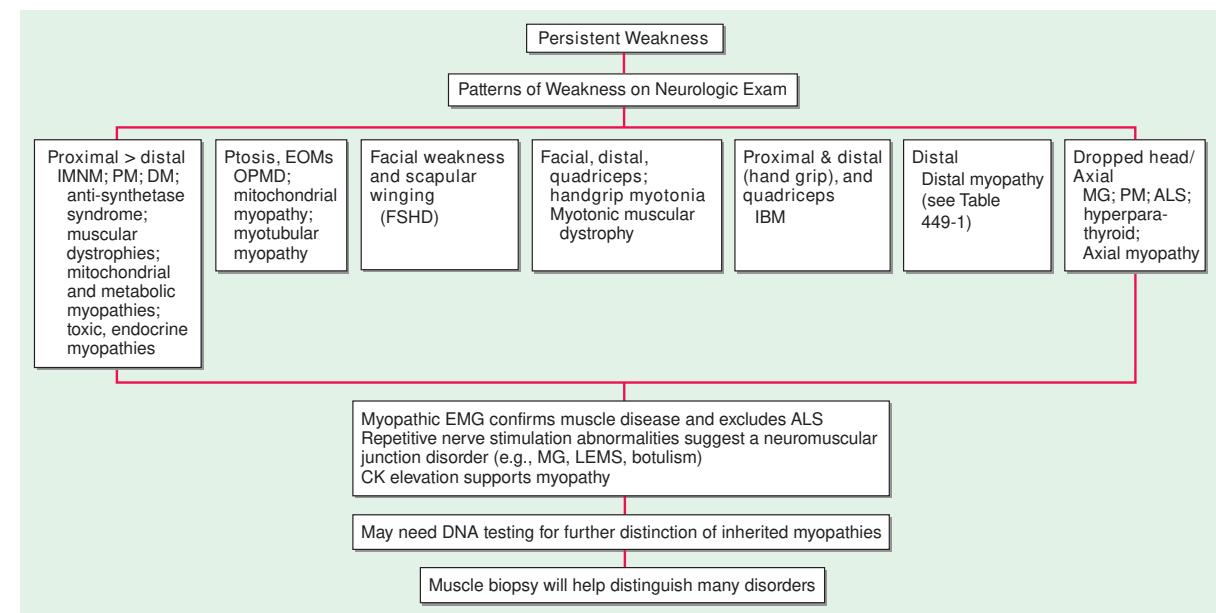




FIGURE 449-3 Facioscapulohumeral dystrophy with prominent scapular winging.

difficulty concentrating on activities such as reading. There may be feelings of overwhelming stress and depression. In contrast, pathologic fatigability occurs in disorders of neuromuscular transmission and in disorders altering energy production, including defects in glycolysis, lipid metabolism, or mitochondrial energy production. Pathologic fatigability also occurs in chronic myopathies because of difficulty accomplishing a task with less muscle. Pathologic fatigability is accompanied by abnormal clinical or laboratory findings. Fatigue without those supportive features almost never indicates a primary muscle disease.

Muscle Pain (Myalgias), Cramps, and Stiffness Some myopathies can be associated with muscle pain, cramps, contractures, stiff or rigid muscles, or inability to relax the muscles (e.g., myotonia) (Table 449-1). *Muscle cramps* are abrupt in onset, short in duration, triggered by voluntary muscle contraction, and may cause abnormal posturing of the joint. Muscle cramps often occur in neurogenic disorders, especially motor neuron disease (Chap. 437), radiculopathies, and polyneuropathies (Chap. 446), but are not a feature of most primary muscle diseases.

A *muscle contracture* is different from a muscle cramp. In both conditions, the muscle becomes hard, but a contracture is associated with energy failure in glycolytic disorders. The muscle is unable to

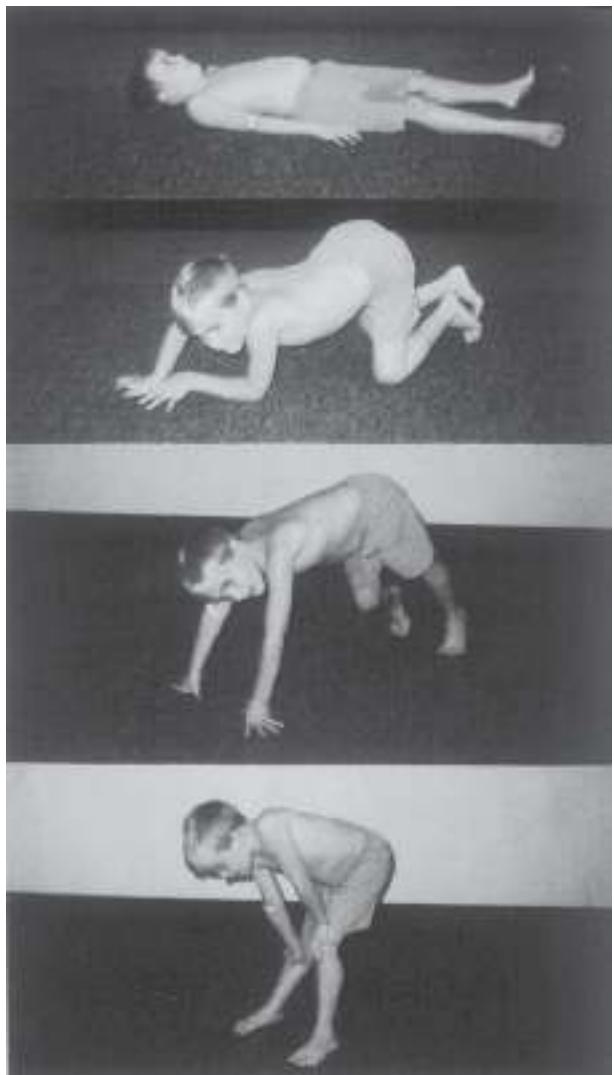


FIGURE 449-4 Gower sign showing a patient using his arms to climb up the legs in attempting to get up from the floor.

TABLE 449-2 Observations on Examination That Disclose Muscle Weakness

FUNCTIONAL IMPAIRMENT	MUSCLE WEAKNESS
Inability to forcibly close eyes	Upper facial muscles
Impaired pucker	Lower facial muscles
Inability to raise head from prone position	Neck extensor muscles
Inability to raise head from supine position	Neck flexor muscles
Inability to raise arms above head	Proximal arm muscles (may be only scapular stabilizing muscles)
Inability to walk without hyperextending knee (back-kneeling or genu recurvatum)	Knee extensor muscles
Inability to walk with heels touching the floor (toe walking)	Shortening of the Achilles tendon
Inability to lift foot while walking (steppage gait or foot drop)	Anterior compartment of leg
Inability to walk without a waddling gait	Hip muscles
Inability to get up from the floor without climbing up the extremities (Gowers' sign)	Hip, thigh, and trunk muscles
Inability to get up from a chair without using arms	Hip muscles

relax after an active muscle contraction. The EMG shows electrical silence. Confusion is created because contracture also refers to a muscle that cannot be passively stretched to its proper length (fixed contracture) because of fibrosis. In some muscle disorders, especially in Emery-Dreifuss muscular dystrophy (EDMD) and Bethlem myopathy, fixed contractures occur early and represent distinctive features of the disease.

Myotonia is a condition of prolonged muscle contraction followed by slow muscle relaxation. It always follows muscle activation (action myotonia), usually voluntary, but may be elicited by mechanical stimulation (percussion myotonia) of the muscle. Myotonia typically causes difficulty in releasing objects after a firm grasp. In myotonic muscular dystrophy type 1 (DM1), distal weakness usually accompanies myotonia, whereas in DM2, proximal muscles are more affected. Myotonia also occurs with *myotonia congenita* (a chloride channel disorder), but in this condition, muscle weakness is not prominent. Myotonia may also be seen in individuals with sodium channel mutations (*hyperkalemic periodic paralysis* or *potassium-sensitive myotonia*). Another sodium channelopathy, *paramyotonia congenita* (PC), also is associated with muscle stiffness. In contrast to other disorders associated with myotonia in which the myotonia is eased by repetitive activity, PC is named for a paradoxical phenomenon whereby the myotonia worsens with repetitive activity. Potassium-aggravated myotonia is an allelic



FIGURE 449-5 Lordotic posture, exaggerated by standing on toes, associated with trunk and hip weakness.

disorder in which myotonia is brought on by consumption of too much potassium-containing foods.

Muscle stiffness can refer to different phenomena. Some patients with inflammation of joints and periarticular surfaces feel stiff. This condition is different from the disorders of hyperexcitable motor nerves causing stiff or rigid muscles. In *stiff-person syndrome*, spontaneous discharges of the motor neurons of the spinal cord cause involuntary muscle contractions mainly involving the axial (trunk) and proximal lower extremity muscles. The gait becomes stiff and labored, with hyperlordosis of the lumbar spine. Superimposed episodic muscle spasms are precipitated by sudden movements, unexpected noises, and emotional upset. The muscles relax during sleep. Serum antibodies against glutamic acid decarboxylase are present in approximately two-thirds of cases. In *acquired neuromyotonia (Isaacs' syndrome)*, there is hyperexcitability of the peripheral nerves manifesting as continuous muscle fiber activity in the form of widespread fasciculations and myokymia with impaired muscle relaxation. Muscles of the leg are stiff, and the constant contractions of the muscle cause increased sweating of the extremities. This peripheral nerve hyperexcitability is mediated by antibodies that target voltage-gated potassium channels.

There are two painful muscle conditions of particular importance, neither of which is associated with muscle weakness. *Fibromyalgia* is a common, yet poorly understood myofascial pain syndrome in which patients complain of severe muscle pain and tenderness, severe fatigue, and often poor sleep. Serum CK, erythrocyte sedimentation rate (ESR), EMG, and muscle biopsy are normal ([Chap. 373](#)). *Polymyalgia rheumatica* occurs mainly in patients aged >50 years and is characterized by stiffness and pain in the shoulders, lower back, hips, and thighs ([Chap. 363](#)). The ESR and CRP are elevated, while serum CK, EMG, and muscle biopsy are normal.

Muscle Enlargement and Atrophy In most myopathies, muscle tissue is replaced by fat and connective tissue, but the size of the muscle

is usually not affected. However, in many limb-girdle muscular dystrophies, enlarged calf muscles are typical. The enlargement represents true muscle hypertrophy; thus, the term *pseudohypertrophy* should be avoided when referring to these patients. The calf muscles remain very strong even late in the course of these disorders. Muscle enlargement can also result from infiltration by sarcoid granulomas, amyloid deposits, bacterial and parasitic infections, and focal myositis. In contrast, muscle atrophy is characteristic of other myopathies. In Miyoshi myopathy, which can be caused by mutations in the genes that encode for dysferlin and anoctamin 5, there is a predilection for early atrophy of the gastrocnemius muscles, particularly the medial aspect. Atrophy of the humeral muscles is characteristic of FSHD and EDMD.

■ LABORATORY EVALUATION

Various tests can be used to evaluate a suspected myopathy, including CK levels, endocrine studies (e.g., thyroid function tests, parathyroid hormone and vitamin D levels), autoantibodies (associated with myositis and systemic disorders), forearm exercise test, muscle biopsy, and genetic testing. Electrodiagnostic studies can be useful to differentiate myopathies from other neuromuscular disorders (motor neuron disease, peripheral neuropathies, neuromuscular junction disorders) but, in most instances, do not help distinguish the specific type of myopathy.

Serum Enzymes CK is the most sensitive measure of muscle damage. The MM isoenzyme predominates in skeletal muscle, whereas CK-myocardial bound (CK-MB) is the marker for cardiac muscle. Serum CK can be elevated in normal individuals without provocation, presumably on a genetic basis or after strenuous activity, trauma, a prolonged muscle cramp, or a generalized seizure. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase, and lactate dehydrogenase (LDH) are enzymes sharing an origin in both muscle and liver. Problems arise when the levels of these enzymes are found to be elevated in a routine screening battery, leading to the erroneous assumption that liver disease is present when in fact muscle could be the cause. An elevated γ-glutamyl transferase (GGT) helps to establish a liver origin because this enzyme is not found in muscle. Rarely, aldose can be elevated in an inflammatory myopathy when CK, AST, and ALT are normal, signifying that the inflammation predominantly affects the perimysium (dermatomyositis, graft-versus-host disease) or the surrounding fascia (fasciitis).

Electrodiagnostic Studies EMG, repetitive nerve stimulation, and nerve conduction studies (NCS) ([Chap. 446](#)) are helpful in differentiating myopathies from motor neuron disease, neuropathies, and neuromuscular junction diseases. Routine NCS are typically normal in myopathies, but reduced amplitudes of compound muscle action potentials may be seen in atrophied muscles. The needle EMG may reveal irritability on needle insertion and spontaneously that is suggestive of a myopathy with active necrosis or muscle membrane instability (inflammatory myopathies, dystrophies, toxic myopathies, myotonic myopathies), whereas a lack of irritability is characteristic of long-standing myopathic disorders (muscular dystrophies with severe fibrofatty replacement, endocrine myopathies, disuse atrophy, and many of the metabolic myopathies between bouts of rhabdomyolysis). In addition, the EMG may demonstrate myotonic discharges that will narrow the differential diagnosis ([Table 449-1](#)). Another important EMG finding is the presence of short-duration, small-amplitude, polyphasic motor unit action potentials (MUAPs). In myopathies, the MUAPs fire early but at a normal rate to compensate for the loss of individual muscle fibers, whereas in neurogenic disorders, the MUAPs fire faster. An EMG is usually normal in steroid or disuse myopathy, both of which are associated with type 2 fiber atrophy; this is because the EMG preferentially assesses the physiologic function of type 1 fibers. The EMG can supplement the clinical examination in choosing an appropriately affected muscle to biopsy.

Imaging Studies Skeletal MRI and ultrasound are increasing utilized to assess the pattern of muscle involvement, which can help in narrowing the diagnosis, and are often more sensitive than the clinical examination and EMG, particularly early in a disease course. For

example, there is early predilection of the vastus lateralis and medialis muscles with relative sparing of the rectus femoris muscles on imaging of thigh muscles in patients with inclusion body myositis, and this can be appreciated on imaging prior to weakness being detected on manual muscle testing. MRI can also demonstrate fascitis when the clinical examination and EMG are normal. Imaging can also be used to help guide what muscle to biopsy in patients with weakness on manual muscle testing and EMG abnormalities only in muscles that are not typically biopsied (e.g., paraspinal or hip girdle). We have found imaging helpful in patients with presumed muscular dystrophy when the muscle biopsy is not diagnostic and genetic testing shows only a variation of unclear significance. In this situation, the pattern of muscle involvement on imaging can support the known pattern of muscle involvement of a specific hereditary myopathy. The cost and availability of MRI preclude routine use in some settings, but ultrasound is more readily available and less expensive.

Genetic Testing This is increasingly available and is the gold standard for diagnosing patients with hereditary myopathies. Next-generation sequencing panels are increasing utilized, but clinicians need to know their limitations; large deletions and duplications can be missed, as can mutations in noncoding (intronic) regions. Furthermore, testing often reveals sequence alterations of unclear significance.

Forearm Exercise Test With exercise-induced muscle pain and myoglobinuria, there may be a defect in glycolysis. For safety, the test should not be performed under ischemic conditions to avoid an unnecessary insult to the muscle, causing rhabdomyolysis. The test is performed by placing a small indwelling catheter into an antecubital vein. A baseline blood sample is obtained for lactic acid and ammonia. The forearm muscles are exercised by asking the patient to vigorously open and close the hand for 1 min. Blood is then obtained at intervals of 1, 2, 4, 6, and 10 min for comparison with the baseline sample. A three- to fourfold rise of lactic acid is typical. The simultaneous measurement of ammonia serves as a control because it should also rise with exercise. In patients with myophosphorylase deficiency and certain other glycolytic defects, the lactic acid rise will be absent or below normal, while the rise in ammonia will reach control values. If there is lack of effort, neither lactic acid nor ammonia will rise. Patients with selective failure to increase ammonia may have myoadenylate deaminase deficiency. This condition has been reported to be a cause of myoglobinuria, but deficiency of this enzyme in asymptomatic individuals makes interpretation controversial.

Muscle Biopsy Muscle biopsy is extremely helpful in evaluation of acquired myopathies but is performed less frequently in suspected hereditary myopathies as genetic testing has become more widely available. However, muscle biopsy can be helpful in cases of suspected hereditary myopathy in which genetic testing was nondiagnostic. Almost any superficial muscle can be biopsied, but it is important to biopsy one that is affected clinically but not too severely (for example grade 4 out of 5 strength or movement against moderate resistance by manual muscle testing [Chap. 422]). A specific diagnosis can be established in many disorders.

HEREDITARY MYOPATHIES

Muscular dystrophy refers to a group of hereditary progressive diseases, each with unique phenotypic and genetic features (Tables 449-3, 449-4, and 449-5, and Fig. 449-6). The prognosis of dystrophies is slow progressive weakness, though the severity and course are variable between and even within subtypes. Some are associated with cardiac and ventilatory muscle involvement, which are the leading causes of mortality. Unfortunately, there are no specific medical therapies for most of the muscular dystrophies, and treatment is aimed at maintaining function with physical and occupational therapy. Noninvasive ventilation and tracheostomy may be warranted. Those with cardiomyopathy may require afterload reduction, antiarrhythmic agents, pacemakers or intracardiac defibrillators, and occasionally cardiac transplantation. We will focus primarily on those that manifest in adulthood.

DUCHENNE AND BECKER MUSCULAR DYSTROPHY DMD AND BMD

DMD and BMD are X-linked recessive muscular dystrophies caused by mutations in the *dystrophin* gene. Affecting 1 in 3000 male births, DMD is the most common mutational disease affecting boys. The incidence of BMD is ~5 per 100,000.

Clinical Features Proximal muscles, especially of the lower extremities, are prominently involved in both disorders. This becomes evident in DMD very early; boys with DMD have difficulty climbing stairs and never run well. As the disease progresses, weakness becomes more generalized. Hypertrophy of muscles, particularly in the calves, is an early and prominent finding. Most patients with BMD first experience difficulties between ages 5 and 15 years, although onset in the third or fourth decade or even later can occur. Life expectancy for DMD and BMD is reduced, but most BMD cases survive into the fourth or fifth decade. Intellectual disability may occur in both disorders but is less common in BMD. Cardiac involvement is common in both DMD and BMD and may result in heart failure; some BMD patients manifest with only heart failure. Other less common presentations of dystrophinopathy are asymptomatic hyper-CK-emia, myalgias without weakness, and myoglobinuria.

Laboratory Features Serum CK levels are usually elevated. Muscle biopsies demonstrate dystrophic features. Western blot analysis of muscle biopsy samples demonstrates absent dystrophin in DMD or reduction in levels or size of dystrophin in BMD. In both disorders, mutations can be established using DNA from peripheral blood leukocytes. In most cases, muscle biopsies are no longer performed when DMD or BMD is suspected, as genetic testing is less invasive, less costly, and routinely available. Deletions within or duplications of the *dystrophin* gene are common in both DMD and BMD; in ~95% of cases, the mutation does not alter the translational reading frame of messenger RNA. These “in-frame” mutations allow for production of some dystrophin, which accounts for the presence of altered rather than absent dystrophin on Western blot analysis and a milder clinical phenotype.

TREATMENT

Duchenne and Becker Muscular Dystrophy

Glucocorticoids slow progression in DMD, but their use has not been adequately studied in BMD. Physical and occupational therapy are important in helping maintain function. As patients often die from the associated cardiomyopathy, it is important to follow patients with a cardiologist and treat appropriately. Recent studies suggest that there is clinical benefit in selected cases of DMD from short oligonucleotides that permit skipping of mutant exons, leading to expression of a short but nonetheless functional dystrophin protein. In parallel, other studies suggest that small molecules may permit read-through of protein-truncating mutations in some DMD cases, again with clinical benefit.

LIMB GIRDLE MUSCULAR DYSTROPHY

The limb-girdle muscular dystrophies (LGMDs) are a genetically heterogeneous group of dystrophies in which males and females are affected equally, with typical onset ranging from late in the first decade to the fourth decade. The LGMDs typically manifest with progressive weakness of pelvic and shoulder girdle musculature and are often clinically indistinguishable from DMD and BMD. Respiratory insufficiency from weakness of the diaphragm may occur, as may cardiomyopathy. Serum CKs are elevated, and the EMG is myopathic. Muscle biopsy reveal dystrophic features, but the findings are not specific to differentiate subtypes from one another unless immunohistochemistry is employed (e.g., immunostaining for various sarcoglycans, dysferlin, alpha-dystroglycan, merosin) or there are features to suggest one of the myofibrillar myopathies. Nonetheless, definitive diagnosis requires genetic testing.

The traditional classification of LGMD is based on autosomal dominant (LGMD1) and autosomal recessive (LGMD2) inheritance.

TABLE 449-3 Autosomal Dominant Limb-Girdle Muscular Dystrophies (LGMDs)

TRADITIONAL CLASSIFICATION/ PROPOSED NEW CLASSIFICATION (WHEN APPLICABLE)	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
LGMD1A/myofibrillar myopathy	Onset second to eighth decade Muscle weakness affects proximal and distal limb muscles, vocal cords, and pharyngeal muscles	Serum CK 2x normal EMG myopathic and may have pseudomotonic discharges Muscle biopsy: features of MFM	Myotilin
LGMD1B/EDMD2	Onset first or second decade Proximal lower limb weakness and cardiomyopathy with conduction defects Some cases indistinguishable from Emery-Dreifuss muscular dystrophy (EDMD) with joint contractures	Serum CK 3–5x normal EMG myopathic	Lamin A/C
LGMD1C/rippling muscle disease	Onset in early childhood Proximal weakness Gower sign, calf hypertrophy, rippling muscles Exercise-related muscle cramps	Serum CK 4–25x normal EMG myopathic	Caveolin-3
LGMD1D/LGMDD1	Onset second to sixth decade Proximal and distal muscle weakness	Serum CK 2–3x normal EMG myopathic Muscle biopsy: features of MFM	DNAJB6
LGMD1E/myofibrillar myopathy	Onset first to sixth decade Proximal or distal muscle weakness Cardiomyopathy and arrhythmias	Serum CK 2–4x normal EMG myopathic and may have pseudomotonic discharges Muscle biopsy: features of MFM	Desmin
LGMD1F/LGMDD2	Onset infancy to sixth decade Proximal or distal weakness May have early contractures resembling Emery-Dreifuss syndrome	Serum CK normal to 20x normal EMG myopathic Muscle biopsy may show enlarged nuclei with central pallor, rimmed vacuoles, and filamentous inclusions	TNPO3
LGMD1G/LGMDD3	Onset teens to sixth decade Proximal weakness contractures of fingers and toes	Muscle biopsies show rimmed vacuoles CK normal to 9x normal	HNRNPDL
LGMD1I/LGMDD4	Onset teens to ninth decade Proximal weakness, scapular winging	CK normal to 50x normal EMG myopathic	Calpain-3
Bethlem myopathy/LGMD1D5	Onset in childhood to adulthood Contractures at elbows, distal fingers, knees, ankles Hyperextensible fingers proximally Keloids	CK normal to 3x normal MRI and ultrasound of muscle show a peripheral > central predilection for fibrofatty replacement in individual muscles	Collagen VI alpha 1 chain

Abbreviations: CK, creatine kinase; EMG, electromyography; HNRNPDL, heterogeneous nuclear ribonucleoprotein D-like protein; MFM, myofibrillar myopathy.

Superimposed on the backbone of LGMD1 and LGMD2, the classification uses a sequential alphabetical lettering system (LGMD1A, LGMD2A, etc.) based on genotype. However, ever-expanding discoveries of new genes have outgrown the alphabet. The European Neuromuscular Centre (ENMC) recently proposed a new nomenclature in which autosomal dominant cases are termed LGMD “D” and autosomal recessive as LGMD “R,” followed by a numerical number based on genotype. Furthermore, this new classification only includes cases in which at least two unrelated families have been reported, the predominant weakness at onset was proximal, independent ambulation was achieved at some time, CK is elevated, and muscle biopsies or imaging revealed dystrophic features. Thus, mutations in the *CPN3* gene leading to a deficiency in calpain-3, which traditionally were classified as LGMD2A, are classified as LGMDR1 by this new system. In contrast, mutations in myotilin (LGMD1A) and desmin (LGMD1E and LGMD2R) and that often have more distal weakness and have biopsies features of a myofibrillar myopathy are not classified as a LGMD in this new scheme but rather as subtypes of myofibrillar myopathy. Likewise, laminopathies (LGMD1B) are considered a subtype of EDMD rather than an LGMD. This new classification of LGMD and distal muscular dystrophies is summarized in Tables 449-3 and 449-4.

The prevalence of LGMD ranges from 80 to 700 per 100,000, while estimated prevalences of individual specific subtypes of LGMDs vary. The most common types of adult-onset LGMD are calpainopathy (LGMD2A/LGMDR1), Fukutin-related protein (FKRP) deficiency (LGMD2I/LGMDR9), and anoctaminopathy (LGMD2L/LGMDR12).

Calpainopathy (LGMD2A/LGMDR1), the most common cause of LGMD in those with ancestry from Spain, France, Italy, and Great Britain, is associated with marked scapular winging, lack of calf muscle hypertrophy, and lack of cardiac and lung involvement. Of note, autosomal dominant mutations in an intron of the calpain-3 gene is responsible for LGMD1I/LGMDD4. LGMD2I/LGMDR9 is more common in individuals with northern European ancestry, is associated with calf muscle hypertrophy, and can have cardiac and lung involvement out of proportion to extremity weakness. LGMD2L/LGMDR12 accounts for ~7% of LGMD in the United States, and the prevalence is higher in northern Europe; as seen in dysferlinopathies (LGMD2B/LGMDR2 and Miyoshi myopathy type 1), anoctaminopathy has an early predilection for medial calf atrophy and weakness.

Importantly, immune-mediated necrotizing myopathies can mimic LGMD clinically and histopathologically (Chap. 365). Anyone suspected of having an LGMD but without definite pathogenic mutation(s) identified on genetic testing should be screened for the presence of serum antibodies against HMGCR and SRP to assess for a treatable autoimmune cause.

■ EMERY DREIFUSS MUSCULAR DYSTROPHY

There are at least five genetically distinct forms of EDMD. *Emerin* mutations are the most common cause of X-linked EDMD, although mutations in *FHL1* may also be associated with a similar phenotype, which is X-linked as well. Mutations involving the gene for Lamin A/C

TABLE 449-4 Autosomal Recessive Limb-Girdle Muscular Dystrophies (LGMDs)

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
LGMD2A/LGMDR1	Onset first or second decade Scapular winging; no calf hypertrophy; no cardiac or respiratory muscle weakness Proximal and distal weakness; may have contractures at elbows, wrists, and fingers	Serum CK 3–15× normal EMG myopathic Muscle biopsy may show lobulated muscle fibers	Calpain-3
LGMD2B/LGMDR2	Onset second or third decade Proximal muscle weakness at onset, later distal (calf) muscles affected Miyoshi myopathy is variant of LGMD2B with calf muscles affected at onset	Serum CK 3–100× normal EMG myopathic Inflammation on muscle biopsy may simulate polymyositis; amyloid deposition in endomysium	Dysferlin
LGMD2C–F/LGMDR3–6	Onset in childhood to teenage years Clinical condition similar to Duchenne and Becker muscular dystrophies Cognitive function normal	Serum CK 5–100× normal EMG myopathic	γ, α, β, δ sarcoglycans
LGMD2G/LGMDR7	Onset age 10–15 Proximal and distal muscle weakness	Serum CK 3–17× normal EMG myopathic Muscle biopsy may show rimmed vacuoles	Telethonin
LGMD2H/LGMDR8	Onset first to third decade Allelic to sarcotubular congenital myopathy Proximal muscle weakness	Serum CK 2–25× normal EMG myopathic Muscle biopsy reveals dilated T-tubules	Tripartite motif-containing 32
LGMD2I/LGMDR9	Onset first to third decade Clinical condition similar to Duchenne or Becker dystrophies Cardiomyopathy and respiratory failure may occur early before significant weakness Cognitive function normal	Serum CK 10–30× normal EMG myopathic	Fukutin-related protein
LGMD2J ^a /LGMDR10	Onset first to third decade Proximal lower limb weakness Mild distal weakness Progressive weakness causes loss of ambulation	Serum CK 1.5–2× normal EMG myopathic Muscle biopsy reveals rimmed vacuoles	Titin
LGMD2K/LGMDR11	Usually presents in infancy as Walker-Warburg syndrome but can present in early adult life with proximal weakness and only minor CNS abnormalities	CK 10–20× normal EMG myopathic	POMT1
LGMD2L/LGMDR12	Presents in childhood or adult life May manifest with quadriceps atrophy and myalgia Some present with early involvement of the calves in the second decade of life, resembling Miyoshi myopathy type 1 (dysferlinopathy)	CK 8–20× normal EMG myopathic	Anoctamin 5
LGMD2M/LGMDR13	Usually presents in infancy as Fukuyama congenital muscular dystrophy but can present in early adult life with proximal weakness and only minor CNS abnormalities	CK 10–50× normal EMG myopathic	Fukutin
LGMD2N/LGMDR14	Usually presents in infancy as muscle-eye-brain disease but can present in early adult life with proximal weakness and only minor CNS abnormalities	CK 5–20× normal EMG myopathic	POMGNT1
LGMD2O/LGMDR15	Usually presents in infancy as Walker-Warburg syndrome but can present in early adult life with proximal weakness and only minor CNS abnormalities	CK 5–20× normal EMG myopathic	POMT2
LGMD2P/LGMDR16	One case reported presenting in early childhood	CK >10× normal	α-Dystroglycan
LGMD2Q/LGMDR17	Onset in infancy to fourth decade; proximal weakness; may have ptosis and extraocular weakness; epidermolysis bullosa (also considered a congenital myasthenic syndrome)	CK variable, but usually only mildly elevated EMG myopathic Repetitive nerve stimulation may show decrement	Plectin 1
LGMD2R/myofibrillar myopathy	See LGMD1E (see Table 449-6)	See LGMD1E	Desmin
LGMD2S/LGMDR18	Onset in infancy to sixth decade of proximal weakness Eye abnormalities common; truncal ataxia and chorea Mild to moderate intellectual disability Hutterite descent	CK 1.5–20× normal	TRAPC11
LGMD2T/LGMDR19	Onset in early childhood to fourth decade Proximal weakness CNS abnormalities, cataracts, cardiomyopathy, and neuromuscular junction dysfunction	CK 3 to >10× normal EMG myopathic	GMPPB

(Continued)

TABLE 449-4 Autosomal Recessive Limb-Girdle Muscular Dystrophies (LGMDs) (Continued)

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
LGMD2U/LGMDR20	Onset typically in early childhood of proximal weakness May have CNS and ocular abnormalities	CK 5 to >20x normal	ISPD
LGMD2V/late-onset Pompe disease	Childhood or adult onset of proximal weakness Ventilatory muscle weakness	CK normal to mildly elevated EMG myopathic (may have myotonic discharges)	Alpha-glucosidase
LGMD2W/PINCH2-related myopathy	Reported in only one family Childhood onset of proximal weakness Macroglossia with broad-based, triangular tongue Cardiomyopathy in third decade	CK 3 to >20x normal	PINCH2
LGMD2Y/TOR1AIP1-related myopathy	Reported in only one family Childhood onset of proximal weakness Rigid spine and contractures	CK normal to 4x normal EMG myopathic	Lamina-associated polypeptide 1B
LGMD2Z/LGMDR21	Adult-onset proximal weakness Scapular winging	CK mildly elevated	POGLUT1
Bethlem myopathy (recessive)/LGMDR22	Onset in childhood to adulthood Contractures at elbows, distal fingers, knees, ankles Hyperextensible fingers proximally Keloids	CK normal to 3x normal MRI and ultrasound of muscle show a peripheral > central predilection for fibrofatty replacement in individual muscles	Collagen VI alpha 1, alpha 2, or alpha 3 chains
Laminin alpha-2 muscular dystrophy/LGMDR23	Congenital to adult onset May have CNS abnormalities	CK 2–5x normal	Laminin alpha 2 (merosin)
POMGNT-related muscular dystrophy/LGMDR24	Congenital to adult onset May have CNS abnormalities	CK 5 to >20x normal	POMGNT2
LGMD2X/LGMDR25	Adult onset of proximal weakness Cardiac arrhythmias	CK 3 to >20x normal	Popeye domain containing protein 1

*Udd-type distal myopathy is a form of titin deficiency with only distal muscle weakness (see Table 449-5).

Abbreviations: CK, creatine kinase; CNS, central nervous system; EMG, electromyography; GMPBP, guanosine diphosphate (GDP)-mannose pyrophosphorylase; B; ISPD, isoprenoid synthase domain containing; PINCH2, particularly interesting new cysteine-histidine rich protein 2; POGLUT1, protein O-glucosyltransferase 1; POMGNT1, O-linked mannose beta 1,2-N-acetylglucosaminyltransferase; POMGNT2, protein O-mannose beta 1,4-N-acetylglucosaminyltransferase-2; POMT1, protein-O-mannosyltransferase 1; POMT2, protein-O-mannosyltransferase 2; TNPO3, transportin 3; TOR1AIP1, DNA sequencing of torsinA-interacting protein 1; TRAPC11, transport (trafficking) protein particle complex, subunit 11.

(*LMNA*) are the most common cause of autosomal dominant EDMD (also known as LGMD1B) and are also a common cause of hereditary cardiomyopathy. Less commonly, autosomal dominant EDMD has been reported with mutations in *SYNE1*, *SYNE2*, *TMEM43*, *SUN1*, *SUN2*, and *TTN* genes encoding nesprin-1, nesprin-2, LUMA, SUN1, SUN2, and titin, respectively.

Clinical Features Prominent contractures can be recognized in early childhood and teenage years, often preceding muscle weakness. The contractures persist throughout the course of the disease and are present at the elbows, ankles, and neck. Muscle weakness affects humeral and peroneal muscles at first and later spreads to a limb-girdle distribution (Table 449-1). The cardiomyopathy is potentially life threatening and may result in sudden death. A spectrum of atrial rhythm and conduction defects includes atrial fibrillation and paroxysmal and atrioventricular heart block. Some patients have a dilated cardiomyopathy. Female carriers of the X-linked variant may manifest with a cardiomyopathy.

Laboratory Features Serum CK is usually slightly elevated, and the EMG is myopathic. Muscle biopsy usually shows nonspecific dystrophic features, although cases associated with *FHL1* mutations have features of myofibrillar myopathy. Immunohistochemistry reveals absent emerin staining of myonuclei in X-linked EDMD due to *emerin* mutations. Electrocardiograms (ECGs) demonstrate atrial and atrioventricular rhythm disturbances.

X-linked EDMD usually arises from defects in the *emerin* gene encoding a nuclear envelope protein. *FHL1* mutations are also a cause of X-linked scapuloperoneal dystrophy but can also present with an X-linked form of EDMD. The autosomal dominant disease can be caused by mutations in the *LMNA* gene encoding Lamin A/C; in the synaptic nuclear envelope protein 1 (*SYNE1*) or 2 (*SYNE2*) encoding

nesprin-1 and nesprin-2, respectively; and in *TMEM43* encoding LUMA. These proteins are essential components of the filamentous network underlying the inner nuclear membrane. Loss of structural integrity of the nuclear envelope from defects in emerin, Lamin A/C, nesprin-1, nesprin-2, and LUMA accounts for overlapping phenotypes.

TREATMENT

Emery-Dreifuss Muscular Dystrophy

Supportive care should be offered for neuromuscular disability, including ambulatory aids, if necessary. Stretching of contractures is difficult. Management of cardiomyopathy and arrhythmias (e.g., early use of a defibrillator or cardiac pacemaker) may be lifesaving.

MYOTONIC DYSTROPHY

There are two distinct forms of myotonic dystrophy (*dystrophia myotonica* [DM]), namely myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2), also called *proximal myotonic myopathy* (PROMM).

Clinical Features The clinical expression of DM1 varies widely and involves many systems other than muscle. Affected patients may have a “hatchet-faced” appearance due to temporalis, masseter, and facial muscle atrophy and weakness. Frontal baldness is frequent. Weakness of wrist and fingers occurs early, as does foot drop. Proximal muscles are less affected. Palatal, pharyngeal, and tongue involvement can lead to dysarthria and dysphagia. Some patients have diaphragm and intercostal muscle weakness, resulting in ventilatory insufficiency. Myotonia is usually apparent by the age of 5 years and is best demonstrable by percussion of the thenar eminence or asking patients to close their fingers very tightly and then relax.

TABLE 449-5 Distal Myopathies

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
Welander distal myopathy	Onset in fifth decade Weakness begins in hands Slow progression with spread to distal lower extremities Life span normal	Serum CK 2–3x normal EMG myopathic NCS normal Muscle biopsy shows dystrophic features and rimmed vacuoles	AD TIA1
Tibial muscular dystrophy (Udd)	Onset fourth to eighth decade Distal lower extremity weakness (tibial distribution) Upper extremities usually normal Life span normal	Serum CK 2–4x normal EMG myopathic NCS normal Muscle biopsy shows dystrophic features and rimmed vacuoles Titin absent in M-line of muscle	AD Titin AR (associated with more proximal weakness—LGMD2J)
Markesberry-Griggs distal myopathy	Onset fourth to eighth decade Distal lower extremity weakness (tibial distribution) with progression to distal arms and proximal muscles	Serum CK is usually mildly elevated EMG reveals irritative myopathy Muscle biopsies demonstrate rimmed vacuoles and features of MFM	AD Z-band alternatively spliced PDX motif-containing protein (ZASP)
Laing distal myopathy	Onset childhood to third decade Distal lower extremity weakness (anterior tibial distribution) and neck flexors affected early May have cardiomyopathy	Serum CK is normal or slightly elevated Muscle biopsies do not typically show rimmed vacuoles, but may show hyaline bodies with accumulation of myosin Large deposits of myosin heavy chain are seen in type 1 muscle fibers	AD Myosin heavy chain 7
GNE myopathy (Nonaka distal myopathy and autosomal recessive hereditary inclusion body myopathy)	Onset second to third decade Distal lower extremity weakness (anterior tibial distribution) Mild distal upper limb weakness may be present early Progression to other muscles sparing quadriceps Ambulation may be lost in 10–15 years	Serum CK 3–10x normal EMG myopathic NCS normal Dystrophic features on muscle biopsy plus rimmed vacuoles and 15- to 19-nm filaments within vacuoles	AR GNE gene: UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase Allelic to a form of hereditary inclusion body myopathy
Miyoshi myopathy ^a	Onset second to third decade Lower extremity weakness in posterior compartment muscles Progression leads to weakness in other muscle groups Ambulation lost after 10–15 years in about one-third of cases	Serum CK 20–100x normal EMG myopathic NCS normal Muscle biopsy shows nonspecific dystrophic features often with prominent inflammatory cell infiltration; no rimmed vacuoles	AR Dysferlin (allelic to LGMD2B) ANO-5 (allelic to LGMD2L)
Williams myopathy	Distal lower extremity weakness (anterior tibial distribution)	Muscle biopsy may show rimmed vacuoles and features of MFM	AD Filamin-C
Myofibrillar myopathies	Onset from early childhood to late adult life Weakness may be distal, proximal, or generalized Cardiomyopathy and respiratory involvement are not uncommon	Serum CKs can be normal or moderately elevated EMG is myopathic and often associated with myotonic discharges Muscle biopsy demonstrates abnormal accumulation of desmin and other proteins, rimmed vacuoles, and myofibrillar degeneration	Genetically heterogeneous AD Myotilin (also known as LGMD1A) ZASP (see Markesberry-Griggs distal myopathy) Filamin-C Desmin Alpha B crystallin Bag3 Titin DNAJB6 TNPO3 AR, AD Desmin X-linked FHL1

^aMiyoshi myopathy phenotype may also be seen with mutations in ANO-5 that encodes for anoctamin 5 (allelic to LGMD2L).

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CK, creatine kinase; EMG, electromyography; MFM, myofibrillar myopathy; NCS, nerve conduction studies.

ECG abnormalities include first-degree heart block and more extensive conduction system involvement. Complete heart block and sudden death can occur. Congestive heart failure occurs infrequently but may result from cor pulmonale secondary to respiratory failure. Other associated features include intellectual impairment, hypersomnia, posterior subcapsular cataracts, gonadal

atrophy, insulin resistance, and decreased esophageal and colonic motility.

Congenital myotonic dystrophy is a more severe form of DM1 and occurs in ~25% of infants of affected mothers. It is characterized by severe facial and bulbar weakness, transient neonatal respiratory insufficiency, and intellectual disability.

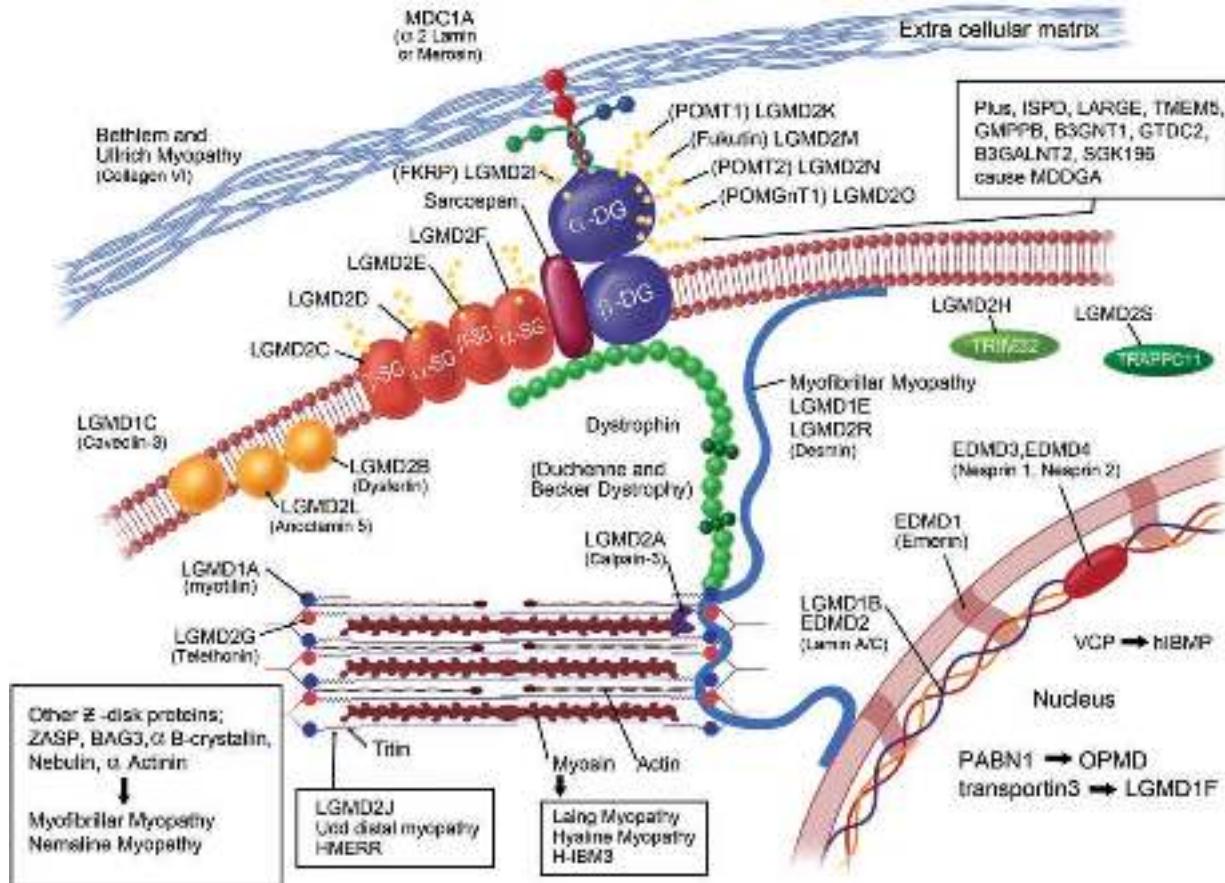


FIGURE 449-6 Proteins involved in the muscular dystrophies. This schematic shows the location of various sarcolemmal, sarcomeric, nuclear, and enzymatic proteins associated with muscular dystrophies. The diseases associated with mutations in the genes responsible for encoding these proteins are shown in boxes. Dystrophin, via its interaction with the dystroglycan complex, connects the actin cytoskeleton to the extracellular matrix. Extracellularly, the sarcoglycan complex interacts with biglycan, which connects this complex to the dystroglycan complex and the extracellular matrix collagen. Various enzymes are important in the glycosylation of the α-dystroglycan and mediate its binding to the extracellular matrix and usually cause a congenital muscular dystrophy with severe brain and eye abnormalities but may cause milder LGMD phenotype. Mutations in genes that encode for sarcomeric and Z-disk proteins cause forms of LGMD and distal myopathies (including myofibrillar myopathy, forms of hereditary inclusion body myopathy) as well as nemaline rod myopathy and other "congenital" myopathies. Mutations affecting nuclear membrane proteins are responsible for most forms of EDMD. Mutations in other nuclear genes cause other forms of dystrophy. (From AA Amato, J Russell: *Neuromuscular Disorders*, 2nd ed. McGraw-Hill, 2016, Figure 27-1, p. 657; with permission.)

DM2 or PROMM involves mainly proximal muscles. Other features of the disease overlap with DM1, including cataracts, testicular atrophy, insulin resistance, constipation, hypersomnia, and cognitive defects. Cardiac conduction defects occur but are less common. The hatchet face and frontal baldness are also less consistent features. A very striking difference is the failure to clearly identify a congenital form of DM2.

Laboratory Features The diagnosis of myotonic dystrophy can usually be made on the basis of clinical findings. Serum CK levels may be normal or mildly elevated. EMG evidence of myotonia is present in most cases of DM1 but is more patchy in DM2. Muscle biopsy is not typically performed for diagnosis but is sometimes done when the clinical features and electrophysiologic features are not recognized. The major histopathologic features in both DM1 and DM2 are numerous internalized nuclei in individual muscle fibers combined with many atrophic fibers with pyknotic nuclear clumps.

DM1 and DM2 are autosomal dominant disorders. DM1 is transmitted by an intronic mutation consisting of an unstable expansion of a CTG trinucleotide repeat in a serine-threonine protein kinase gene (named *DMPK*). An increase in the severity of the disease phenotype in successive generations (genetic anticipation) is accompanied by an increase in the number of trinucleotide repeats. The unstable triplet repeat in myotonic dystrophy can be used for prenatal diagnosis.

Congenital disease occurs almost exclusively in infants born to affected mothers.

DM2 is caused by a DNA expansion mutation consisting of a CCTG repeat in intron 1 of the *CNBP* gene encoding the CCHC-type zinc finger nucleic acid binding protein. The DNA expansions in DM1 and DM2 impair muscle function by a toxic gain of function of the mutant mRNA. In both DM1 and DM2, the mutant RNA appears to form intranuclear inclusions composed of aberrant RNA. These RNA inclusions sequester RNA-binding proteins essential for proper splicing of a variety of other mRNAs. This leads to abnormal transcription of multiple proteins in a variety of tissues/organ systems, in turn causing the systemic manifestations of DM1 and DM2.

TREATMENT

Myotonic Dystrophy

The myotonia in DM1 and DM2 is usually not so bothersome to warrant treatment, but when it is, mexiletine may be helpful. A cardiac pacemaker or implantable cardioverter defibrillator should be considered for patients with significant arrhythmia. Molded ankle-foot orthoses help stabilize gait in patients with foot drop. Excessive daytime somnolence with or without sleep apnea is not

uncommon. Sleep studies, noninvasive respiratory support (biphasic positive airway pressure [BiPAP]), and treatment with modafinil may be beneficial.

■ FACIOSCAPULOHUMERAL FSHD MUSCULAR DYSTROPHY

There are two forms of FSHD that have similar pathogenesis. Most patients have FSHD type 1 (95%), whereas ~5% have FSHD2. Both forms are clinically and histopathologically identical. The prevalence of FSHD is ~5 per 100,000 individuals.

Clinical Features FSHD typically presents in childhood or young adulthood. In most cases, facial weakness is the initial manifestation, appearing as an inability to smile, whistle, or fully close the eyes. Loss of scapular stabilizer muscles makes arm elevation difficult. Scapular winging (Fig. 449-3) becomes apparent with attempts at abduction and forward movement of the arms. Biceps and triceps muscles may be severely affected, with relative sparing of the deltoid muscles. Weakness is invariably worse for wrist extension than for wrist flexion, and weakness of the anterior compartment muscles of the legs may lead to foot drop. In 20% of patients, weakness progresses to involve the pelvic muscles, and severe functional impairment and possible wheelchair dependency result. The heart is not involved, but there can be ventilatory muscle weakness in 5% of affected individuals. There is an increased incidence of nerve deafness. *Coats' disease*, a disorder consisting of telangiectasia, exudation, and retinal detachment, also occurs.

Laboratory Features The serum CK level may be normal or mildly elevated. EMG and muscle biopsy show nonspecific abnormalities but on occasion can reveal a prominent inflammatory infiltrate leading to an incorrect diagnosis of myositis (Chap. 365).

FSHD1 is associated with deletions of tandem 3.3-kb repeats at 4q35. The deletion reduces the number of repeats to a fragment of <35 kb in most patients. Within these repeats lies the *DUX4* gene, which usually is not expressed after early muscle development. In patients with FSHD1, these deletions in the setting of a specific polymorphism lead to hypomethylation of the region and toxic expression of the *DUX4* gene. In cases of FSHD2, there is no deletion, but rather mutations in three different genes have been identified, each of which interestingly leads to hypomethylation of the *DUX4* region and the permissive expression of the *DUX4* gene. Dominant mutations in the structural maintenance of chromosomes hinge domain 1 (*SMCHD1*) gene is the most common cause of FSHD2, but recently, heterozygous mutations in the DNA methyltransferase 3B (*DNMT3B*) gene and homozygous mutations in the ligand-dependent nuclear receptor-interacting factor 1 (*LRIF1*) gene have been reported in rare cases of autosomal recessive FSHD2. These proteins normally interact with *SMCHD1*, and mutations lead to hypomethylation of the *DUX4* region and, as in FSHD1, to an overexpression of the *DUX4* transcript.

TREATMENT

Faciocapulohumeral Muscular Dystrophy

No specific treatment is available; ankle-foot orthoses are helpful for foot drop. Scapular stabilization procedures improve scapular winging but may not improve function.

■ OCULOPHARYNGEAL DYSTROPHY OPMD

OPMD represents one of several disorders characterized by progressive external ophthalmoplegia, which consists of slowly progressive ptosis and limitation of eye movements with sparing of pupillary reactions for light and accommodation. Patients usually do not complain of diplopia, in contrast to patients having conditions with a more acute onset of ocular muscle weakness (e.g., myasthenia gravis).

Clinical Features OPMD has a late onset; it usually presents in the fourth to sixth decade with ptosis or dysphagia. The extraocular muscle impairment is less prominent in the early phase but may become severe over time. The swallowing problem may lead to aspiration. Weakness

of the neck and proximal extremities can develop but is usually mild in degree.

Laboratory Features The serum CK level may be two to three times normal. EMG can identify myopathic changes in weak muscles. Muscle biopsies are no longer necessary for diagnosis in most cases but, when performed, demonstrate muscle fibers with rimmed vacuoles. On electron microscopy, a distinctive feature of OPMD is the presence of 8.5-nm tubular filaments in some muscle cell nuclei.

OPMD is an autosomal dominant disorder that has a high incidence in certain populations (e.g., French-Canadians, individuals of Spanish ancestry, and Ashkenazi Jews). The molecular defect in OPMD is an expansion of a polyalanine repeat tract in a poly-RNA-binding protein (*PABP2*) gene.

TREATMENT

Oculopharyngeal Dystrophy

Dysphagia can lead to significant undernourishment and aspiration. Cricopharyngeal myotomy may improve swallowing. Eyelid crutches can improve vision when ptosis obstructs vision; candidates for ptosis surgery must be carefully selected—those with severe facial weakness are not suitable.

■ DISTAL MYOPATHIES/ DYSTROPHIES

The distal myopathies are notable for their preferential distal distribution of muscle weakness in contrast to most muscle conditions associated with proximal weakness. The major distal myopathies are summarized in Tables 449-1 and 449-5.

Clinical Features *Welander, Udd, and Markesberry-Griggs type distal myopathies* are all late-onset, dominantly inherited disorders of distal limb muscles, usually beginning after age 40 years. Welander distal myopathy preferentially involves the wrist and finger extensors, whereas the others are associated with anterior tibial weakness leading to progressive foot drop. *Laing distal myopathy* is also a dominantly inherited disorder heralded by tibial weakness; however, it is distinguished by onset in childhood or early adult life. *GNE myopathy* (also known as *Nonaka distal myopathy* and autosomal recessive hereditary inclusion body myopathy) and *Miyoshi myopathy* are distinguished by autosomal recessive inheritance and onset in the late teens or twenties. GNE and Williams myopathy produce prominent anterior tibial weakness, whereas Miyoshi myopathy is unique in that gastrocnemius muscles are preferentially affected at onset. Finally, the *myofibrillar myopathies* (MFMs) are a clinically and genetically heterogeneous group of muscular dystrophies that can be associated with prominent distal weakness; they can be inherited in an autosomal dominant or recessive pattern. Of note, Markesberry-Griggs myopathy (caused by mutations in ZASP), LGMD1E and LGMD2R (caused by mutations in desmin), and LGMD1A (caused by mutations in myotilin) are subtypes of MFM.

Laboratory Features Serum CK levels are markedly elevated in Miyoshi myopathy, but in the other conditions, serum CK is only slightly increased. EMGs are myopathic and can be irritable with myotonic discharges in MFM. Muscle biopsy shows nonspecific dystrophic features and, with the exception of Laing and Miyoshi myopathies, often shows rimmed vacuoles. MFM is associated with the accumulation of dense inclusions and amorphous material best seen on Gomori trichrome staining along with myofibrillar disruption on electron microscopy. Immune staining sometimes demonstrates accumulation of desmin and other proteins in MFM, large deposits of myosin heavy chain in the subsarcolemmal region of type 1 muscle fibers in Laing myopathy, and reduced or absent dysferlin in Miyoshi myopathy type I.

TREATMENT

Distal Myopathies

Occupational therapy is offered for loss of hand function; ankle-foot orthoses can support distal lower limb muscles. The MFMs

can be associated with cardiomyopathy (congestive heart failure or arrhythmias) and respiratory failure that may require medical management. Laing-type distal myopathy can also be associated with a cardiomyopathy.

DISORDERS OF MUSCLE ENERGY METABOLISM

There are two principal sources of energy for skeletal muscle—fatty acids and glucose. Abnormalities in either glucose or lipid utilization can be associated with distinct clinical presentations that can range from an acute, painful syndrome with rhabdomyolysis and myoglobinuria to a chronic, progressive muscle weakness simulating muscular dystrophy (Table 449-1). As with the muscular dystrophies, there are no specific medical treatments available.

■ GLYCOGEN STORAGE AND GLYCOLYTIC DEFECTS

Disorders of Glycolysis Causing Exercise Intolerance Several glycolytic defects are associated with recurrent myoglobinuria. The most common is *McArdle disease* caused by mutations in the *PYGM* gene leading to *myophosphorylase deficiency*. Symptoms of muscle pain and stiffness usually begin in adolescence. With severe episodes, myoglobinuria can occur.

Certain features help distinguish some enzyme defects. In McArdle disease, exercise tolerance can be enhanced by a slow induction phase (warm-up) or brief periods of rest, allowing for the start of the “second-wind” phenomenon (switching to utilization of fatty acids). Varying degrees of hemolytic anemia accompany deficiencies of both phosphofructokinase (mild) and phosphoglycerate kinase (severe). In phosphoglycerate kinase deficiency, the usual clinical presentation is a seizure disorder associated with intellectual disability; exercise intolerance is an infrequent manifestation.

In all of these conditions, the serum CK levels fluctuate widely and may be elevated even during symptom-free periods. CK levels >100 times normal are expected accompanying myoglobinuria. A forearm exercise test reveals a blunted rise in venous lactate with a normal rise in ammonia. A definitive diagnosis of glycolytic disease can be made by muscle biopsy with appropriate staining and enzyme assays, but genetic testing is now done in lieu of biopsy in most cases.

Training may enhance exercise tolerance, perhaps by increasing perfusion to muscle. Dietary intake of free glucose or fructose prior to activity may improve function, but care must be taken to avoid obesity from ingesting too many calories.

Disorders of Glycogen Storage Causing Progressive Weakness

α GLUCOSIDASE, OR ACID MALTASE, DEFICIENCY POMPE DISEASE Three clinical forms of α -glucosidase, or acid maltase, deficiency (*type II glycogenesis*) can be distinguished. The infantile form is the most common, with onset of symptoms in the first 3 months of life. Infants develop severe muscle weakness, cardiomegaly, hepatomegaly, and respiratory insufficiency. Glycogen accumulation in motor neurons of the spinal cord and brainstem contributes to muscle weakness. Death usually occurs by 1.5 years of age. In the childhood form, the picture resembles DMD with delayed motor milestones resulting from proximal limb muscle weakness and involvement of respiratory muscles. The heart may be involved, but the liver and brain are unaffected. The adult form usually begins in the third or fourth decade but can present as late as the seventh decade. Ventilatory weakness can be the initial and only manifestation in 20–30% of late-onset cases.

The serum CK level is 2–10 times normal in infantile or childhood-onset Pompe disease but can be normal in adult-onset cases. EMG can demonstrate muscle membrane irritability, particularly in the paraspinal muscles. The muscle biopsy in infants typically reveals vacuoles containing glycogen and the lysosomal enzyme acid phosphatase. Electron microscopy reveals membrane-bound and free tissue glycogen. However, muscle biopsies in late-onset Pompe disease may demonstrate only nonspecific abnormalities. Enzyme analysis of dried blood spots is a sensitive technique to screen for Pompe disease. A definitive diagnosis is established by genetic testing.

Pompe disease is inherited as an autosomal recessive disorder caused by mutations of the α -glucosidase gene. Enzyme replacement therapy (ERT) with IV recombinant human α -glucosidase is beneficial in infantile-onset Pompe disease. In late-onset cases, ERT has a more modest benefit.

OTHER GLYCOGEN STORAGE DISEASES WITH PROGRESSIVE WEAKNESS In *debranching enzyme deficiency* (*type III glycogenesis*), a slowly progressive form of muscle weakness can develop after puberty. Rarely, myoglobinuria may be seen. Patients are usually diagnosed in infancy, however, because of hypotonia and delayed motor milestones; hepatomegaly, growth retardation, and hypoglycemia are other manifestations. *Branching enzyme deficiency* (*type IV glycogenesis*) is a rare and fatal glycogen storage disease characterized by failure to thrive and hepatomegaly. Hypotonia and muscle wasting may be present, but the skeletal muscle manifestations are minor compared to liver failure. Recently, the first autosomal dominant glycogen storage disease was reported in a family and was caused by a mutation in the *PYGM* gene that typically causes autosomal recessive McArdle disease. Affected individuals presented with progressive proximal weakness, no exercise intolerance, normal CK, and a normal lactic acid increase with exercise.

■ LIPID AS AN ENERGY SOURCE AND ASSOCIATED DEFECTS

Lipid is an important muscle energy source during rest and during prolonged, submaximal exercise. Oxidation of fatty acids occurs in the mitochondria. To enter the mitochondria, a fatty acid must first be converted to an “activated fatty acid,” acyl-CoA. The acyl-CoA must be linked with carnitine by the enzyme CPT for transport into the mitochondria.

Carnitine Palmitoyltransferase 2 Deficiency CPT2 deficiency is the most common recognizable cause of recurrent myoglobinuria. Onset is usually in the teenage years or early twenties. Muscle pain and myoglobinuria typically occur after prolonged exercise but can also be precipitated by fasting or infections; up to 20% of patients do not exhibit myoglobinuria, however. Strength is normal between attacks. In contrast to disorders caused by defects in glycolysis, in which muscle cramps follow short, intense bursts of exercise, the muscle pain in CPT2 deficiency does not occur until the limits of utilization have been exceeded and muscle breakdown has already begun.

Serum CK levels and EMG findings are both usually normal between episodes. A normal rise of venous lactate during forearm exercise distinguishes this condition from glycolytic defects. Muscle biopsy does not show lipid accumulation and is usually normal between attacks. The diagnosis requires direct measurement of muscle CPT or genetic testing. Attempts to improve exercise tolerance with frequent meals and a low-fat, high-carbohydrate diet, or by substituting medium-chain triglycerides in the diet, have not proven to be beneficial.

MITOCHONDRIAL MYOPATHIES

Mitochondria play a key role in energy production. Oxidation of the major nutrients derived from carbohydrate, fat, and protein leads to the generation of reducing equivalents. The latter are transported through the respiratory chain in the process known as *oxidative phosphorylation*. The energy generated by the oxidation-reduction reactions of the respiratory chain is stored in an electrochemical gradient coupled to ATP synthesis.

A novel feature of mitochondria is their genetic composition. Each mitochondrion possesses a DNA genome that is distinct from that of the nuclear DNA. Human mitochondrial DNA (mtDNA) consists of a double-strand, circular molecule comprising 16,569 base pairs (bp). It codes for 22 transfer RNAs, 2 ribosomal RNAs, and 13 polypeptides of the respiratory chain enzymes. The genetics of mitochondrial diseases differ from the genetics of chromosomal disorders. The DNA of mitochondria is directly inherited from the cytoplasm of the gametes, mainly from the oocyte. The sperm contributes very little of its mitochondria to the offspring at the time of fertilization. Thus, mitochondrial genes are derived almost exclusively from the mother, accounting for maternal inheritance of some mitochondrial disorders.

Patients with mitochondrial myopathies have clinical manifestations that usually fall into three groups: chronic progressive external ophthalmoplegia (CPEO), skeletal muscle–CNS syndromes, and pure myopathy simulating muscular dystrophy or metabolic myopathy. Unfortunately, no specific medical therapies are clearly beneficial, although coenzyme Q10 supplements are often prescribed.

Kearns-Sayre Syndrome (KSS) This is a widespread multiorgan system disorder with a defined triad of clinical findings: onset before age 20, CPEO, and pigmentary retinopathy, plus one or more of the following features: complete heart block, cerebrospinal fluid (CSF) protein >1 g/L (100 mg/dL), or cerebellar ataxia. The cardiac disease includes syncopal attacks and cardiac arrest related to the abnormalities in the cardiac conduction system: prolonged intraventricular conduction time, bundle branch block, and complete atrioventricular block. Death attributed to heart block occurs in ~20% of the patients. Varying degrees of progressive limb muscle weakness and easy fatigability affect activities of daily living. Many affected individuals have intellectual disabilities. Endocrine abnormalities are also common, including gonadal dysfunction in both sexes with delayed puberty, short stature, and infertility. Diabetes mellitus occurs in ~13% of KSS patients. Other less common endocrine disorders include thyroid disease, hyperaldosteronism, Addison's disease, and hypoparathyroidism.

Serum CK and lactate levels are normal or slightly elevated. EMG is myopathic. NCS may be abnormal related to an associated neuropathy. Muscle biopsies reveal ragged red fibers and cytochrome oxidase (COX)–negative fibers. By electron microscopy, there are increased numbers of mitochondria that often appear enlarged and contain paracrystalline inclusions.

KSS is a sporadic disorder caused by single mtDNA deletions that are presumed to arise spontaneously in the ovum or zygote. The most common deletion, occurring in about one-third of patients, removes 4977 bp of contiguous mtDNA. Monitoring for cardiac conduction defects is critical. Prophylactic pacemaker implantation is indicated when ECGs demonstrate a bifascicular block.

Progressive External Ophthalmoplegia (PEO) PEO can be caused by nuclear DNA mutations affecting mtDNA and thus inherited in a Mendelian fashion or by mutations in mtDNA. Onset is usually after puberty. Fatigue, exercise intolerance, dysphagia, and complaints of muscle weakness are typical. The neurologic examination confirms the ptosis and ophthalmoplegia, usually asymmetric in distribution. Patients do not complain of diplopia. Mild facial, neck flexor, and proximal weakness is typical. Rarely, respiratory muscles may be progressively affected and may be the direct cause of death.

Serum CK and lactate can be normal or mildly elevated. The EMG can be myopathic. Ragged red and COX-negative fibers are prominently displayed in the muscle biopsy.

This autosomal dominant form of CPEO is most commonly caused by mutations in the genes encoding adenine nucleotide translocator 1 (*ANT1*), twinkle gene (*C10orf2*), and mtDNA polymerase 1 (*POLG1*). Autosomal recessive PEO can also be caused by mutations in *POLG1*. Point mutations have been identified within various mitochondrial tRNA (Leu, Ile, Asn, Trp) genes in families with maternal inheritance of PEO.

There is no specific medical treatment available; exercise may improve function, but this will depend on the patient's ability to participate.

Myoclonic Epilepsy with Ragged Red Fibers (MERRF) The onset of MERRF is variable, ranging from late childhood to middle adult life. Characteristic features include myoclonic epilepsy, cerebellar ataxia, and progressive proximal muscle weakness. The seizure disorder is an integral part of the disease and may be the initial symptom. Cerebellar ataxia precedes or accompanies epilepsy. Other more variable features include dementia, peripheral neuropathy, optic atrophy, hearing loss, and diabetes mellitus.

Serum CK levels and lactate may be normal or elevated. EMG is myopathic, and in some patients, NCS show a neuropathy. The

electroencephalogram is abnormal, corroborating clinical findings of epilepsy. Typical ragged red fibers are seen on muscle biopsy. MERRF is caused by maternally inherited point mutations of mitochondrial tRNA genes. The most common mutation found in 80% of MERRF patients is an A to G substitution at nucleotide 8344 of tRNA lysine (A8344G tRNA^{lys}). Only supportive treatment is possible, with special attention to epilepsy.

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS) MELAS is the most common mitochondrial encephalomyopathy. The term *stroke-like* is appropriate because the cerebral lesions do not conform to a strictly vascular distribution. The onset in the majority of patients is before age 20. Seizures, usually partial motor or generalized, are common and may represent the first clearly recognizable sign of disease. The cerebral insults that resemble strokes cause hemiparesis, hemianopia, and cortical blindness. A presumptive stroke occurring before age 40 should place this mitochondrial encephalomyopathy high in the differential diagnosis. Associated conditions include hearing loss, diabetes mellitus, hypothalamic pituitary dysfunction causing growth hormone deficiency, hypothyroidism, and absence of secondary sexual characteristics. In its full expression, MELAS leads to dementia, a bedridden state, and a fatal outcome. Serum lactic acid is typically elevated.

The CSF protein is also increased but is usually ≤ 1 g/L (100 mg/dL). Muscle biopsies show ragged red fibers. Neuroimaging demonstrates basal ganglia calcification in a high percentage of cases. Focal lesions that mimic infarction are present predominantly in the occipital and parietal lobes. Strict vascular territories are not respected, and cerebral angiography fails to demonstrate lesions of the major cerebral blood vessels.

MELAS is usually caused by maternally inherited point mutations of mitochondrial tRNA genes. The A3243G point mutation in tRNA^{Leu(UUR)} is the most common, occurring in ~80% of MELAS cases. No specific treatment is available. Supportive treatment is essential for the stroke-like episodes, seizures, and endocrinopathies.

Mitochondrial DNA Depletion Syndromes Mitochondrial DNA depletion syndrome (MDS) is a heterogeneous group of disorders that are inherited in an autosomal recessive fashion and can present in infancy or in adults. MDS can be caused by mutations in several genes (*TK2*, *DGUOK*, *RRM2B*, *TYMP*, *SUCLA1*, and *SUCLA2*) that lead to depletion of mitochondrial deoxyribonucleotides (dNTP) necessary for mtDNA replication. The other major cause of MDS is a set of mutations in genes essential for mtDNA replication (e.g., *POLG1* and *C10orf2*). The clinical phenotypes associated with MDS vary. Patients may develop a severe encephalopathy (e.g., Leigh's syndrome), PEO, an isolated myopathy, myo-neuro-gastrointestinal encephalopathy (MNGIE), and a sensory neuropathy with ataxia.

DISORDERS OF MUSCLE MEMBRANE EXCITABILITY

Muscle membrane excitability is affected in a group of disorders referred to as *channelopathies*. These disorders usually present with episodic muscle weakness (periodic paralysis) and sometimes myotonia or paramyotonia (Table 449-1).

■ CALCIUM CHANNEL DISORDERS OF MUSCLE

Hypokalemic Periodic Paralysis (HypoKPP) This is an autosomal dominant disorder with onset in adolescence. Males are more often affected because of decreased penetrance in females. Episodic weakness with onset after age 25 is almost never due to periodic paroxysms, with the exception of thyrotoxic periodic paralysis. Attacks are often provoked by meals high in carbohydrates or sodium and may accompany rest following prolonged exercise. Weakness usually affects proximal limb muscles more than distal. Ocular and bulbar muscles are less likely to be affected. Respiratory muscles are usually spared, but when they are involved, the condition may prove fatal. Weakness may

3530 take as long as 24 h to resolve. Life-threatening cardiac arrhythmias related to hypokalemia may occur during attacks. As a late complication, patients commonly develop severe, disabling proximal lower extremity weakness.

Attacks of thyrotoxic periodic paralysis resemble those of primary HypoKPP. Despite a higher incidence of thyrotoxicosis in women, men, particularly those of Asian descent, are more likely to manifest this complication. Attacks abate with treatment of the underlying thyroid condition.

A low serum potassium level during an attack, excluding secondary causes, establishes the diagnosis. In the midst of an attack of weakness, motor conduction studies may demonstrate reduced amplitudes, whereas EMG may show electrical silence in severely weak muscles. In between attacks, the EMG and routine NCS are normal. However, a long exercise NCS test may demonstrate decrementing amplitudes.

HypoKPP type 1 is the most common form and is caused by mutations in the voltage-sensitive, skeletal muscle calcium channel gene, *CALCLIA3*. Approximately 10% of cases are HypoKPP type 2, arising from mutations in the voltage-sensitive sodium channel gene (*SCN4A*). In both forms, the mutations lead to an abnormal gating pore current that predisposes the muscle cell to depolarize when potassium levels are low.

TREATMENT

Hypokalemic Periodic Paralysis

Mild attacks usually do not require medical treatment. However, severe attacks of weakness can be improved by the administration of potassium. Oral KCl (0.2–0.4 mmol/kg) can be given every 30 min. Only rarely is IV therapy necessary (e.g., when swallowing problems or vomiting is present). The long-term goal of therapy is to avoid attacks. Patients should be made aware of the importance of a low-carbohydrate, low-sodium diet and consequences of intense exercise. Prophylactic administration of acetazolamide or dichlorphenamide can reduce attacks of periodic weakness. However, in patients with HypoKPP type 2, attacks of weakness can be exacerbated with these medications.

SODIUM CHANNEL DISORDERS OF MUSCLE

Hyperkalemic Periodic Paralysis (HyperKPP) The term *hyperkalemic* is misleading because patients are often normokalemic during attacks. That attacks are precipitated by potassium administration best defines the disease. The onset is usually in the first decade; males and females are affected equally. Attacks are brief and mild, usually lasting 30 min to several hours. Weakness affects proximal muscles, sparing bulbar muscles. Attacks are precipitated by rest following exercise and fasting.

Potassium may be slightly elevated or normal during an attack. As in HypoKPP, NCS in HyperKPP muscle may demonstrate reduced motor amplitudes and the EMG may be silent in very weak muscles. A long exercise NCS test can reveal diminished amplitudes as well. The EMG may demonstrate myotonic discharges. HyperKPP is caused by mutations of the voltage-gated sodium channel *SCN4A* gene. Acetazolamide or dichlorphenamide can reduce the frequency and severity of attacks. Mexiletine may be helpful in patients with significant clinical myotonia.

Paramyotonia Congenita In PC, the attacks of weakness are cold-induced or occur spontaneously and are mild. Myotonia is a prominent feature but worsens with muscle activity (paradoxic myotonia). This is in contrast to classic myotonia in which exercise alleviates the condition. Attacks of weakness are seldom severe enough to require emergency room treatment. Over time, patients develop inter-attack weakness as they do in other forms of periodic paralysis.

Serum CK is usually mildly elevated. Routine NCS are normal. Short exercise NCS tests may be abnormal, however, and cooling of the muscle often dramatically reduces the amplitude of the compound muscle

action potentials. EMG reveals diffuse myotonic potentials in PC. Upon local cooling of the muscle, the myotonic discharges disappear as the patient becomes unable to activate MUAPs.

PC is inherited as an autosomal dominant condition; voltage-gated sodium channel mutations are responsible, and thus, this disorder is allelic with HyperKPP. Mexiletine is reported to be helpful in reducing the myotonia.

POTASSIUM CHANNEL DISORDERS

Andersen-Tawil Syndrome This rare disease is characterized by episodic weakness, cardiac arrhythmias, and dysmorphic features (short stature, scoliosis, clinodactyly, hypertelorism, small or prominent low-set ears, micrognathia, and broad forehead). The cardiac arrhythmias are potentially serious and life threatening. They include long QT, ventricular ectopy, bidirectional ventricular arrhythmias, and tachycardia. The disease is most commonly caused by mutations of the inwardly rectifying potassium channel (*Kir 2.1*) gene that heighten muscle cell excitability. The episodes of weakness may differ between patients because of potassium variability. Acetazolamide may decrease the attack frequency and severity.

CHLORIDE CHANNEL DISORDERS

Two forms of this disorder, autosomal dominant (*Thomsen disease*) and autosomal recessive (*Becker disease*), are both caused by mutations in the chloride channel 1 gene (*CLCN1*). Symptoms are noted in infancy and early childhood. The severity lessens in the third to fourth decade. Myotonia is worsened by cold and improved by activity. The gait may appear slow and labored at first but improves with walking. In Thomsen disease, muscle strength is normal, but in Becker disease, which is usually more severe, there may be muscle weakness. Muscle hypertrophy is usually present. Myotonic discharges are prominently displayed by EMG recordings. Serum CK is normal or mildly elevated. Mexiletine is helpful in relieving the myotonia.

ENDOCRINE AND METABOLIC MYOPATHIES

Endocrinopathies can cause weakness, but fatigue is more common than true weakness. The serum CK level is often normal (except in hypothyroidism) and the muscle histology is characterized by atrophy rather than destruction of muscle fibers. Nearly all endocrine myopathies respond to treatment.

THYROID DISORDERS

Hypothyroidism (Chap. 383) Patients with hypothyroidism have frequent muscle complaints, and about one-third have proximal muscle weakness. Muscle cramps, pain, and stiffness are common. Some patients have enlarged muscles. Features of slow muscle contraction and relaxation occur in 25% of patients; the relaxation phase of muscle stretch reflexes is characteristically prolonged and best observed at the ankle or biceps brachii reflexes. The serum CK level is often elevated (up to 10 times normal). EMG is typically normal. Muscle biopsy shows no distinctive morphologic abnormalities.

Hyperthyroidism (Chap. 384) Patients who are thyrotoxic commonly have proximal muscle weakness, but they rarely complain of myopathic symptoms. Activity of deep tendon reflexes may be enhanced. Fasciculations may be apparent and, when coupled with increased muscle stretch reflexes, may lead to an erroneous diagnosis of amyotrophic lateral sclerosis. A form of hypokalemic periodic paralysis can occur in patients who are thyrotoxic. Mutations in the *KCNJ18* gene that encodes for the inwardly rectifying potassium channel, Kir 2.6, have been discovered in up to a third of cases.

PARATHYROID DISORDERS SEE ALSO CHAP. 410

Hyperparathyroidism Proximal muscle weakness, muscle wasting, and brisk muscle stretch reflexes are the main features of this endocrinopathy. Some patients develop neck extensor weakness (part

of the dropped head syndrome). Serum CK levels are usually normal or slightly elevated. Serum parathyroid hormone levels are elevated, while vitamin D and calcium levels are usually reduced. Muscle biopsies show only mild type 2 fiber atrophy.

Hypoparathyroidism An overt myopathy due to hypocalcemia rarely occurs. Neuromuscular symptoms are usually related to localized or generalized tetany. Serum CK levels may be increased secondary to muscle damage from sustained tetany. Hyporeflexia or areflexia is usually present and contrasts with the hyperreflexia in hyperparathyroidism.

■ ADRENAL DISORDERS SEE ALSO CHAP. 386

Conditions associated with glucocorticoid excess cause a myopathy; steroid myopathy is the most commonly diagnosed endocrine muscle disease. Proximal muscle weakness combined with a cushingoid appearance are the key clinical features. Serum CK and EMG are normal. Muscle biopsy, not typically done for diagnostic purposes, reveals type 2b muscle fiber atrophy. In primary hyperaldosteronism (*Conn's syndrome*), neuromuscular complications are due to potassium depletion. The clinical picture is one of persistent muscle weakness. Long-standing hyperaldosteronism may lead to proximal limb weakness and wasting. Serum CK levels may be elevated, and a muscle biopsy may demonstrate necrotic fibers. These changes relate to hypokalemia and are not a direct effect of aldosterone on skeletal muscle.

■ PITUITARY DISORDERS SEE ALSO CHAP. 380

Patients with acromegaly usually have mild proximal weakness. Muscles often appear enlarged but exhibit decreased force generation. The duration of acromegaly, rather than the serum growth hormone levels, correlates with the degree of myopathy.

■ DIABETES MELLITUS SEE ALSO CHAP. 405

Neuromuscular complications of diabetes mellitus are most often related to neuropathy. The only notable myopathy is ischemic infarction of leg muscles, usually involving one of the thigh muscles but on occasion affecting the distal leg. This condition occurs in patients with poorly controlled diabetes and presents with the abrupt onset of pain, tenderness, and edema of a thigh or calf. The area of muscle infarction is hard and indurated. The muscles most often affected include the vastus lateralis, thigh adductors, and biceps femoris. Computed tomography (CT) or MRI can demonstrate focal abnormalities in the affected muscle. Diagnosis by imaging is preferable to muscle biopsy, if possible, as hemorrhage into the biopsy site can occur.

MYOPATHIES OF SYSTEMIC ILLNESS

Systemic illnesses such as chronic respiratory, cardiac, or hepatic failure are frequently associated with severe muscle wasting and complaints of weakness. Fatigue is usually a more significant problem than weakness, which is typically mild.

DRUG INDUCED OR TOXIC MYOPATHIES

The most common toxic myopathies are caused by the cholesterol-lowering agents and glucocorticoids. Others impact practice to a lesser degree but are important to consider in specific situations. Table 449-6 provides a comprehensive list of drug-induced myopathies with their distinguishing features.

■ MYOPATHY FROM LIPID LOWERING AGENTS

All classes of lipid-lowering agents have been implicated in muscle toxicity, including HMG-CoA reductase inhibitors (statins) and, to a much lesser extent, fibrates, niacin, and ezetimibe. Myalgia and elevated CKs are the most common manifestations. Rarely, patients exhibit proximal weakness or myoglobinuria. Concomitant use of statins with fibrates and cyclosporine increases the risk of severe myotoxicity. EMG demonstrates irritability, and myopathic units and muscle biopsies reveal necrotic muscle fibers in weak muscles. Severe myalgia, weakness, marked elevations in serum CK (>3–5 times baseline), and

TABLE 449-6 Drug-Induced Myopathies

DRUGS	MAJOR TOXIC REACTION
Lipid-lowering agents HMG-CoA reductase inhibitors Fibratc acid derivatives Niacin (nicotinic acid)	Drugs belonging to all three of the major classes of lipid-lowering agents can produce a spectrum of toxicity: asymptomatic serum creatine kinase elevation, myalgias, exercise-induced pain, rhabdomyolysis, and myoglobinuria.
Glucocorticoids	Acute, high-dose glucocorticoid treatment can cause acute quadriplegic myopathy. These high doses of steroids are often combined with nondepolarizing neuromuscular blocking agents, but the weakness can occur without their use. Chronic steroid administration produces predominantly proximal weakness.
Nondepolarizing neuromuscular blocking agents	Acute quadriplegic myopathy can occur with or without concomitant glucocorticoids.
Zidovudine	Mitochondrial myopathy with ragged red fibers
Drugs of abuse Alcohol Amphetamines Cocaine Heroin Phencyclidine Meperidine	All drugs in this group can lead to widespread muscle breakdown, rhabdomyolysis, and myoglobinuria. Local injections cause muscle necrosis, skin induration, and limb contractures.
Autoimmune myopathy Statins Check point inhibitors D-Penicillamine	Use of statins may cause an immune-mediated necrotizing myopathy associated with HMG-CoA reductase antibodies. Checkpoint inhibitors can be complicated by myositis, myasthenia gravis, and immune-mediated neuropathies. Myasthenia gravis has also been reported with penicillamine.
Amphophilic cationic drugs Amiodarone Chloroquine Hydroxychloroquine	All amphophilic drugs have the potential to produce painless, proximal weakness associated with necrosis and autophagic vacuoles in the muscle biopsy.
Antimicrotubular drugs Colchicine	This drug produces painless, proximal weakness especially in the setting of renal failure. Muscle biopsy shows necrosis and fibers with autophagic vacuoles.

myoglobinuria are indications for stopping the drug. Patients usually improve with drug cessation, although this may take several weeks. Rare cases continue to progress after the offending agent is discontinued. It is possible that in such cases the statin may have triggered an immune-mediated necrotizing myopathy, as these individuals require immunotherapy (e.g., intravenous immunoglobulin or immunosuppressive agents) to improve and often relapse when these therapies are discontinued (Chap. 365). Autoantibodies directed against HMG-CoA reductase have been identified in many of these cases.

■ GLUCOCORTICOID RELATED MYOPATHIES

Glucocorticoid myopathy occurs with chronic treatment or as “acute quadriplegic” myopathy secondary to high-dose IV glucocorticoid use. Chronic administration produces proximal weakness accompanied by cushingoid manifestations, which can be quite debilitating; the chronic use of prednisone at a daily dose of ≥ 30 mg/d is most often associated with toxicity. Patients taking fluorinated glucocorticoids (triamcinolone, betamethasone, dexamethasone) appear to be at especially high risk for myopathy. In chronic steroid myopathy, the serum CK is usually normal. Serum potassium may be low. The muscle biopsy in chronic cases shows preferential type 2 muscle fiber atrophy; this is not reflected in the EMG, which is usually normal.

Patients receiving high-dose IV glucocorticoids for status asthmaticus, chronic obstructive pulmonary disease, organ transplantation, or other indications may develop severe generalized weakness (critical illness myopathy). This myopathy, also known as acute quadriplegic myopathy, can also occur in the setting of sepsis. Involvement of the diaphragm and intercostal muscles causes ventilatory muscle weakness and is usually appreciated when patients are unable to be weaned off a ventilator in the intensive care unit. NCS demonstrate reduced compound muscle action potentials in the setting of relatively preserved sensory potentials. EMG can demonstrate abnormal insertional and spontaneous activity and early recruitment of myopathic appearing units in those muscles that can be activated. Muscle biopsy can show a distinctive loss of thick filaments (myosin) by electron microscopy. Treatment is withdrawal of glucocorticoids and physical therapy, but the recovery is slow. Patients require supportive care and rehabilitation.

■ OTHER DRUG INDUCED MYOPATHIES

Certain drugs produce painless, largely proximal muscle weakness. These drugs include the amphophilic cationic drugs (amiodarone, chloroquine, hydroxychloroquine) and antimicrotubular drugs (colchicine) (Table 449-6). Muscle biopsy can be useful in the identification of toxicity because autophagic vacuoles are prominent pathologic features of these toxins.

■ GLOBAL ISSUES

As previously discussed, certain dystrophies have an increased prevalence in different parts of the world. LGMD2A/LGMDR1 is the most common LGMD in individuals from Spain, France, Italy, and Great Britain; LGMD2I/LGMDR9 is more common in those with northern European ancestry. GNE myopathy is the most common form of distal myopathy in Japan but is also prevalent in the Ashkenazi population. OPMD is most common in those with ancestry from Spain and French-Canada as well as among Ashkenazi. Epidemiologic studies are lacking regarding other forms of myopathy and their prevalence in different areas of the world.

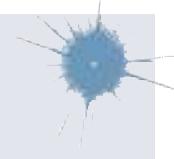
■ FURTHER READING

- A AA, R JA (eds): *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill Education, 2016.
- D CT, A AA: Toxic myopathies. *Continuum* (Minneapolis Minn) 25:1712, 2019.
- H SA et al: Emery-Dreifuss muscular dystrophy. *Muscle Nerve* 61:436, 2020.
- J NE: Myotonic muscular dystrophies. *Continuum* (Minneapolis Minn) 25:1682, 2019.
- N P et al: Summary of evidence-based guideline: Diagnosis and treatment limb-girdle and distal muscular dystrophies. *Neurology* 83:1453, 2014.
- R LK, A AA: The role of electrodiagnostic testing, imaging, and muscle biopsy in the investigation of muscle disease. *Continuum* (Minneapolis Minn) 22:1787, 2016.
- S S et al: FSHD1 and FSHD2 form a disease continuum. *Neurology* 92:e2273, 2019.
- S VA et al: Randomized, placebo-controlled trials of dichlorphenamide in periodic paralysis. *Neurology* 86:1408, 2016.
- S V et al: LGMD Workshop Study Group. 229th ENMC international workshop: Limb girdle muscular dystrophies—Nomenclature and reformed classification Naarden, the Netherlands, 17–19 March 2017. *Neuromuscul Disord* 28:702, 2018.
- T R et al: Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. *Neurology* 85:357, 2015.
- W MP: The limb-girdle muscular dystrophies. *Continuum* (Minneapolis Minn) 25:1599, 2019.

Section 4 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

450

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome



Elizabeth R. Unger, Jin-Mann S. Lin,
Jeanne Bertolli

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic complex illness with multisystem manifestations and long-term impact on functional impairment comparable to multiple sclerosis, rheumatoid arthritis, and congestive heart failure. The hallmark of ME/CFS is persistent and unexplained fatigue resulting in significant impairment in daily functioning along with worsening symptoms following physical or mental exertion that would have been tolerated before illness (post-exertional malaise). Besides intense fatigue, many patients report concomitant symptoms such as pain, cognitive dysfunction, and unrefreshing sleep. Additional symptoms can include headache, sore throat, tender lymph nodes, muscle aches, joint aches, feverishness, difficulty sleeping, psychiatric problems, allergies, and abdominal cramps.

The condition has been known by many names and debate about the name and case definition continues. The composite name ME/CFS was adopted by the U.S. Department of Health and Human Services in recognition of the limitations of either ME (absence of definitive inflammation in brain and spinal cord) or CFS (trivializes an often devastating illness through confusion with fatigue that everyone experiences). An alternative name, systemic exertion intolerance disease (SEID), proposed by the 2015 Institute of Medicine (IOM, now the National Academy of Medicine) committee reviewing ME/CFS, has not gained acceptance.

EPIDEMIOLOGY

Determining how frequently ME/CFS occurs and characteristics of those affected has been complicated by variability in study design and application of case definitions. In the absence of a simple diagnostic test, evaluation by an experienced clinician is required for case identification. Clinic-based studies most accurately identify patients with ME/CFS but overrepresent higher socioeconomic groups with access to ME/CFS clinics. Population-based surveys that included a clinical evaluation estimated a prevalence of 0.2–0.7%, suggesting ≥1 million Americans have ME/CFS. However, these surveys found that ≥80% of those meeting criteria for ME/CFS had not been diagnosed by a health care provider. ME/CFS is three to four times more common in women than men. The highest prevalence of illness is among those 40–50 years of age, but the age range is broad and includes children and adolescents. Persons of all race and ethnicities are affected, and there is some evidence that socioeconomically disadvantaged groups are at increased risk.

RISK FACTORS AND PATHOPHYSIOLOGY

A wide variety of infectious agents have been reported to be associated with a postinfectious fatiguing illness resembling ME/CFS. These include both viral and nonviral pathogens, such as Epstein-Barr virus, Ross River virus, *Coxiella burnetti* (Q fever), Ebola virus, SARS-CoV-1, and *Giardia*. While recovery from these infections is the rule, approximately 10% of those infected remain ill for ≥ months. Most recently, published reports suggest that SARS-CoV-2 infection is also associated

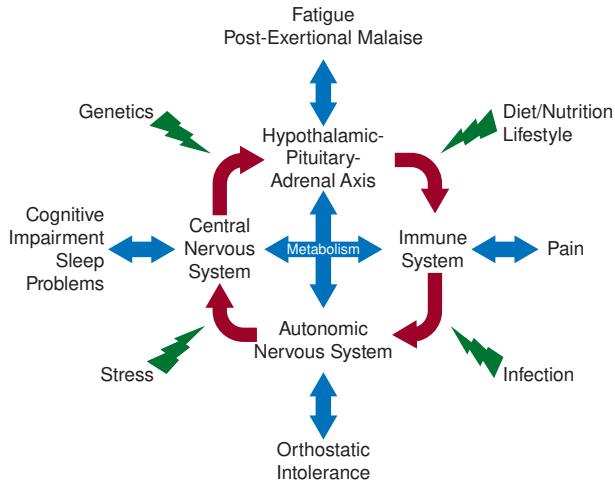


FIGURE 450-1 A multisystem model for ME/CFS. An example of a unifying model for ME/CFS demonstrating the interactions of multiple organ systems, environmental, genetic, and behavioral factors contributing to symptoms.

with prolonged fatiguing illness. Host and pathogen factors associated with recovery versus persistent disease remain elusive. In addition to infectious insults, a variety of stressors, including physical trauma, adverse events, and allostatic load (or “wear and tear” on the body) have been found to be associated with ME/CFS. Twin studies and family histories suggest a role for shared environment as well as genetic factors.

Evidence for immunologic dysfunction is inconsistent. Modest elevations in titers of antinuclear antibodies, reductions in immunoglobulin subclasses, deficiencies in mitogen-driven lymphocyte proliferation, reductions in natural killer cell activity, disturbances in cytokine production, and altered T-cell metabolism have been described. None of these immune findings has been firmly established and none of these changes appear in most patients. In theory, symptoms of ME/CFS could result from excessive production of a cytokine, such as interleukin 1 or interferon alpha, which induces fatigue and other flulike symptoms; however, compelling data in support of this hypothesis are lacking.

Other studies have reported various nonspecific changes in regional brain structures estimated by MRI; dysfunction of the autonomic nervous system; abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis; altered metabolism; and dysbiosis of the intestinal microbiome. Confirmatory studies are needed and none of the findings are consistent enough to be used for diagnosis. It is clear that ME/CFS represents a complex disorder with alterations in multiple interrelated homeostatic systems. A variety of unifying models for the illness have been proposed and discoveries about the pathophysiology of ME/CFS hold promise for elucidating novel mechanisms and interactions important in other illnesses (Fig. 450-1).

APPROACH TO THE PATIENT

DIAGNOSIS

A diagnosis of ME/CFS is made based on patient-reported symptoms that fit a characteristic profile. After a careful review of the literature and symptom-based case definitions for ME, CFS, or ME/CFS, the IOM committee recommended in 2015 a straightforward clinical case definition (Table 450-1). This includes the symptoms consistently noted in prior consensus case definitions: fatigue limiting the patient's ability to participate in his/her usual pre-illness activities, sleep problems, and post-exertional malaise (PEM). PEM is a relapse in symptoms triggered by physical, emotional, or cognitive exertion that would not have been problematic

TABLE 450-1 2015 Institute of Medicine Clinical Case Definition for ME/CFS

Substantial reduction or impairment in the ability to engage in pre-illness levels of activity (occupational, educational, social, or personal life) that:
a. lasts for more than 6 months
b. is accompanied by fatigue that is often profound, of new or definite onset (not lifelong), not the result of ongoing excessive exertion, and is not substantially alleviated by rest
Post-exertional malaise (PEM)—worsening of symptoms after physical, mental, or emotional exertion that would not have caused a problem before the illness
Unrefreshing sleep
Cognitive impairment or orthostatic intolerance
Frequency and severity of symptoms should be assessed; should be present at least half of the time and with at least moderate intensity

for the patient before onset of ME/CFS. The relapse lasts more than a day, and sometimes weeks. In addition, either difficulty thinking and concentrating (often referred to by patients as “brain fog”) or orthostatic intolerance should be present.

Patients with ME/CFS may experience a wide range of other symptoms not specified in the IOM clinical case definition (Table 450-2). As a result, patients meeting the case definition could have very different clinical features based on the type, frequency, and severity of their symptoms. Patients may describe a precipitating cause for their illness, such as a known or presumed infection, but frequently no initiating factor is recognized. The symptoms may occur suddenly within a day or week or may occur gradually.

While the case definition indicates illness must be present at least 6 months, the possibility of ME/CFS should be considered for patients with consistent symptoms persisting >1 month, and evaluation and supportive care can begin as early as 4–6 weeks after onset. Listening to patients' descriptions of what they are experiencing is important. Asking questions can help patients accurately describe their experience with fatigue and PEM. These include asking about current activity levels compared with before they became ill, what happens when they are as active as they were pre-illness, and how long it takes to recover after exertion. Whereas patients recognize relapses, the relation of relapse to activity level may not be apparent, and as a result PEM may not be recognized. Patients may also appear well during an office visit, only to relapse afterwards from exertion surrounding the consultation.

Although the IOM definition does not list medical or psychological conditions that exclude the diagnosis of ME/CFS, a careful clinical evaluation is required to identify and treat other illness that could explain or contribute to the patient's symptoms. The initial evaluation also requires reviewing family history; medical history (including infections, traumas/surgeries, occupational exposure to environmental toxins); a review of medications and supplements; physical examination, including lean test for postural orthostatic tachycardia syndrome (POTS; Chap. 440); mental health assessment (screen for depression and anxiety); and routine screening laboratory tests (if recent results are not on record). As routine

TABLE 450-2 Additional Symptoms Experienced by Patients with ME/CFS

Joint pain without swelling or redness
Muscle aches
New headaches
Tender lymph nodes
Sensitivity to sensory stimuli (e.g., light, noise, smells)
Sore throat
Alcohol intolerance
Difficulties with temperature regulation (feeling feverish or chilled)

TABLE 450-3 ME/CFS Comorbid Conditions

Chronic overlapping pain conditions: fibromyalgia (FM), chronic migraine, temporomandibular joint disease (TMJ), irritable bowel syndrome (IBS), endometriosis, vulvodynia, urologic chronic pelvic pain syndromes (UCPPS)
Postural orthostatic tachycardia syndrome (POTS)
Allergies
Sjögren's syndrome
Ehlers-Danlos syndrome
Mast-cell activation syndrome (MCAS)
Dysautonomia
Multiple chemical sensitivities

laboratory tests are usually within normal limits, their role is in identifying other illnesses and the specific panel of tests should be adjusted based on the patient's presentation. Typically the tests include complete blood count, erythrocyte sedimentation rate, electrolytes, fasting glucose, renal function tests (blood urea nitrogen, glomerular filtration rate), calcium, phosphate, liver function (bilirubin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma-glutamyl transferase, total protein, albumin/globulin ratio), C-reactive protein, thyroid function (thyroid-stimulating hormone, free thyroxine), iron studies to assess both iron overload and iron deficiency (serum iron, transferrin saturation, ferritin), celiac disease screening tests, and urinalysis.

DIFFERENTIAL DIAGNOSIS AND COMORBID CONDITIONS

While the differential diagnosis for fatigue is quite broad, further workups and referrals should be chosen carefully based on the patient's history, symptoms (particularly those that are new, worsening, or unusual), and results of initial laboratory tests. Conditions reported to occur in association with ME/CFS (Table 450-3) should be kept in mind during the evaluation and follow-up, as management and treatment modalities for these comorbidities could contribute to an improved quality of life.

MANAGEMENT

While there are no approved drugs to treat or cure ME/CFS, patients benefit from receiving a diagnosis and an individualized plan that addresses the symptoms that are most problematic for the patient. Some symptoms, in particular, disturbed sleep (Chap. 31) and pain (Chap. 13), may improve with nonpharmacologic therapies (such as sleep hygiene, massage, acupuncture, hot or cold packs) or medications. Any medications should be started at lower doses than usual and only slowly increased. Patients with ME/CFS have been reported to be more sensitive to medications than the general population, and benefits with fewer toxicities may be achieved at lower doses. Narcotics should be avoided, and referral to sleep centers or other specialists may be required.

Controlled therapeutic trials have not established significant benefit for patients with ME/CFS from acyclovir, fludrocortisone, galantamine, modafinil, and IV immunoglobulin, among other agents. These studies have been limited by small numbers and lack power to investigate benefit in patient subgroups. Preliminary small studies reported the possible effectiveness of the B-cell targeting anti-CD20 monoclonal antibody rituximab in ME/CFS, but a subsequent large, well-designed prospective double-blind study found no benefit. Numerous anecdotes circulate regarding other traditional and non-traditional therapies. It is important to guide patients away from therapeutic modalities that are toxic, expensive, or unreasonable.

Educating the patient and family about PEM can be helpful in avoiding the harmful cycle of overexertion during "good days" followed by relapse that can negate any functional gains. This is often referred to as "push and crash." Recognizing limits and using activity management (pacing) can help limit PEM. It is important to maintain tolerated activity levels to minimize deconditioning. Activity may be advanced very gradually as tolerated.

Counseling may help patients and their families cope with the long-term consequences of living with a chronic illness. Consultation with a physical or occupational therapist may identify energy-saving strategies for activities of daily living as well as needed accommodations, such as a wheelchair for activities that require walking longer distances or prolonged standing.

COURSE AND PROGNOSIS

The illness severity varies from mild or moderate, with patients retaining varying degrees of pre-illness function, to severe, with patients essentially homebound. Most patients experience some improvement and stabilize, although return to their prior level of function is unusual. A continued decline in function should prompt evaluation for other illnesses. Patients should be re-evaluated at scheduled intervals to adjust treatments and detect any intercurrent disease. New or changing symptoms should be worked up to identify any new illnesses. Given the social isolation and loss of hope associated with a debilitating chronic illness, serious depression and an increased risk of suicide is reported for patients with ME/CFS. Clinicians should be prepared to screen for this and refer patients as needed.

FURTHER READING

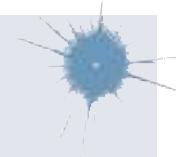
- B Let al: Myalgic encephalomyelitis/chronic fatigue syndrome: Essentials of diagnosis and Management. Mayo Clin Proc 2021. <https://doi.org/10.1016/j.mayocp.2021.07.004>
- C D C P : Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Available from <https://www.cdc.gov/me-cfs/index.html>. Accessed March 15, 2021.
- I M : Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: The National Academies Press, 2015.
- K AL: Advances in understanding the pathophysiology of chronic fatigue syndrome. JAMA 322:499, 2019.
- L CW: Initiating care of a patient with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Front Pediatr 6:415, 2019.
- R PC et al: Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: A primer. Front Pediatr 5: 121, 2017.

Section 5 Psychiatric and Addiction Disorders

451

Biology of Psychiatric Disorders

Robert O. Messing, Eric J. Nestler,
Matthew W. State



Psychiatric disorders are central nervous system diseases characterized by disturbances in emotion, cognition, motivation, and socialization. They are highly heritable, with genetic risk comprising 20–90% of disease vulnerability. As a result of their prevalence, early onset, and persistence, they contribute substantially to the burden of illness worldwide. All psychiatric disorders are broad heterogeneous syndromes that currently lack well-defined neuropathology and bona fide biologic markers. Therefore, diagnoses continue to be made solely from clinical observations using criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, of the American Psychiatric Association (see Chap. 452).

There is increasing agreement that the classification of psychiatric illnesses in DSM does not accurately reflect the underlying biology of these disorders. Uncertainties in diagnosis complicate efforts to study the genetic basis and attendant neurobiological mechanisms underlying mental illness, though recent advances in genomic and neuroscience technologies along with the consolidation of very large patient cohorts have, for multiple disorders, led to major progress in these realms. In addition, there have been efforts to address the limitations of a categorical nosology directly through the development of an alternative diagnostic scheme, termed Research Domain Criteria (RDoC). This system classifies mental illness on the basis of core behavioral abnormalities shared across several syndromes—such as psychosis (loss of reality) or anhedonia (decreased ability to experience pleasure)—and the associated brain circuitry that controls these behavioral domains. It is anticipated that such classifications will assist in defining the biologic basis of key symptoms. Other factors that have impeded progress in understanding mental illness include the lack of access to pathologic brain tissue except upon death and the inherent limitations of animal models for disorders defined largely by behavioral abnormalities (e.g., hallucinations, delusions, guilt, suicidality) that are inaccessible in animals.

Despite these limitations, the past decade has been marked by real progress. Neuroimaging methods are beginning to provide evidence of brain pathology; genome-wide association studies and high-throughput sequencing are reliably identifying genes and genomic loci that confer risk for severe forms of mental illness; and investigations of better validated animal models, leveraging a host of new methods to study molecular, cellular, and circuit-level processes, are offering new insight into disease pathogenesis. There is also excitement in the utility of neurons, glia, and brain organoids induced *in vitro* from patient-derived pluripotent stem cells, providing novel ways to study disease pathophysiology and screen for new treatments. There is consequently justified optimism that the field of psychiatry will better integrate behaviorally defined syndromes with an understanding of biological substrates in a way that will drive the development of improved treatments and eventually cures and preventive measures. This chapter describes several examples of recent discoveries in basic neuroscience and genetics that have informed our current understanding of disease mechanisms in psychiatry.

■ NEUROGENETICS

Because the human brain can only be examined indirectly during life, genome analyses have been extremely important for obtaining molecular clues about the pathogenesis of psychiatric disorders. Moreover, the identification of germline risk alleles and mutations provides potential traction on the question of cause versus effect. In other types of cross-sectional studies, it may be impossible to determine whether a phenotype or biomarker observed in affected humans or model systems reflects an etiologic factor or a compensatory response. In contrast, germline genetic risk is present before the brain develops—at least theoretically allowing for experiments to address temporal sequencing.

A wealth of new information has been made possible by recent technologic developments that have permitted affordable, large-scale genome-wide association studies and high-throughput sequencing. As an example of the latter, there has been significant progress in the genetics of autism spectrum disorders (ASDs), which are a heterogeneous group of neurodevelopmental diseases that share clinical features of impaired social communication and restricted, repetitive patterns of behavior. ASDs are highly heritable; concordance rates in monozygotic twins (~60–90%) are five- to tenfold higher than in dizygotic twins and siblings, and first-degree relatives show approximately tenfold increased risk compared with the general population. ASDs are also genetically heterogeneous. More than 100 individual risk genes, along with dozens of submicroscopic deletions and duplications often containing multiple genes, have been identified, almost exclusively through the study of rare, large-effect, new (*de novo*) mutations (Fig. 451-1). All told, genes and genomic regions vulnerable to these types of mutations account for ~20–30% of formerly idiopathic cases that present in the clinic, although none individually accounts for >1%. In addition, ~10% of individuals with ASD have

well-described intellectual disability syndromes including *fragile X syndrome*, *Rett syndrome*, and *tuberous sclerosis* (Chap. 90). However, it appears that most of the risk for ASD in the population involves true polygenic inheritance. There is considerable evidence, for example, that >50% of the genetic liability is carried in common alleles of very small individual effect. To date, studies of tens of thousands of cases have identified five reproducible associations of loci meeting gold standard genome-wide association statistical thresholds. With continually increasing cohort sizes, and thus power, this number is certain to grow in the future.

Amid the genetic heterogeneity that has so far been identified, common themes have emerged that inform pathogenesis of ASDs. For instance, many identified rare mutations are in genes that encode proteins involved in synaptic function and early transcriptional and chromatin regulation (Fig. 451-1) and have a clear relationship to activity-dependent neural responses that can affect the development of neural systems underlying cognition and social behaviors. One particularly intriguing hypothesis is that these genes may lead to ASD risk by changing the balance of excitatory versus inhibitory synaptic signaling in local and extended circuits and by altering mechanisms that control brain growth. Some mutations affect genes (e.g., *PTEN*, *TSC1*, and *TSC2*) that negatively regulate signaling from several types of extracellular stimuli, including those transduced by receptor tyrosine kinases. Their dysregulation can alter neuronal growth, resulting in altered brain size, as well as synaptic development and function. Finally, several recent studies have focused on the question of when and where multiple functionally diverse risk genes converge with respect to human brain development. Interestingly, these studies have thus far tended to overlap with expression patterns of glutamatergic neurons in mid-fetal cortex (Fig. 451-1). Given the pleiotropic biological effects of the ASD genes identified to date, an understanding of the developmental or “spatiotemporal” dimensions of risk is likely to serve as a useful complement to studies of the function of individual genes. In short, it may turn out that when and where genetic variation has its impact in the developing brain may be as important as the key processes that are identified.

With further understanding of pathogenesis and the definition of specific ASD subtypes, there is reason to believe that effective therapies will be identified. Work in mouse models has already demonstrated that some autism-like behaviors can be reversed, even in fully developed adult animals, by modifying the underlying genetic or functional pathology. These results suggest that key phenotypes arising from some ASD-related large-effect mutations may well reflect ongoing functional derangements, offering hope that interventions can be successful well after the initial developmental insult and the emergence of symptoms. Treatments that target excitation-inhibition imbalance or altered mRNA translation are one area of early promise. For example, the genes *TSC1*, *TSC2*, and *PTEN* are negative regulators of signaling through the target of rapamycin complex 1 (TORC1), which regulates protein synthesis. Rapamycin, a selective inhibitor of TORC1, can reverse several behavioral and synaptic defects in mice carrying null mutations in these genes.

Increasingly, attention has turned to the strategy of targeting the genetic “lesion” early in development to treat or prevent ASD and related phenotypes in those cases in which a single, highly penetrant coding mutation is present. However, even with the relatively large number of risk genes (>100) that have been identified carrying *de novo* putative loss-of-function coding mutations, there is a much smaller number of potential targets that carry sufficiently high and predictable risks for severe outcomes to consider directly targeting nucleic acids, for example, with CRISPR-based therapies or the use of antisense oligonucleotides (ASOs). Clearly, however, recent successes with very early intervention in spinal muscular atrophy, using both strategies, are driving increased interest in their utility in a range of brain-based disorders. Currently, with regard to neurodevelopmental conditions, these approaches are being most actively pursued for well-known intellectual disability syndromes that may also carry elevated risk for ASD, such as Angelman syndrome, Rett and *MECP2* duplication syndrome, and *fragile X* syndrome. Such efforts could be transformational

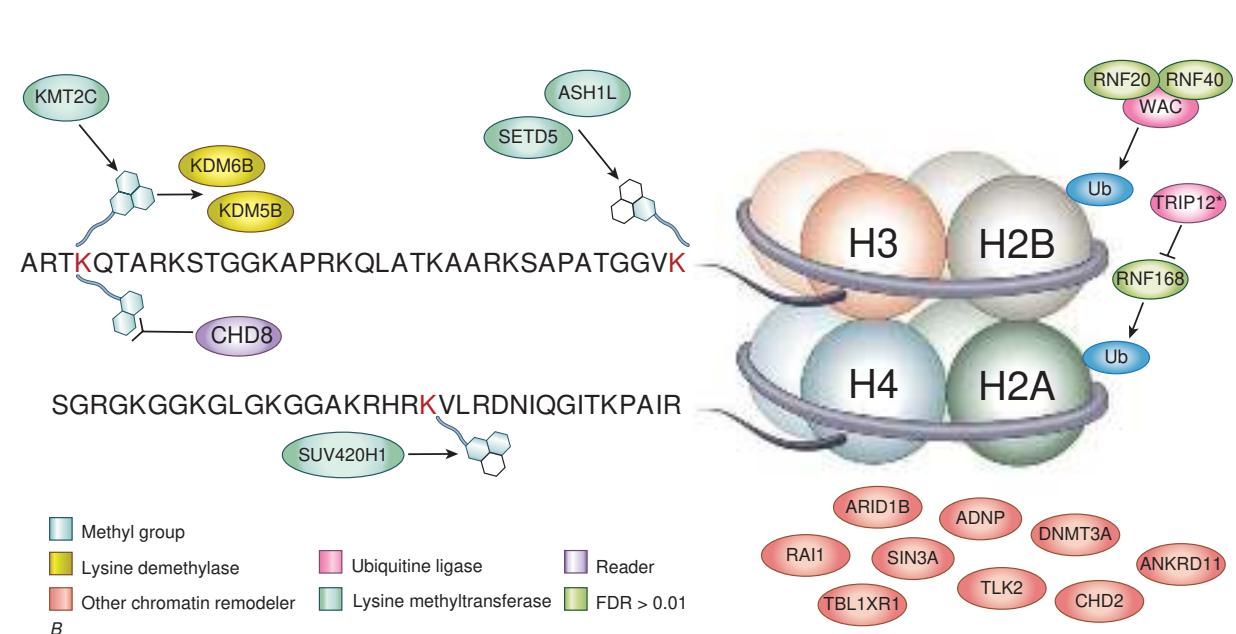
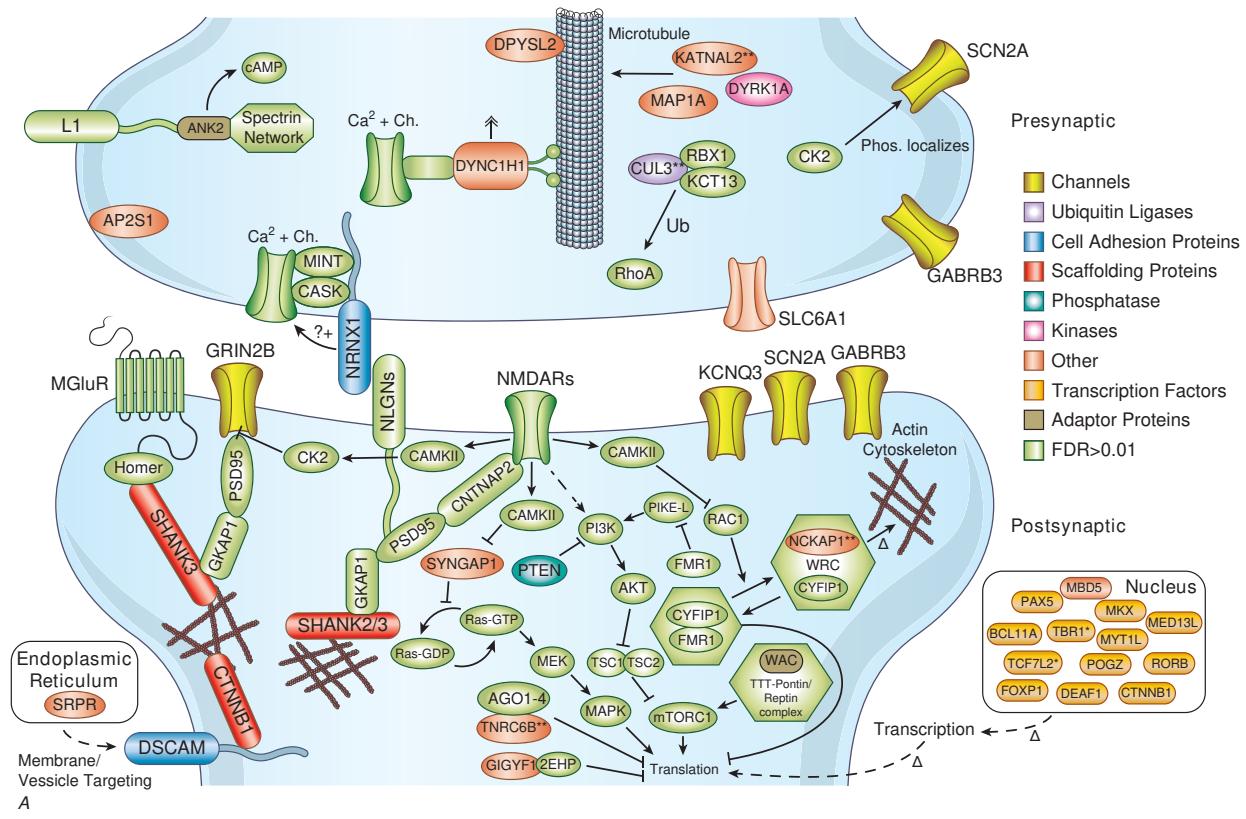


FIGURE 451-1 Functional characteristics and developmental convergence of autism spectrum disorder (ASD) associated genes: genes associated with ASD based on recurrent de novo and transmitted coding mutations are shown in **A** and **B**. Those genes encoding proteins with a false discovery rate (FDR) < 0.01 in Sanders et al, *Neuron* 2015, and Satterstrom et al, *Cell* 2020, are highlighted with respect to their putative functions. Genes meeting the highest confidence criteria in Sanders et al 2015 and showing either an FDR > 0.01 or an FDR > 0.3 in Satterstrom are noted (*) and **, respectively). Additional interacting and functionally related molecules that do not meet the above criteria are shown in green. *FMR1*, *TSC1*, and *TSC2* are syndromic ASD genes included in the figure (**A**). Multiple gene ontology analyses of ASD genes have highlighted both pre- and postsynaptic molecules (**A**) and chromatin modifiers (**B**) as points of enrichment. In **C**, an alternative strategy for grouping ASD risk genes is highlighted (Willsey et al, *Cell* 2013), based on their spatiotemporal expression patterns as opposed to putative functions. One analytic strategy, illustrated in **C** leveraged only high-confidence ASD genes and examined their developmental expression patterns using the BrainSpan data set. Convergence for ASD risk was identified in deep layer (V and VI) excitatory neurons in mid-fetal human cortex. Multiple analyses have similarly found glutamatergic neurons in mid-fetal prefrontal cortex as one point of convergence, with somewhat less agreement on layer specificity and potential additional spatiotemporal points of convergence.

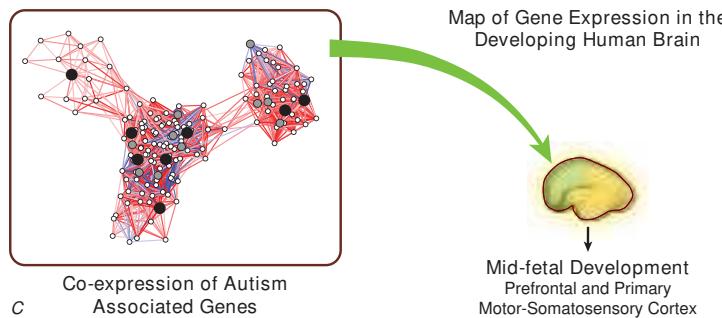
Convergence of Autism Associated Genes
& Co-expression Network Analysis

FIGURE 451-1 (Continued)

for very small numbers of individuals and may well yield important insights into biology that have impact beyond those carrying rare very highly penetrant mutations. They will undoubtedly raise significant practical as well as ethical challenges as treatments for more common forms of ASD.

The ability to catalog common genetic variants and assay them on array-based platforms and, more recently, to carry out whole exome sequencing has allowed investigators to leverage very large patient cohorts to detect risk loci for schizophrenia and bipolar disorder with genome-wide significance. In contrast to ASD, where the lion's share of early success in gene identification has resulted from the study of rare, large-effect, de novo mutations, much of gene discovery to date for these syndromes has resulted from genome-wide association studies of common inherited polymorphisms. It is noteworthy that there is also striking overlap among the submicroscopic deletions and duplications, called copy number variants (CNVs), that have been found to carry large risks for ASD, schizophrenia, and bipolar disorder, as well as epilepsy and intellectual disability.

To date, >200 distinct genomic regions, marked by associated single nucleotide polymorphisms, have been identified in schizophrenia, some of which show risk as well for bipolar disorder. Several of the identified genes are parts of molecular complexes, such as voltage-gated calcium channels (in particular, *CACNA1C* and *CACNB2*) and the postsynaptic density of excitatory synapses. Genes that promote risk for addiction and depression have also begun to emerge from large studies. The best-established susceptibility locus for addiction is the *CHRNA5-A3-B4* nicotinic acetylcholine receptor gene cluster on chromosome 15 associated with nicotine and alcohol addiction. Recent genome-wide association studies of depression have required hundreds of thousands of cases and controls to identify the first statistically significant loci using state-of-the-art approaches. These findings collectively point to the tremendous heterogeneity of depressive disorders as well as the very small biologic effects conferred by any individual common allele.

A recurrent theme that has emerged from genetic studies of psychiatric disorders is phenotypic pleiotropy, namely, that many genes are associated with multiple psychiatric syndromes. For example, mutations in *MECP2*, *FMR1*, and *TSC1* and *TSC2* can cause intellectual disability without ASD, others in *MECP2* can cause obsessive-compulsive and attention-deficit/hyperactivity disorders, some alleles of *NRXN1* are associated with symptoms of both ASD and schizophrenia, and common polymorphisms in *CACNA1C* are strongly associated with both schizophrenia and bipolar disorder. Likewise, duplication of chromosome 16p is associated with both schizophrenia and autism, whereas deletions in the DiGeorge's (velocardiofacial) syndrome region are associated with schizophrenia, autism, and bipolar disorder. The association of genes and genomic regions with multiple syndromes attests to the complexity of psychiatric disorders, the very large gap between molecular mechanisms and the current categorical diagnostic schemes, and the influence of additional factors that combine to specify the ultimate phenotype. The latter might include polygenic

"background," variations in regulatory regions of the genome that determine cell-type specificity and timing of gene expression, protective variants, stochastic events, and epigenetic effects. This pleiotropy of consequences for a given genetic mutation in psychiatry is akin to the pleiotropy seen for many cancer-causing mutations, where the same mutation can lead to many different types of cancers across the population.

SIGNAL TRANSDUCTION

Studies of signal transduction have revealed numerous intracellular signaling pathways that are perturbed in psychiatric disorders, and such research has provided insight into development of new therapeutic agents. For example, lithium is a highly effective drug for bipolar disorder and competes with magnesium to inhibit numerous magnesium-dependent enzymes, including the enzyme GSK3 β and several enzymes involved in phosphoinositide signaling that lead to activation of protein kinase C. These findings have led to discovery programs focused on developing GSK3 β or protein kinase C inhibitors as potential novel treatments for mood disorders, although none have demonstrated clinical efficacy to date.

The observations that tricyclic antidepressants (e.g., imipramine) inhibit serotonin and/or norepinephrine reuptake and that monoamine oxidase inhibitors (e.g., tranylcypromine) are effective antidepressants initially led to the view that depression is caused by a deficiency of these monoamines. However, this hypothesis has not been substantiated. A cardinal feature of these drugs is that long-term (weeks to months) administration is needed for their antidepressant effects. This means that their short-term actions, namely promotion of serotonin or norepinephrine function, are not per se antidepressant but rather induce a cascade of adaptations in the brain that underlie their slowly developing clinical effects. The nature of these therapeutic drug-induced adaptations has not been identified with certainty. One hypothesis holds that, in a subset of depressed patients who display upregulation of the hypothalamic-pituitary-adrenal (HPA) axis characterized by increased secretion of corticotropin-releasing factor (CRF) and glucocorticoids, excessive glucocorticoids cause atrophy of hippocampal neurons, which is associated with reduced hippocampal volumes seen clinically. Chronic antidepressant administration might reverse this atrophy by increasing brain-derived neurotrophic factor (BDNF) or a host of other neurotrophic factors in the hippocampus. A role for stress-induced decreases in the generation of newly born hippocampal granule cell neurons, and its reversal by antidepressants through BDNF or other growth factors, has also been suggested.

A major advance in recent years has been the identification of several rapidly acting antidepressants with non-monoamine-based mechanisms of action. The best established is ketamine, a non-competitive antagonist of *N*-methyl-*D*-aspartate (NMDA) glutamate receptors among other actions, which exerts rapid (hours) and robust antidepressant effects in severely depressed patients who have not responded to other treatments. Ketamine, which at higher doses is psychotomimetic and anesthetic, exerts these antidepressant effects

at lower doses with minimal side effects. However, the response to ketamine is transient, which has led to several approaches to maintain treatment response, such as repeated ketamine delivery. The mechanism underlying ketamine's antidepressant action is not known, and its action as an NMDA receptor antagonist has recently been called into question. Nevertheless, ketamine's striking clinical efficacy has stimulated animal research on the role of glutamate neurotransmission and synaptic plasticity in key limbic regions. Recent evidence supports a role for TORC1 or BDNF activation, as blockade of either blocks the antidepressant-like effects of ketamine in animal models. Mechanisms by which ketamine activates these signaling cascades are currently an active area of investigation.

A major goal in the field of substance use disorders has been to identify neuroadaptive mechanisms that lead from recreational use to addiction. Such research has determined that repeated intake of abused drugs induces specific changes in cellular signal transduction, leading to changes in synaptic strength (long-term potentiation or depression) and neuronal structure (altered dendritic branching or cell soma size) within the brain's reward circuitry. These drug-induced modifications are mediated in part by changes in gene expression, achieved by regulation of transcription factors (e.g., CREB [cAMP response element-binding protein] and ΔFosB [a Fos family protein]) and their target genes. Such alterations in gene expression are associated with lasting alterations in epigenetic modifications, including histone acetylation and methylation and DNA methylation. These adaptations provide opportunities for developing treatments targeted to drug-addicted individuals. The fact that the spectrum of these adaptations differs in part depending on the particular addictive substance used raises hope that treatments could be developed that are specific for different classes of addictive drugs and less likely to disturb basic mechanisms that govern normal motivation and reward.

Increasingly, causal relationships are being established between individual molecular and cellular adaptations and specific behavioral abnormalities that characterize the addicted state. For example, acute activation of μ -opioid receptors by morphine or other opiates activates $G_{i/o}$ proteins, leading to inhibition of adenylyl cyclase (AC), resulting in reduced cyclic AMP (cAMP) production, protein kinase A (PKA) activation, and activation of the transcription factor CREB. Repeated administration of these drugs (Fig. 451-2) evokes a homeostatic response involving upregulation of ACs and PKA and increased activation of CREB. Such upregulation of cAMP-CREB signaling has been identified in the locus coeruleus (LC), periaqueductal gray, ventral tegmental area (VTA), nucleus accumbens (NAc), and several other central nervous system (CNS) regions and contributes to opiate craving and signs of opiate withdrawal. The fact that endogenous opioid peptides do not produce tolerance and dependence, while morphine and heroin do, may relate to the observation that, unlike endogenous opioids, morphine and heroin are weak inducers of μ -opioid receptor desensitization and endocytosis. Therefore, these drugs cause prolonged receptor activation and inhibition of ACs, which provides a powerful stimulus for the upregulation of cAMP-CREB signaling that characterizes the opiate-dependent state.

SYSTEMS NEUROSCIENCE

The study of interconnected brain circuits that drive behavior has been greatly advanced through newer methods in brain imaging that have documented abnormalities in neural function and connectivity in psychiatric disorders. Electroceutical devices, which use electrical or magnetic stimulation to control neuronal activity, have had some success in depression, obsessive-compulsive disorder, pain, and addiction. The past decade has also witnessed the development of revolutionary new techniques—optogenetics, designer receptors, and ligands—that provide unprecedented temporal and spatial control of neural circuits. The development of genetically encoded calcium detectors and electrode arrays has allowed *in vivo* monitoring of thousands of neurons in multiple brain regions simultaneously. Advances in histology and microscopy now permit three-dimensional imaging of specific proteins in the intact brain, while advances in endoscopic microscopy allow imaging of hundreds of neurons within deep brain structures in awake,

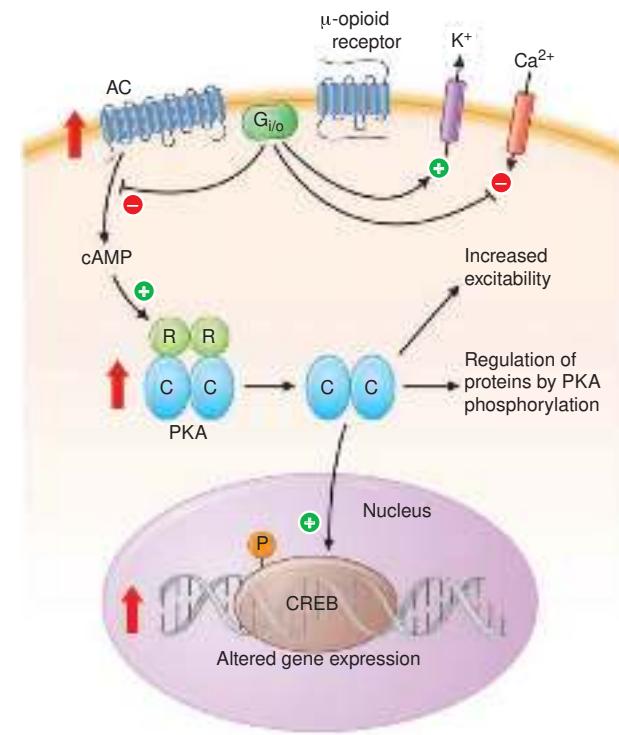


FIGURE 451-2 Opiate action in the locus coeruleus (LC). Binding of opiate agonists to μ -opioid receptors on LC neurons catalyzes nucleotide exchange on G_i and G_o proteins, leading to inhibition of adenylyl cyclase (AC), neuronal hyperpolarization via activation of K^+ channels and perhaps inhibition of Ca^{2+} channels. Inhibition of AC reduces protein kinase A (PKA) activity and phosphorylation of several PKA substrate proteins, thereby altering their function. For example, opiates reduce phosphorylation of the cAMP response element-binding protein (CREB), which initiates longer term changes in neuronal function. Chronic administration of opiates increases levels of AC isoforms, PKA catalytic (C) and regulatory (R) subunits, and the phosphorylation of several proteins, including CREB (indicated by red arrows). These changes contribute to the altered phenotype of the drug-addicted state. For example, the excitability of LC neurons is increased by enhanced cAMP signaling. Activation of CREB causes upregulation of AC isoforms and tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis.

freely moving animals. These new methods are revolutionizing our ability to understand the circuit basis of brain function.

Positron emission tomography (PET), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI) have identified neural circuits that contribute to psychiatric disorders, for example, defining the neural circuitry of mood within the brain's limbic system (Fig. 451-3). Integral to this system are the NAc (important also for brain reward—see below), amygdala, hippocampus, and regions of prefrontal cortex. Recent optogenetic research in animals, where the activity of specific types of neurons in defined circuits can be controlled with light, has confirmed the importance of this limbic circuitry in controlling depression-related behavioral abnormalities. Given that many symptoms of depression (so-called neurovegetative symptoms) involve physiologic functions, a key role for the hypothalamus is presumed as well. A subset of depressed individuals shows a small reduction in hippocampal size, as noted above. In addition, brain imaging investigations have revealed increased activation of the amygdala by negative stimuli and reduced activation of the NAc by rewarding stimuli. There is also evidence for altered activity in prefrontal cortex, such as hyperactivity of subgenual area 25 in anterior cingulate cortex. Such findings have led to trials of deep brain stimulation (DBS) of either the NAc or subgenual area 25 (see Fig. 30-1), which appears to be therapeutic in some severely depressed individuals.

In schizophrenia, structural and functional imaging studies have confirmed earlier pathologic studies that show enlargement of the ventricular system and reduction of cortical and subcortical gray matter

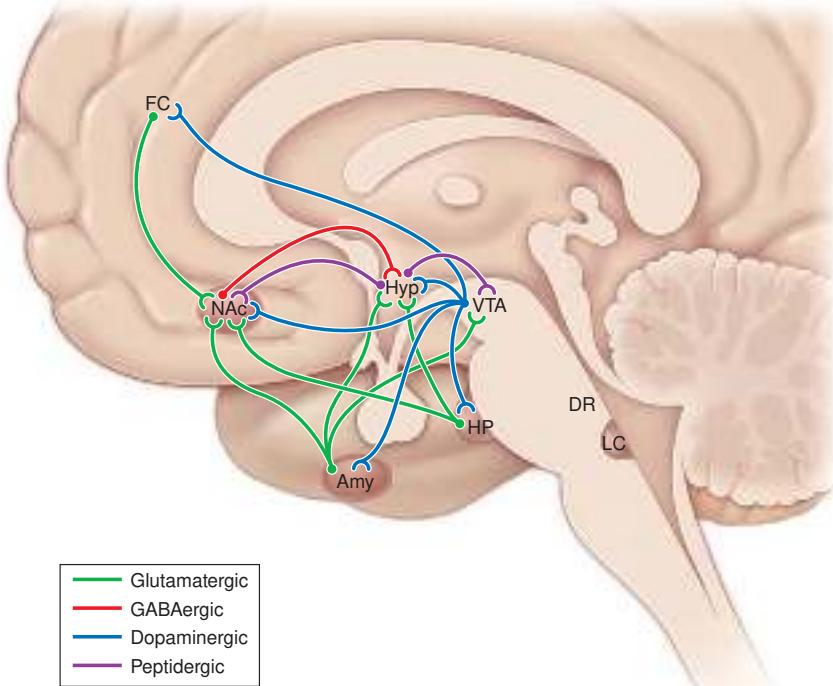


FIGURE 451-3 Neural circuitry of depression and addiction. The figure shows a simplified summary of a series of limbic circuits in brain that regulate mood and motivation and are implicated in depression and addiction. Shown in the figure are the hippocampus (HP) and amygdala (Amy) in the temporal lobe, regions of prefrontal cortex, nucleus accumbens (NAc), and hypothalamus (Hyp). Only a subset of the known interconnections among these brain regions is shown. Also shown is the innervation of several of these brain regions by monoaminergic neurons. The ventral tegmental area (VTA) provides dopaminergic input to each of the limbic structures. Norepinephrine (from the locus coeruleus [LC]) and serotonin (from the dorsal raphe [DR] and other raphe nuclei) innervate all of the regions shown. In addition, there are strong connections between the hypothalamus and the VTA-NAc pathway. Important peptidergic projections from the hypothalamus include those from the arcuate nucleus that release β -endorphin and melanocortin and from the lateral hypothalamus that release orexin.

in frontal and temporal lobes and in the limbic system. Functional imaging studies show reduced metabolic (presumably neural) activity in the dorsolateral prefrontal cortex at rest and when performing tests of executive function, including working memory. There is also evidence for impaired structural and task-related functional connectivity, mainly in frontal and temporal lobes. The reduction in cortical thickness seen in schizophrenia is associated with increased cell packing density and reduced neuropil (defined as axons, dendrites, and glial cell processes) without an apparent change in neuronal cell number. Specific classes of interneurons in prefrontal cortex consistently show reduced expression of the gene encoding the enzyme glutamic acid decarboxylase 1 (*GAD1*), which synthesizes γ -aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain. Recently, results from well-powered genome-wide association studies point to synaptic pruning, including the involvement of microglia, as a potential contributing mechanism. In the region of the genome most strongly associated with schizophrenia risk, variations in the relative expression of two isoforms of complement component 4, C4A and C4B, have been found to account for a significant proportion of this genetic signal. Studies of loss of C4 in mice show deficient synaptic pruning, leading to the hypothesis that increased expression of C4A in humans may result in excessive synaptic pruning. Such results point to the potential for a gene-driven understanding of pathophysiology; however, the findings also leave some important questions unanswered. The strongest effect haplotype in humans still only accounts for a very small increase in risk, with an odds ratio of <1.3. In contrast, having a sibling with schizophrenia increases risk approximately tenfold. In short, whether this allele reflects a driving pathophysiologic mechanism remains to be determined. Moreover, humans have diverged at the C4 locus compared with rodents such that only a single C4 isotype

is present in the mouse, preventing any analysis of the putative effects of changing the ratio of C4A to C4B—the phenomenon associated with disease risk in humans. Nonetheless, all the aforementioned findings support the notion that schizophrenia is a developmental neurodegenerative disorder with some evidence pointing to loss of cortical interneurons in frontal and temporal lobes.

Work in rodent and nonhuman primate models of addiction has established the brain's reward regions as key neural substrates for the acute actions of drugs of abuse and for addiction induced in vulnerable individuals by repeated drug administration (Fig. 451-3). Midbrain dopamine neurons in the VTA function normally as rheostats of reward: they are activated by natural rewards (food, sex, social interaction) or even by the expectation of such rewards, and many are suppressed by the absence of an expected reward or by aversive stimuli. These neurons thereby transmit crucial survival signals to the rest of the limbic brain to promote reward-related behavior, including motor responses to seek and obtain the rewards (NAc), memories of reward-related cues and contexts (amygdala, hippocampus), and executive control of obtaining rewards (prefrontal cortex).

Drugs of abuse alter neurotransmission through initial actions at different classes of ion channels, neurotransmitter receptors, or neurotransmitter transporters (Table 451-1). Studies in animal models have demonstrated that although the initial targets differ, the actions of these

drugs converge on the brain's reward circuitry by promoting dopamine neurotransmission in the NAc and other limbic targets of the VTA. In addition, some drugs promote activation of opioid and cannabinoid receptors, which modulate this reward circuitry. By these mechanisms, drugs of abuse produce powerful rewarding signals, which, after repeated drug administration, corrupt a vulnerable brain's reward circuitry in ways that promote addiction. Three major pathologic adaptations have been described. First, drugs produce tolerance in reward circuits and increased activity in stress circuits, which promote escalating drug intake and a negative emotional state during drug withdrawal that promotes relapse. Second, sensitization to the rewarding effects of the drugs and associated cues is seen during prolonged abstinence and also triggers relapse. Third, executive function is impaired in such a way as to increase impulsivity and compulsivity, both of which promote relapse.

Imaging studies in humans confirm that addictive drugs, as well as craving for them, activate the brain's reward circuitry. In addition, patients who abuse alcohol or psychostimulants show reduced gray matter in the prefrontal cortex as well as reduced activity in anterior cingulate and orbitofrontal cortex during tasks of attention and inhibitory control. It is thought that damage to these cortical areas contributes to addiction by impairing decision-making and increasing impulsivity.

■ NEUROINFLAMMATION

There is increasing evidence for the involvement of inflammatory mechanisms in a wide range of psychiatric syndromes. For example, a subset of depressed patients displays elevated blood levels of interleukin 6 (IL-6), tumor necrosis factor α (TNF- α), and other proinflammatory cytokines. Moreover, rodents exposed to chronic stress exhibit

TABLE 451-1 Initial Actions of Drugs of Abuse

DRUG	NEUROTRANSMITTER AFFECTED	DRUG TARGET (ACTION)
Opiates	Endorphins, enkephalins	μ - and δ -opioid receptors (agonist)
Psychostimulants (cocaine, amphetamine, methamphetamine)	Dopamine	Dopamine transporter (antagonist—cocaine; reverse transport—amphetamine, methamphetamine)
Nicotine	Acetylcholine	Nicotinic cholinergic receptors (agonist)
Ethanol	GABA	GABA _A receptors (positive allosteric modulator)
	Glutamate	NMDA glutamate receptors (antagonist)
	Acetylcholine	Nicotinic cholinergic receptors (allosteric modulator)
	Serotonin	5-HT ₃ receptor (positive allosteric modulator)
	Others	Calcium-activated K ⁺ channel (activator)
Marijuana	Endocannabinoids (anandamide, 2-arachidonoylglycerol)	CB ₁ receptor (agonist)
Phencyclidine	Glutamate	NMDA glutamate receptor (antagonist)

Abbreviations: GABA, γ -aminobutyric acid; NMDA, *N*-methyl-D-aspartate

similar increases in peripheral levels of these cytokines, and peripheral or central delivery of those cytokines to normal rodents increases their susceptibility to chronic stress. These findings have led to the novel idea of using peripheral cytokines as biomarkers of a subtype of depression and the potential utility of developing new antidepressants that oppose the actions of specific cytokines.

Recent evidence has also linked proinflammatory signaling in the brain to addiction, particularly to alcohol. Human alcoholism is associated with impaired innate immunity, increases in circulating proinflammatory cytokines, and increases in brain expression of several immune-related genes. Many of these genes are expressed by astrocytes and microglia, and by neurons under certain pathologic conditions, where they play important roles in modifying neuronal function and plasticity. For example, cytokine monocyte chemotactic protein-1 (MCP-1) modulates the release of certain neurotransmitters and, when administered into the VTA, increases neuronal excitability, promotes dopamine release, and increases locomotor activity. Gene expression studies of alcohol drinking in mice have identified a network of regulated neuroimmune proteins in brain, and a role in regulation of alcohol consumption has been validated for several, including chemokines MCP-1 and chemokine (C-C motif) ligand 3 (CCL3), beta-2 microglobulin, CD14, IL-1 receptor antagonist, and cathepsins S and F. This work has led to discovery of anti-inflammatory medications that reduce alcohol intake in animals, such as antagonists of phosphodiesterase 4, which regulates cAMP availability, or agonists of peroxisome proliferator-activated receptors (PPARs), which are transcription factors that repress key inflammatory signaling molecules such as nuclear factor- κ B (NF- κ B) and nuclear factor of activated T cells (NFAT). A major focus of current research is to define the sites and mechanisms by which proinflammatory cytokines impair brain function to elicit a depressive episode or promote drug abuse.

CONCLUSIONS

This brief narrative illustrates the substantial progress that is being made in understanding the genetic and neurobiological basis of mental illness. It is anticipated that biologic measures will be used increasingly to more accurately diagnose and subtype psychiatric disorders and that targeted therapeutics will become available for these complex conditions.

FURTHER READING

- G MJ et al: The road to precision psychiatry: Translating genetics into disease mechanisms. *Nat Neurosci* 19:1397, 2016.
- K GF, V ND: Neurobiology of addiction: A neurocircuitry analysis. *Lancet Psychiatry* 3:760, 2016.
- R P et al: Targeting neural circuits. *Cell* 165:524, 2016.
- R D, B S: Molecular mechanisms underlying alcohol-drinking behaviours. *Nat Rev Neurosci* 17:576, 2016.
- S SJ et al: Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. *Neuron* 87:1215, 2015.
- S FK et al: Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell* 180:568, 2020.
- W JA et al: Coexpression networks implicate human mid-fetal deep cortical projection neurons in the pathogenesis of autism. *Cell* 155:997, 2013.
- W ES et al: Integrating neuroimmune systems in the neurobiology of depression. *Nat Rev Neurosci* 17:497, 2016.

452 Psychiatric Disorders

Victor I. Reus



Psychiatric disorders are common in medical practice and may present either as a primary disorder or as a comorbid condition. The prevalence of mental or substance use disorders in the United States is ~30%, but only one-third of affected individuals are currently receiving treatment. Global burden of disease statistics indicates that 4 of the 10 most important causes of morbidity and attendant health care costs worldwide are psychiatric in origin.

Changes in health care delivery underscore the need for primary care physicians to assume responsibility for the initial diagnosis and treatment of the most common mental disorders. Prompt diagnosis is essential to ensure that patients have access to appropriate medical services and to maximize the clinical outcome. Validated patient-based questionnaires have been developed that systematically probe for signs and symptoms associated with the most prevalent psychiatric diagnoses and guide the clinician into targeted assessment. The Primary Care Evaluation of Mental Disorders (PRIME-MD; a self-report form, the Patient Health Questionnaire) and the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC) are inventories that require only 10 min to complete and link patient responses to the formal diagnostic criteria of anxiety, mood, somatoform, and eating disorders and to alcohol abuse or dependence. A variety of smart phone apps for assessment and monitoring of psychiatric conditions and for psychological and pharmacologic treatment interventions are also available.

A physician who refers patients to a psychiatrist should know not only when doing so is appropriate but also how to refer because societal misconceptions and the stigma of mental illness impede the process. Primary care physicians should base referrals to a psychiatrist on the presence of signs and symptoms of a mental disorder and not simply on the absence of a physical explanation for a patient's complaint. The physician should discuss with the patient the reasons for requesting the referral or consultation and provide reassurance that he or she will continue to provide medical care and work collaboratively with the mental health professional. Consultation with a psychiatrist or transfer of care is appropriate when physicians encounter evidence of psychotic symptoms, mania, severe depression, or anxiety; symptoms of posttraumatic stress disorder (PTSD); suicidal or homicidal preoccupation; or a failure to respond to first-order treatment. This chapter reviews the clinical assessment and treatment of some of the most common mental disorders presenting in primary care and is based on

the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), the framework for categorizing psychiatric illness used in the United States. [Eating disorders are discussed later in this chapter, and the biology of psychiatric and addictive disorders is discussed in Chap. 451.](#)

■ GLOBAL CONSIDERATIONS

The DSM-5 and the tenth revision of the International Classification of Diseases (ICD-10), which is used more commonly worldwide, have taken somewhat differing approaches to the diagnosis of mental illness, but considerable effort has been expended to provide an operational translation between the two nosologies. Both systems are in essence purely descriptive and emphasize clinical pragmatism, in distinction to the Research Domain Criteria (RDOC) proposed by the National Institute of Mental Health, which aspires to provide a causal framework for classification of behavioral disturbance. None of these diagnostic systems has as yet achieved adequate validation. The Global Burden of Disease Study (2019), using available epidemiologic data, nevertheless has reinforced the conclusion that, regardless of nosologic differences, mental and substance abuse disorders are the major cause of life-years lost to disability among all medical illnesses, affecting >300 million individuals worldwide. There is general agreement that high-income countries will need to build capacity in professional training in low- and middle-income countries in order to provide an adequate balanced care model for the delivery of evidence-based therapies for mental disorders. Recent surveys that indicate a dramatic increase in mental disorder prevalence in rapidly developing countries, such as China, may reflect both an increased recognition of the issue, but also the consequence of social turmoil, stigma, and historically inadequate resources. A salient example of the ways in which societal disruption and isolation may contribute to exacerbating already unmet mental health needs can be seen in the COVID-19 pandemic, which has resulted in an increased incidence of diagnosed psychiatric disorders in both affected and unaffected individuals, as well as caregivers. The need for improved prevention strategies and for more definitive and effective interventional treatments remains a global concern.

ANXIETY DISORDERS

Anxiety disorders, the most prevalent psychiatric illnesses in the general community, are present in 15–20% of medical clinic patients. Anxiety, defined as a subjective sense of unease, dread, or foreboding, can indicate a primary psychiatric condition or can be a component of, or reaction to, a primary medical disease. The primary anxiety disorders are classified according to their duration and course and the existence and nature of precipitants.

When evaluating the anxious patient, the clinician must first determine whether the anxiety antedates or postdates a medical illness or is due to a medication side effect. Approximately one-third of patients presenting with anxiety have a medical etiology for their psychiatric symptoms, but an anxiety disorder can also present with somatic symptoms in the absence of a diagnosable medical condition.

■ PANIC DISORDER

Clinical Manifestations Panic disorder is defined by the presence of recurrent and unpredictable panic attacks, which are distinct episodes of intense fear and discomfort associated with a variety of physical symptoms, including palpitations, sweating, trembling, shortness of breath, chest pain, dizziness, and a fear of impending doom or death. Paresthesias, gastrointestinal distress, and feelings of unreality are also common. Diagnostic criteria require at least 1 month of concern or worry about the attacks or a change in behavior related to them. The lifetime prevalence of panic disorder is 2–3%. Panic attacks have a sudden onset, developing within 10 min and usually resolving over the course of an hour, and they occur in an unexpected fashion. Some may occur when waking from sleep. The frequency and severity of panic attacks vary, ranging from once a week to clusters of attacks separated by months of well-being. The first attack is usually outside the home, and onset is typically in late adolescence to early adulthood. In some individuals, anticipatory anxiety develops over time and results in a

generalized fear and a progressive avoidance of places or situations in which a panic attack might recur. *Agoraphobia*, which occurs commonly in patients with panic disorder, is an acquired irrational fear of being in places where one might feel trapped or unable to escape. It may, however, be diagnosed even if panic disorder is not present. Typically, it leads the patient into a progressive restriction in lifestyle and, in a literal sense, in geography. Frequently, patients are embarrassed that they are housebound and dependent on the company of others to go out into the world and do not volunteer this information; thus, physicians will fail to recognize the syndrome if direct questioning is not pursued.

Differential Diagnosis A diagnosis of panic disorder is made after a medical etiology for the panic attacks has been ruled out. A variety of cardiovascular, respiratory, endocrine, and neurologic conditions can present with anxiety as the chief complaint. Patients with true panic disorder will often focus on one specific feature to the exclusion of others. For example, 20% of patients who present with syncope as a primary medical complaint have a primary diagnosis of a mood, anxiety, or substance abuse disorder, the most common being panic disorder. The differential diagnosis of panic disorder is complicated by a high rate of comorbidity with other psychiatric conditions, especially alcohol and benzodiazepine abuse, which patients initially use in an attempt at self-medication. Some 75% of panic disorder patients will also satisfy criteria for major depression at some point in their illness.

When the history is nonspecific, physical examination and focused laboratory testing must be used to rule out anxiety states resulting from medical disorders such as pheochromocytoma, thyrotoxicosis, or hypoglycemia. Electrocardiogram (ECG) and echocardiogram may detect some cardiovascular conditions associated with panic such as paroxysmal atrial tachycardia and mitral valve prolapse. In two studies, panic disorder was the primary diagnosis in 43% of patients with chest pain who had normal coronary angiograms and was present in 9% of all outpatients referred for cardiac evaluation. Panic disorder has also been diagnosed in many patients referred for pulmonary function testing or with symptoms of irritable bowel syndrome.

Etiology and Pathophysiology The etiology of panic disorder is unknown but appears to involve a genetic predisposition, altered autonomic responsiveness, and social learning. Panic disorder shows familial aggregation; the disorder is concordant in 30–45% of monozygotic twins, and genome-wide screens have identified suggestive risk loci. Acute panic attacks appear to be associated with increased noradrenergic discharges in the locus coeruleus. Intravenous infusion of sodium lactate evokes an attack in two-thirds of panic disorder patients, as do the α -adrenergic antagonist yohimbine, cholecystokinin tetrapeptide (CCK-4), and carbon dioxide inhalation. It is hypothesized that each of these stimuli activates a pathway involving noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe. Resting-state fMRI has identified abnormalities in the default mode network involving the medial temporal lobe, with greater activation in the sensorimotor cortex in panic disorder and in amygdala-frontal connectivity in social anxiety disorder. Agents that block serotonin reuptake can prevent attacks. Patients with panic disorder have a heightened sensitivity to somatic symptoms, which triggers increasing arousal, setting off the panic attack; accordingly, therapeutic intervention involves altering the patient's cognitive interpretation of anxiety-producing experiences as well as preventing the attack itself.

TREATMENT

Panic Disorder

Achievable goals of treatment are to decrease the frequency of panic attacks and to reduce their intensity. The cornerstone of drug therapy is antidepressant medication ([Tables 452-1 through 452-3](#)). Selective serotonin reuptake inhibitors (SSRIs) benefit the majority of panic disorder patients and do not have the adverse effects of tricyclic antidepressants (TCAs). Fluoxetine, paroxetine, sertraline, and the selective serotonin-norepinephrine reuptake inhibitor

TABLE 452-1 Antidepressants

Name	Usual Daily Dose (mg)	Side Effects	Comments
SSRIs			
Fluoxetine (Prozac)	10–80	Headache; nausea and other GI effects; jitteriness; insomnia; sexual dysfunction; can affect plasma levels of other medicines (except sertraline); akathisia rare	Once-daily dosing, usually in the morning; fluoxetine has very long half-life; must not be combined with MAOIs
Sertraline (Zoloft)	50–200		
Paroxetine (Paxil)	20–60		
Fluvoxamine (Luvox)	100–300		
Citalopram (Celexa)	20–60		
Escitalopram (Lexapro)	10–30		
TCAs and Tetracyclics			
Amitriptyline (Elavil)	150–300	Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision); sweating; tremor; postural hypotension; cardiac conduction delay; sedation; weight gain	Once-daily dosing, usually qhs; blood levels of most TCAs available; can be lethal in overdose (lethal dose = 2 g); nortriptyline best tolerated, especially by elderly
Nortriptyline (Pamelor)	50–200		
Imipramine (Tofranil)	150–300		
Desipramine (Norpramin)	150–300		
Doxepin (Sinequan)	150–300	Nausea, anxiety, dry mouth	FDA-approved for OCD
Gomipramine (Anafranil)	150–300		
Maprotiline (Ludiomil)	25–150		
Protriptyline (Vivactil)	15–40	Drowsiness, constipation, dry mouth	TID or QID dosing required
Trimipramine (Surmontil)	75–200		
Amoxapine (Asendin)	100–300		Lethality in OD, EPS possible
Mixed Norepinephrine/Serotonin Reuptake Inhibitors (SNRI) and Receptor Blockers			
Venlafaxine (Effexor), XR	75–375	Nausea; dizziness; dry mouth; headaches; increased blood pressure; anxiety and insomnia	Bid–tid dosing (extended-release available); lower potential for drug interactions than SSRIs; contraindicated with MAOIs
Desvenlafaxine (Pristiq)	50–400	Nausea, dizziness, insomnia	Primary metabolite of venlafaxine; no increased efficacy with higher dosing
Duloxetine (Cymbalta)	40–60	Nausea, dizziness, headache, insomnia, constipation	May have utility in treatment of neuropathic pain and stress incontinence
Mirtazapine (Remeron)	15–45	Somnolence, weight gain; neutropenia rare	Once-a-day dosing; 5HT3 antagonist
Vilazodone (Viibryd)	40	Nausea, diarrhea, headache; dosage adjustment if given with CYP3A4 inhibitor/stimulator	Also 5-HT _{1a} receptor partial agonist
Vortioxetine (Trintellix)	5–20	Nausea, diarrhea, sweating, headache; low incidence of sedation or weight gain	No specific p450 effects; 5-HT _{3a} and 5-HT _{1b} receptor antagonist, 5-HT _{1b} partial agonist, and 5-HT _{1a} agonist
Levomilnacipran (Fetzima)	40–120	Nausea, constipation, sweating; rare increase in blood pressure/pulse	Most noradrenergic of SNRIs
Mixed-Action Drugs			
Bupropion (Wellbutrin), CR, XR	250–450	Jitteriness; flushing; seizures in at-risk patients; anorexia; tachycardia; psychosis	Tid dosing, but sustained-release also available; fewer sexual side effects than SSRIs or TCAs; may be useful for adult ADD
Trazodone (Desyrel)	200–600	Sedation; dry mouth; ventricular irritability; postural hypotension; priapism rare	Useful in low doses for sleep because of sedating effects with no anticholinergic side effects
Trazodone extended-release (Oleptro)	150–375	Daytime somnolence, dizziness, nausea	
Nefazodone	300–600	Headache, nausea, dizziness	Rare risk of liver failure, priapism
MAOIs			
Phenelzine (Nardil)	45–90	Insomnia; hypotension; edema; anorgasmia; weight gain; neuropathy; hypertensive crisis; toxic reactions with SSRIs; narcotics	May be more effective in patients with atypical features or treatment-refractory depression
Tranylcypromine (Parnate)	20–50		
Isocarboxazid (Marplan)	20–60		Less weight gain and hypotension than phenelzine
Transdermal selegiline (Emsam)	6–12	Local skin reaction, hypertension	No dietary restrictions with 6-mg dose

Abbreviations: ADD, attention deficit disorder; EPS, extrapyramidal symptoms; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; MAOIs, monoamine oxidase inhibitors; OCD, obsessive-compulsive disorder; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

(SNRI) venlafaxine have received approval from the U.S. Food and Drug Administration (FDA) for this indication. These drugs should be started at one-third to one-half of their usual antidepressant dose (e.g., 5–10 mg fluoxetine, 25–50 mg sertraline, 10 mg paroxetine, venlafaxine 37.5 mg). Monoamine oxidase inhibitors (MAOIs) are also effective and may specifically benefit patients who have comorbid features of atypical depression (i.e., hypersomnia and weight gain). Insomnia, orthostatic hypotension, and the need to maintain a low-tyramine diet (avoidance of cheese and wine) have limited their use, however. Antidepressants typically take 2–6 weeks

to become effective, and doses may need to be adjusted based on the clinical response.

Because of anticipatory anxiety and the need for immediate relief of panic symptoms, benzodiazepines are useful early in the course of treatment and sporadically thereafter (Table 452-4). FDA-approved agents include alprazolam and clonazepam. A recent Cochrane review found no difference between antidepressants and benzodiazepines in response rate, although benzodiazepines were somewhat better tolerated by patients. In treatment-resistant cases, short-term augmentation with aripiprazole,

TABLE 452-2 Management of Antidepressant Side Effects

SYMPTOMS	COMMENTS AND MANAGEMENT STRATEGIES
Gastrointestinal	Nausea, loss of appetite Usually short-lived and dose-related; consider temporary dose reduction or administration with food and antacids
	Diarrhea Famotidine, 20–40 mg/d
	Constipation Wait for tolerance; try diet change, stool softener, exercise; avoid laxatives
Sexual dysfunction	Consider dose reduction; drug holiday
	Anorgasmia/impotence; impaired ejaculation Bethanechol, 10–20 mg, 2 h before activity, or cyproheptadine, 4–8 mg, 2 h before activity, or bupropion, 100 mg bid, or amantadine, 100 mg bid/tid
Orthostasis	Tolerance unlikely; increase fluid intake, use calf exercises/support hose; fludrocortisone, 0.025 mg/d
Anticholinergic	Wait for tolerance
Dry mouth, eyes	Maintain good oral hygiene; use artificial tears, sugar-free gum
Tremor/jitteriness	Antiparkinsonian drugs not effective; use dose reduction/slow increase; lorazepam, 0.5 mg bid, or propranolol, 10–20 mg bid
Insomnia	Schedule all doses for the morning; trazodone, 50–100 mg qhs
Sedation	Caffeine; schedule all dosing for bedtime; bupropion, 75–100 mg in afternoon
Headache	Evaluate diet, stress, other drugs; try dose reduction; amitriptyline, 50 mg/d
Weight gain	Decrease carbohydrates; exercise; consider fluoxetine
Loss of therapeutic benefit over time	Related to tolerance? Increase dose or drug holiday; add amantadine, 100 mg bid, buspirone, 10 mg tid, or pindolol, 2.5 mg bid

divalproex sodium, or pindolol has some evidence for efficacy. There also is no clear difference in short-term efficacy between psychological therapies and antidepressant or benzodiazepine treatment, alone or in combination.

Early psychotherapeutic intervention and education aimed at symptom control enhance the effectiveness of drug treatment. Patients can be taught breathing techniques, be educated about physiologic changes that occur with panic, and learn to expose themselves voluntarily to precipitating events in a treatment program spanning 12–15 sessions. Homework assignments and monitored compliance are important components of successful treatment. Once patients have achieved a satisfactory response, drug treatment should be maintained for 1–2 years to prevent relapse. Controlled

trials indicate a success rate of 75–85%, although the likelihood of complete remission is somewhat lower.

■ GENERALIZED ANXIETY DISORDER

Clinical Manifestations Patients with generalized anxiety disorder (GAD) have persistent, excessive, and/or unrealistic worry associated with muscle tension, impaired concentration, autonomic arousal, feeling “on edge” or restless, and insomnia (**Table 452-5**). Onset is usually before age 20 years, and a history of childhood fears and social inhibition may be present. The lifetime prevalence of GAD is 5–6%; the risk is higher in first-degree relatives of patients with the diagnosis. Interestingly, family studies indicate that GAD and panic disorder segregate independently. More than 80% of patients with GAD also suffer from major depression, dysthymia, or social phobia. Comorbid substance abuse is common in these patients, particularly alcohol and/or sedative/hypnotic abuse. Patients with GAD worry excessively over minor matters, with life-disrupting effects; unlike in panic disorder, complaints of shortness of breath, palpitations, and tachycardia are relatively rare.

Etiology and Pathophysiology Most anxiogenic and anxiolytic agents act on the γ -aminobutyric acid (GABA)_A receptor/chloride ion channel complex, implicating this neurotransmitter system in the pathogenesis of anxiety and panic attacks. Benzodiazepines are thought to bind to two separate GABA_A receptor sites: type I, which has a broad neuroanatomic distribution, and type II, which is concentrated in the hippocampus, striatum, and neocortex. The antianxiety effects of the various benzodiazepines are influenced by their relative binding to alpha 2 and 3 subunits of the GABA_A receptor, and sedation and memory impairment to the alpha 1 subunit. Serotonin (5-hydroxytryptamine [5-HT]), and 3 α -reduced neuroactive steroids (allosteric modulators of GABA_A) also appear to have a role in anxiety, and buspirone, a partial 5-HT_{1A} receptor agonist, and certain 5-HT_{2A} and 5-HT_{2C} receptor antagonists (e.g., mirtazapine and nefazodone) may have beneficial effects.

TREATMENT

Generalized Anxiety Disorder

A combination of pharmacologic and psychotherapeutic interventions is most effective in GAD, but complete symptomatic relief is rare. A short course of a benzodiazepine is usually indicated, preferably lorazepam, oxazepam, clonazepam or, alprazolam, although only the last two are FDA approved. (The first two of these agents are metabolized via conjugation rather than oxidation and thus do not accumulate if hepatic function is impaired; the latter also has limited active metabolites.) Treatment should be initiated at the lowest dose possible and prescribed on an as-needed basis as symptoms warrant. Benzodiazepines differ in their milligram per kilogram potency, half-life, lipid solubility, metabolic pathways, and presence of active metabolites. Agents that are absorbed rapidly and are lipid soluble, such as diazepam, have a rapid onset of action and a higher abuse potential. Benzodiazepines should generally not be prescribed for >4–6 weeks because of the development of tolerance and the serious risk of abuse and dependence. Withdrawal must be closely monitored as relapses can occur. It is important to warn patients that concomitant use of alcohol or other sedating drugs may exacerbate side effects and impair their ability to function. An optimistic approach that encourages the patient to clarify environmental precipitants, anticipate his or her reactions, and plan effective response strategies is an essential element of therapy.

Adverse effects of benzodiazepines generally parallel their relative half-lives. Longer-acting agents, such as diazepam, chlorodiazepoxide, flurazepam, and clonazepam, tend to accumulate active metabolites, with resultant sedation, impairment of cognition, and poor psychomotor performance. Shorter-acting compounds, such as alprazolam, lorazepam, and oxazepam, can produce daytime anxiety, early-morning insomnia, and, with discontinuation,

TABLE 452-3 Possible Drug Interactions with Selective Serotonin Reuptake Inhibitors

AGENT	EFFECT
Monoamine oxidase inhibitors	Serotonin syndrome—absolute contraindication
Serotonergic agonists, e.g., tryptophan, fenfluramine, triptans	Potential serotonin syndrome
Drugs that are metabolized by P450 isoenzymes: tricyclics, other SSRIs, antipsychotics, beta blockers, codeine, triazolobenzodiazepines, calcium channel blockers	Delayed metabolism resulting in increased blood levels and potential toxicity
Drugs that are bound tightly to plasma proteins, e.g., warfarin	Increased bleeding secondary to displacement
Drugs that inhibit the metabolism of SSRIs by P450 isoenzymes, e.g., quinidine	Increased SSRI side effects

Abbreviation: SSRIs, selective serotonin reuptake inhibitors.

TABLE 452-4 Anxiolytics

Name	Equivalent PO Dose (mg)	Onset of Action	Half-life (h)	Comments
Benzodiazepines				
Diazepam (Valium)	5	Fast	20–70	Active metabolites; quite sedating
Flurazepam (Dalmane)	15	Fast	30–100	Flurazepam is a prodrug; metabolites are active; quite sedating
Triazolam (Halcion)	0.25	Intermediate	1.5–5	No active metabolites; can induce confusion and delirium, especially in elderly
Lorazepam (Ativan)	1	Intermediate	10–20	No active metabolites; direct hepatic glucuronide conjugation; quite sedating; FDA-approved for anxiety with depression
Alprazolam (Xanax)	0.5	Intermediate	12–15	Active metabolites; not too sedating; FDA-approved for panic disorder and anxiety with depression; tolerance and dependence develop easily; difficult to withdraw
Chlordiazepoxide (Librium)	10	Intermediate	5–30	Active metabolites; moderately sedating
Oxazepam (Serax)	15	Slow	5–15	No active metabolites; direct glucuronide conjugation; not too sedating
Temazepam (Restoril)	15	Slow	9–12	No active metabolites; moderately sedating
Clonazepam (Klonopin)	0.5	Slow	18–50	No active metabolites; moderately sedating; FDA-approved for panic disorder
Clorazepate (Tranxene)	15	Fast	40–200	Low sedation; unreliable absorption
Nonbenzodiazepines				
Buspirone (BuSpar)	7.5	2 weeks	2–3	Active metabolites; tid dosing—usual daily dose 10–20 mg tid; nonsedating; no additive effects with alcohol; useful for controlling agitation in demented or brain-injured patients

Abbreviation: FDA, U.S. Food and Drug Administration.

rebound anxiety and insomnia. Although patients develop tolerance to the sedative effects of benzodiazepines, they are less likely to habituate to the adverse psychomotor effects. Withdrawal from the longer half-life benzodiazepines can be accomplished through gradual, stepwise dose reduction (by 10% every 1–2 weeks) over 6–12 weeks. It is usually more difficult to taper patients off shorter-acting benzodiazepines. Physicians may need to switch the patient to a benzodiazepine with a longer half-life or use an adjunctive medication such as a beta blocker or carbamazepine, before attempting to discontinue the benzodiazepine. Withdrawal reactions vary in severity and duration; they can include depression, anxiety, lethargy, diaphoresis, autonomic arousal, and, rarely, seizures.

Buspirone is a nonbenzodiazepine anxiolytic agent. It is nonsedating, does not produce tolerance or dependence, does not interact with benzodiazepine receptors or alcohol, and has no abuse or disinhibition potential. However, it requires several weeks to take

effect and requires thrice-daily dosing. Patients who were previously responsive to a benzodiazepine are unlikely to rate buspirone as equally effective, but patients with head injury or dementia who have symptoms of anxiety and/or agitation may do well with this agent. Escitalopram, paroxetine, duloxetine, and venlafaxine are FDA approved for the treatment of GAD, usually at doses that are comparable to their efficacy in major depression, and may be preferable to usage of benzodiazepines in the treatment of chronic anxiety. Benzodiazepines are contraindicated during pregnancy and breast-feeding.

Anticonvulsants with GABAergic properties may also be effective against anxiety. Gabapentin, oxcarbazepine, tiagabine, pregabalin, and divalproex have all shown some degree of benefit in a variety of anxiety-related syndromes in off-label usage.

TABLE 452-5 Diagnostic Criteria for Generalized Anxiety Disorder

- A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
- B. The individual finds it difficult to control the worry.
- C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months): (1) restlessness or feeling keyed up or on edge; (2) being easily fatigued; (3) difficulty concentrating or mind going blank; (4) irritability; (5) muscle tension; (6) sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
- D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
- F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Source: Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (Copyright © 2013). American Psychiatric Association. All Rights Reserved.

PHOBIC DISORDERS

Clinical Manifestations The cardinal feature of phobic disorders is a marked and persistent fear of objects or situations, exposure to which results in an immediate anxiety reaction. The patient avoids the phobic stimulus, and this avoidance usually impairs occupational or social functioning. Panic attacks may be triggered by the phobic stimulus or may occur spontaneously. Unlike patients with other anxiety disorders, individuals with phobias usually experience anxiety only in specific situations. Common phobias include fear of closed spaces (claustrophobia), fear of blood, and fear of flying. Social phobia is distinguished by a specific fear of social or performance situations in which the individual is exposed to unfamiliar individuals or to possible examination and evaluation by others. Examples include having to converse at a party, use public restrooms, and meet strangers. In each case, the affected individual is aware that the experienced fear is excessive and unreasonable given the circumstance. The specific content of a phobia may vary across gender, ethnic, and cultural boundaries.

Phobic disorders are common, affecting ~7–9% of the population. Twice as many females are affected than males. Full criteria for diagnosis are usually satisfied first in early adulthood, but behavioral avoidance of unfamiliar people, situations, or objects dating from early childhood is common.

In one study of female twins, concordance rates for agoraphobia, social phobia, and animal phobia were found to be 23% for monozygotic twins and 15% for dizygotic twins. A twin study of fear conditioning, a model for the acquisition of phobias, demonstrated a heritability of 35–45%. Animal studies of fear conditioning have indicated that

processing of the fear stimulus occurs through the lateral nucleus of the amygdala, extending through the central nucleus and projecting to the periaqueductal gray region, lateral hypothalamus, and paraventricular hypothalamus.

TREATMENT

Phobic Disorders

Beta blockers (e.g., propranolol, 20–40 mg orally 2 h before the event) are particularly effective in the treatment of “performance anxiety” (but not general social phobia) and appear to work by blocking the peripheral manifestations of anxiety such as perspiration, tachycardia, palpitations, and tremor. MAOIs alleviate social phobia independently of their antidepressant activity, and paroxetine, sertraline, fluvoxamine CR, and venlafaxine XR have received FDA approval for treatment of social anxiety. Benzodiazepines can be helpful in reducing fearful avoidance, but the chronic nature of phobic disorders limits their usefulness.

Behaviorally focused psychotherapy is an important component of treatment because relapse rates are high when medication is used as the sole treatment. Cognitive-behavioral strategies are based

on the finding that distorted perceptions and interpretations of fear-producing stimuli play a major role in perpetuation of phobias. Individual and group therapy sessions teach the patient to identify specific negative thoughts associated with the anxiety-producing situation and help to reduce the patient’s fear of loss of control. In desensitization therapy, hierarchies of feared situations are constructed, and the patient is encouraged to pursue and master gradual exposure to the anxiety-producing stimuli.

Patients with social phobia, in particular, have a high rate of comorbid alcohol abuse, as well as of other psychiatric conditions (e.g., eating disorders), necessitating the need for parallel management of each disorder if anxiety reduction is to be achieved.

■ STRESS DISORDERS

Clinical Manifestations Patients may develop anxiety after exposure to extreme traumatic events such as the threat of personal death or injury or the death of a loved one. The reaction may occur shortly after the trauma (*acute stress disorder*) or be delayed and subject to recurrence (PTSD) (Table 452-6). In both syndromes, individuals experience associated symptoms of detachment and loss of emotional responsiveness. The patient may feel depersonalized and unable to recall

TABLE 452-6 Diagnostic Criteria for Posttraumatic Stress Disorder

- A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
 - 1. Directly experiencing the traumatic event(s).
 - 2. Witnessing, in person, the event(s) as it occurred to others.
 - 3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
 - 4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).
- B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
 - 1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
 - 2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).
 - 3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)
 - 4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
 - 5. Marked physiologic reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
- C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
 - 1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
 - 2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
- D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred as evidenced by two (or more) of the following:
 - 1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
 - 2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., “I am bad,” “No one can be trusted,” “The world is completely dangerous,” “My whole nervous system is permanently ruined”).
 - 3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
 - 4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
 - 5. Markedly diminished interest or participation in significant activities.
 - 6. Feelings of detachment or estrangement from others.
 - 7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).
- E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
 - 1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
 - 2. Reckless or self-destructive behavior.
 - 3. Hypervigilance.
 - 4. Exaggerated startle response.
 - 5. Problems with concentration.
 - 6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).
- F. Duration of the disturbance (criteria B, C, D, and E) is >1 month.
- G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- H. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication, alcohol) or another medical condition.

Source: Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (Copyright © 2013). American Psychiatric Association. All Rights Reserved.

specific aspects of the trauma, although typically it is reexperienced through intrusions in thought, dreams, or flashbacks, particularly when cues of the original event are present. Patients often actively avoid stimuli that precipitate recollections of the trauma and demonstrate a resulting increase in vigilance, arousal, and startle response. Patients with stress disorders are at risk for the development of other disorders related to anxiety, mood, and substance abuse (especially alcohol). Between 5 and 10% of Americans will at some time in their life satisfy criteria for PTSD, with women more likely to be affected than men. A validated four-item screen for PTSD (PC-PTSD) is available.

Risk factors for the development of PTSD include a past psychiatric history and personality characteristics of high neuroticism and extroversion. Twin studies show a substantial genetic influence on all symptoms associated with PTSD, with less evidence for an environmental effect.

Etiology and Pathophysiology It is hypothesized that in PTSD there is excessive release of norepinephrine from the locus coeruleus in response to stress and increased noradrenergic activity at projection sites in the hippocampus and amygdala. These changes theoretically facilitate the encoding of fear-based memories. Greater sympathetic responses to cues associated with the traumatic event occur in PTSD, although pituitary adrenal responses are blunted. In addition to fear learning, changes in threat detection (insula overactivity), executive function, emotional regulation, and contextual learning have been documented. Predictive biomarkers include increased heart rate and serum lactate, decreased coagulation, insulin resistance, and alterations in glycolysis and fatty acid uptake.

TREATMENT

Stress Disorders

Acute stress reactions are usually self-limited, and treatment typically involves the short-term use of benzodiazepines and supportive/expressive psychotherapy. The chronic and recurrent nature of PTSD, however, requires a more complex approach using drug and behavioral treatments. PTSD is highly correlated with peritraumatic dissociative symptoms and the development of an acute stress disorder at the time of the trauma. The SSRIs (paroxetine and sertraline are FDA approved for PTSD), venlafaxine, fluoxetine, and topiramate can all reduce anxiety, symptoms of intrusion, and avoidance behaviors. Recently, the psychedelic agent MDMA demonstrated efficacy as an adjunct to intensive psychotherapeutic intervention, as did stellate ganglion block. Low-dose trazodone and mirtazapine, sedating antidepressants, are frequently used at night to help with insomnia. Benzodiazepines and SSRIs, however, should not be given in the early aftermath of trauma. Psychotherapeutic strategies for PTSD help the patient overcome avoidance behaviors and demoralization and master fear of recurrence of the trauma; therapies that encourage the patient to dismantle avoidance behaviors through stepwise focusing on the experience of the traumatic event, such as trauma-focused cognitive-behavioral and processing therapy and prolonged exposure therapy utilizing augmented or virtual reality are the most effective. Debriefing after the traumatic event does not prevent PTSD and may exacerbate symptoms.

OBSESSIVE-COMPULSIVE DISORDER

Clinical Manifestations Obsessive-compulsive disorder (OCD) is characterized by obsessive thoughts and compulsive behaviors that impair everyday functioning. Fears of contamination and germs are common, as are handwashing, counting behaviors, and having to check and recheck such actions as whether a door is locked. The degree to which the disorder is disruptive for the individual varies, but in all cases, obsessive-compulsive activities take up >1 h per day and are undertaken to relieve the anxiety triggered by the core fear. Patients often conceal their symptoms, usually because they are embarrassed by the content of their thoughts or the nature of their actions. Physicians

must ask specific questions regarding recurrent thoughts and behaviors, particularly if physical clues such as chafed and reddened hands or patchy hair loss (from repetitive hair pulling, or trichotillomania) are present. Comorbid conditions are common, the most frequent being depression, other anxiety disorders, eating disorders, and tics. OCD has a lifetime prevalence of 2–3% worldwide. Onset is usually gradual, beginning in early adulthood, but childhood onset is not rare. The disorder usually has a waxing and waning course, but some cases may show a steady deterioration in psychosocial functioning.

Etiology and Pathophysiology A genetic contribution to OCD is suggested by twin studies, but no susceptibility gene for OCD has been identified to date. Insulin signaling has been implicated in some recent reports. Family studies show an aggregation of OCD with Tourette's disorder, and both are more common in males and in first-born children.

The anatomy of obsessive-compulsive behavior is thought to include the orbital frontal cortex, caudate nucleus, and globus pallidus. The caudate nucleus appears to be involved in the acquisition and maintenance of habit and skill learning, and interventions that are successful in reducing obsessive-compulsive behaviors also decrease metabolic activity measured in the caudate.

TREATMENT

Obsessive-Compulsive Disorder

Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline are approved for the treatment of OCD in adults (and all but paroxetine are also approved for children). Clomipramine is a TCA that is often tolerated poorly owing to anticholinergic and sedative side effects at the doses required to treat the illness (25–250 mg/d); its efficacy in OCD is unrelated to its antidepressant activity. Fluoxetine (5–60 mg/d), fluvoxamine (25–300 mg/d), paroxetine (40–60 mg/d), and sertraline (50–150 mg/d) are as effective as clomipramine and have a more benign side-effect profile. Venlafaxine and duloxetine also have shown efficacy but are not FDA approved. Only 50–60% of patients with OCD show adequate improvement with pharmacotherapy alone. In treatment-resistant cases, augmentation with other serotonergic agents such as buspirone, or with a neuroleptic or benzodiazepine, may be beneficial, and in severe cases, deep-brain stimulation has been found to be effective. When a therapeutic response is achieved, long-duration maintenance therapy is usually indicated.

For many individuals, particularly those with time-consuming compulsions, behavior therapy and exposure response prevention will result in as much improvement as that afforded by medication. Effective techniques include the gradual increase in exposure to stressful situations, maintenance of a diary to clarify stressors, and homework assignments that substitute new activities for compulsive behaviors.

MOOD DISORDERS

Mood disorders are characterized by a disturbance in the regulation of mood, behavior, and affect. Mood disorders are subdivided into (1) depressive disorders, (2) bipolar disorders, and (3) depression in association with medical illness or alcohol and substance abuse ([Chaps. 453 through 457](#)). Major depressive disorder (MDD) is differentiated from bipolar disorder by the absence of a manic or hypomanic episode. The relationship between pure depressive syndromes and bipolar disorders is not well understood; MDD is more frequent in families of bipolar individuals, but the reverse is not true. In the most recent Global Burden of Disease Study conducted by the World Health Organization (2019), depression was the single largest factor contributing to disability, which had increased 61% as measured by disability-adjusted life-years (DALYs) since 1990. Moreover, the COVID pandemic has been associated with a major increase in reported symptoms of depression and anxiety worldwide. In the United States, lost productivity directly related to mood disorders has been estimated at \$55.1 billion per year.

■ DEPRESSION IN ASSOCIATION WITH MEDICAL ILLNESS

Depression occurring in the context of medical illness is difficult to evaluate. Depressive symptomatology may reflect the psychological stress of coping with the disease, may be caused by the disease process itself or by the medications used to treat it, or may simply coexist in time with the medical diagnosis.

Virtually every class of *medication* includes some agent that can induce depression. Antihypertensive drugs, anticholesterolemic agents, and antiarrhythmic agents are common triggers of depressive symptoms. Iatrogenic depression should also be considered in patients receiving glucocorticoids, antimicrobials, systemic analgesics, anti-parkinsonian medications, and anticonvulsants. To decide whether a causal relationship exists between pharmacologic therapy and a patient's change in mood, it may sometimes be necessary to undertake an empirical trial of an alternative medication.

Between 20–30% of *cardiac* patients manifest a depressive disorder; an even higher percentage experience depressive symptomatology when self-reporting scales are used. Depressive symptoms following unstable angina, myocardial infarction, cardiac bypass surgery, or heart transplant impair rehabilitation and are associated with higher rates of mortality and medical morbidity. Depressed patients often show decreased variability in heart rate (an index of reduced parasympathetic nervous system activity), which may predispose individuals to ventricular arrhythmia and increased morbidity. Depression also appears to increase the risk of coronary heart disease, possibly through increased platelet aggregation. TCAs are contraindicated in patients with bundle branch block, and TCA-induced tachycardia is an additional concern in patients with congestive heart failure. SSRIs appear not to induce ECG changes or adverse cardiac events and thus are reasonable first-line drugs for patients at risk for TCA-related complications. SSRIs may interfere with hepatic metabolism of anticoagulants, however, causing increased anticoagulation.

In patients with *cancer*, the mean prevalence of depression is 25%, but depression occurs in 40–50% of patients with cancers of the pancreas or oropharynx. This association is not due to the effect of cachexia alone, as the higher prevalence of depression in patients with pancreatic cancer persists when compared to those with advanced gastric cancer. Initiation of antidepressant medication in cancer patients has been shown to improve quality of life as well as mood. Psychotherapeutic approaches, particularly group therapy, may have some effect on short-term depression, anxiety, and pain symptoms.

Depression occurs frequently in patients with *neurologic disorders*, particularly cerebrovascular disorders, Parkinson's disease, dementia, multiple sclerosis, and traumatic brain injury. One in five patients with left-hemisphere stroke involving the dorsolateral frontal cortex experiences major depression. Late-onset depression in otherwise cognitively normal individuals increases the risk of a subsequent diagnosis of Alzheimer's disease. All classes of antidepressant agents are effective against these depressions, as are, in some cases, stimulant compounds. SNRIs such as duloxetine or levomilnacipran may be more effective in depression associated with chronic pain.

The reported prevalence of depression in patients with *diabetes mellitus* varies from 8–27%, with the severity of the mood state correlating with the level of hyperglycemia and the presence of diabetic complications. Treatment of depression may be complicated by effects of antidepressive agents on glycemic control. MAOIs can induce hypoglycemia and weight gain, whereas TCAs can produce hyperglycemia and carbohydrate craving. SSRIs and SNRIs, like MAOIs, may reduce fasting plasma glucose, but are easier to use and may also improve dietary and medication compliance.

Hypothyroidism is frequently associated with features of depression, most commonly depressed mood and memory impairment. Hyperthyroid states may also present in a similar fashion, usually in geriatric populations. Improvement in mood usually follows normalization of thyroid function, but adjunctive antidepressant medication is sometimes required. Patients with subclinical hypothyroidism can also experience symptoms of depression and cognitive difficulty that respond to thyroid replacement.

The lifetime prevalence of depression in *HIV-positive* individuals has been estimated at 22–45%. The relationship between depression and disease progression is multifactorial and likely to involve psychological and social factors, alterations in immune function, and central nervous system (CNS) disease. Chronic hepatitis C infection is also associated with depression, which may worsen with interferon- α treatment.

Some chronic disorders of uncertain etiology, such as chronic fatigue syndrome (Chap. 450) and fibromyalgia (Chap. 373), are strongly associated with depression and anxiety; patients may benefit from antidepressant treatment or anticonvulsant agents such as pregabalin.

■ DEPRESSIVE DISORDERS

Clinical Manifestations Major depression is defined as depressed mood on a daily basis for a minimum duration of 2 weeks (Table 452-7). An episode may be characterized by sadness, indifference, apathy, or irritability and is usually associated with changes in sleep patterns, appetite, and weight; motor agitation or retardation; fatigue; impaired concentration and decision-making; feelings of shame or guilt; and thoughts of death or dying. Patients with depression have a profound loss of pleasure in all enjoyable activities, exhibit early-morning awakening, feel that the dysphoric mood state is qualitatively different from sadness, and often notice a diurnal variation in mood (worse in morning hours). Patients experiencing bereavement or grief may exhibit many of the same signs and symptoms of major depression, although the emphasis is usually on feelings of emptiness and loss, rather than anhedonia and loss of self-esteem, and the duration is usually limited. In certain cases, however, the diagnosis of major depression may be warranted even in the context of a significant loss.

TABLE 452-7 Criteria for a Major Depressive Episode

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. (Note: Do not include symptoms that are clearly attributable to another medical condition.)
 - 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).
 - 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
 - 3. Significant weight loss when not dieting or weight gain (e.g., a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day.
 - 4. Insomnia or hypersomnia nearly every day.
 - 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
 - 6. Fatigue or loss of energy nearly every day.
 - 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
 - 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
 - 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The episode is not attributable to the physiologic effects of a substance or to another medical condition.
- D. The occurrence of the major depressive episode is not better explained by seasonal affective disorder, schizophrenia, schizopreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- E. There has never been a manic episode or a hypomanic episode.

Source: Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (Copyright © 2013). American Psychiatric Association. All Rights Reserved.

Approximately 15% of the population experiences a major depressive episode at some point in life, and 6–8% of all outpatients in primary care settings satisfy diagnostic criteria for the disorder. Depression is often undiagnosed, and even more frequently, it is treated inadequately. If a physician suspects the presence of a major depressive episode, the initial task is to determine whether it represents unipolar or bipolar depression or is one of the 10–15% of cases that are secondary to general medical illness or substance abuse. Physicians should also assess the risk of suicide by direct questioning, as patients are often reluctant to verbalize such thoughts without prompting. If specific plans are uncovered or if significant risk factors exist (e.g., a past history of suicide attempts, profound hopelessness, concurrent medical illness, substance abuse, or social isolation), the patient must be referred to a mental health specialist for immediate care. The physician should specifically probe each of these areas in an empathic and hopeful manner, being sensitive to denial and possible minimization of distress. The presence of anxiety, panic, or agitation significantly increases near-term suicidal risk. Approximately 4–5% of all depressed patients will commit suicide; most will have sought help from physicians within 1 month of their deaths.

In some depressed patients, the mood disorder does not appear to be episodic and is not clearly associated with either psychosocial dysfunction or change from the individual's usual experience in life. Persistent depressive disorder (*dysthymic disorder*) consists of a pattern of chronic (at least 2 years), ongoing depressive symptoms that are usually less severe and/or less numerous than those found in major depression, but the functional consequences may be equivalent to or even greater; the two conditions are sometimes difficult to separate and can occur together ("double depression"). Many patients who exhibit a profile of pessimism, disinterest, and low self-esteem respond to antidepressant treatment. Persistent and chronic depressive disorders occur in ~2% of the general population.

Depression is approximately twice as common in women as in men, and the incidence increases with age in both sexes. Twin studies indicate that the liability to major depression of early onset (before age 25 years) is largely genetic in origin. Negative life events can precipitate and contribute to depression, but genetic factors influence the sensitivity of individuals to these stressful events. In most cases, both biologic and psychosocial factors are involved in the precipitation and unfolding of depressive episodes. The most potent stressors appear to involve death of a relative, assault, or severe marital or relationship problems.

Unipolar depressive disorders usually begin in early adulthood and recur episodically over the course of a lifetime. The best predictor of future risk is the number of past episodes; 50–60% of patients who have a first episode have at least one or two recurrences. Some patients experience multiple episodes that become more severe and frequent over time. The duration of an untreated episode varies greatly, ranging from a few months to ≥1 year. The pattern of recurrence and clinical progression in a developing episode are also variable. Within an individual, the nature of episodes (e.g., specific presenting symptoms, frequency, and duration) may be similar over time. In a minority of patients, a severe depressive episode may progress to a psychotic state and in elderly patients, depressive symptoms can be associated with cognitive deficits mimicking dementia ("pseudodementia"). A seasonal pattern of depression, called *seasonal affective disorder*, may manifest with onset and remission of episodes at predictable times of the year. This disorder is more common in women, with symptoms of anergy, fatigue, weight gain, hypersomnia, and episodic carbohydrate craving. The prevalence increases with distance from the equator, and improvement may occur by altering light exposure.

Etiology and Pathophysiology Although evidence for genetic transmission of unipolar depression is not as strong as in bipolar disorder, monozygotic twins have a higher concordance rate (46%) than dizygotic siblings (20%), with little support for any effect of a shared family environment. Large-scale genome-wide association studies (GWAS) involving hundreds of thousands of cases and controls have identified several hundred loci across the genome, some of which are unique to major depression, but others of which overlap with findings

from disparate psychiatric disorders, indicating possible pleiotropy. Epigenetic changes are also likely to contribute to risk.

Neuroendocrine abnormalities that reflect the neurovegetative signs and symptoms of depression include increased cortisol and corticotropin-releasing hormone (CRH) secretion, a decreased inhibitory response of glucocorticoids to dexamethasone, and a blunted response of thyroid-stimulating hormone (TSH) level to infusion of thyroid-releasing hormone (TRH). Antidepressant treatment leads to normalization of these abnormalities. Major depression is also associated with changes in levels of proinflammatory cytokines and neurotrophins, an increase in measures of oxidative stress and cellular aging, telomere shortening, epigenetic changes, and mitochondrial dysfunction. Alterations in the gut microbiome may also be involved.

Diurnal variations in symptom severity and alterations in circadian rhythmicity of a number of neurochemical and neurohumoral factors suggest that a primary defect may be present in regulation of biologic rhythms. Patients with major depression show consistent findings of a decrease in rapid eye movement (REM)–sleep onset (REM latency), an increase in REM density, and, in some subjects, a decrease in stage IV delta slow-wave sleep.

Although antidepressant drugs inhibit neurotransmitter uptake within hours, their therapeutic effects typically emerge over several weeks, implicating adaptive changes in second messenger systems and neurotrophic and transcription factors as possible mechanisms of action.

TREATMENT

Depressive Disorders

Treatment planning requires coordination of short-term strategies to induce remission combined with longer-term maintenance designed to prevent recurrence. The most effective intervention for achieving remission and preventing relapse is medication, but combined treatments, incorporating psychotherapy to help the patient cope with decreased self-esteem and demoralization, improve outcomes, as do self-help strategies such as exercise (Fig. 452-1). Approximately 40% of primary care patients with depression drop out of treatment and discontinue medication if symptomatic improvement is not noted within a month, unless additional support is provided. Outcome improves with (1) increased intensity and frequency of visits during the first 4–6 weeks of treatment, (2) supplemental educational materials, and (3) psychiatric consultation as indicated. Despite the widespread use of SSRIs and other second-generation antidepressant drugs, there is no convincing evidence that these classes of antidepressants are more efficacious than TCAs. Between 60–70% of all depressed patients respond to any drug chosen, if it is given in a sufficient dose for 6–8 weeks.

A rational approach to selecting which antidepressant to use (Table 452-1) involves matching the patient's preference and medical history with the metabolic and side-effect profile of the drug (Tables 452-2 and 452-3). A previous response, or a family history of a positive response, to a specific antidepressant often suggests that drug should be tried first. Before initiating antidepressant therapy, the physician should evaluate the possible contribution of comorbid illnesses and consider their specific treatment. In individuals with suicidal ideation, particular attention should be paid to choosing a drug with low toxicity if taken in overdose. Newer antidepressant drugs are distinctly safer in this regard; nevertheless, the advantages of TCAs have not been completely superseded. The existence of generic equivalents makes TCAs relatively cheap, and for secondary tricyclics, particularly nortriptyline and desipramine, well-defined relationships among dose, plasma level, and therapeutic response exist. The steady-state plasma level achieved for a given drug dose can vary more than tenfold between individuals, and plasma levels may help in interpreting apparent resistance to treatment and/or unexpected drug toxicity. The principal side effects of TCAs are antihistaminergic (sedation) and anticholinergic

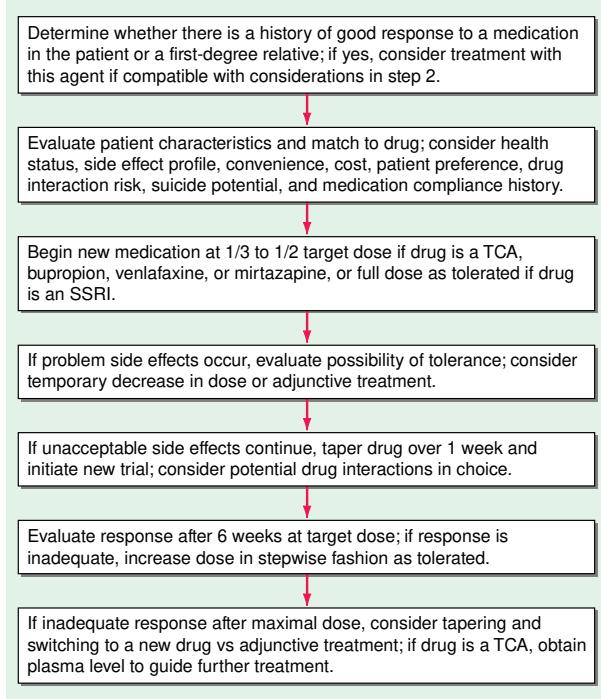


FIGURE 452-1 A guideline for the medical management of major depressive disorder. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

(constipation, dry mouth, urinary hesitancy, blurred vision). TCAs are contraindicated in patients with serious cardiovascular risk factors, and overdoses of tricyclic agents can be lethal, with desipramine carrying the greatest risk. It is judicious to prescribe only a 10-day supply when suicide is a risk. Most patients require a daily dose of 150–200 mg of imipramine or amitriptyline or its equivalent to achieve a therapeutic blood level of 150–300 ng/mL and a satisfactory remission; some patients show a partial effect at lower doses. Geriatric patients may require a low starting dose and slow escalation. Ethnic differences in drug metabolism are significant, with Hispanic, Asian, and black patients generally requiring lower doses to achieve a comparable blood level.

Second-generation antidepressants are similar to tricyclics in their effect on neurotransmitter reuptake, although some also have specific actions on catecholamine and indolamine receptors as well. Amoxapine is a dibenzoxazepine derivative that blocks norepinephrine and serotonin reuptake and has a metabolite that shows a degree of dopamine blockade. Long-term use of this drug carries a risk of tardive dyskinesia. Maprotiline is a potent noradrenergic reuptake blocker that has little anticholinergic effect but may produce seizures. Bupropion is a novel antidepressant whose mechanism of action is thought to involve enhancement of noradrenergic function. It has no anticholinergic, sedating, or orthostatic side effects and has a low incidence of sexual side effects. It may, however, be associated with stimulant-like side effects, may lower seizure threshold, and has an exceptionally short half-life, requiring frequent dosing. An extended-release preparation is available.

SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, and escitalopram cause a lower frequency of anticholinergic, sedating, and cardiovascular side effects but a possibly greater incidence of gastrointestinal complaints, sleep impairment, and sexual dysfunction than do TCAs. Akathisia, involving an inner sense of restlessness and anxiety in addition to increased motor activity, may also be more common, particularly during the first week of treatment. One concern is the risk of “serotonin syndrome,” which is thought to

result from hyperstimulation of brainstem 5-HT_{1A} receptors and is characterized by myoclonus, agitation, abdominal cramping, hyperpyrexia, hypertension, and potentially death. Serotonergic agonists taken in combination should be monitored closely for this reason. Considerations such as half-life, compliance, toxicity, and drug-drug interactions may guide the choice of a particular SSRI. Fluoxetine and its principal active metabolite, norfluoxetine, for example, have a combined half-life of almost 7 days, resulting in a delay of 5 weeks before steady-state levels are achieved and a similar delay for complete drug excretion once their use is discontinued; paroxetine appears to incur a greater risk of withdrawal symptoms with abrupt discontinuation. All the SSRIs may impair sexual function, resulting in diminished libido, impotence, or difficulty in achieving orgasm. Sexual dysfunction frequently results in noncompliance and should be asked about specifically. Sexual dysfunction can sometimes be ameliorated by lowering the dose, by instituting weekend drug holidays (two or three times a month), or by treatment with amantadine (100 mg tid), bethanechol (25 mg tid), buspirone (10 mg tid), or bupropion (100–150 mg/d). Paroxetine appears to be more anticholinergic than either fluoxetine or sertraline, and sertraline carries a lower risk of producing an adverse drug interaction than the other two. Rare side effects of SSRIs include angina due to vasospasm and prolongation of the prothrombin time. Escitalopram is the most specific of currently available SSRIs and appears to have no significant inhibitory effects on the P450 system.

Venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran block the reuptake of both norepinephrine and serotonin but produce relatively little in the way of traditional tricyclic side effects. Vortioxetine, also a 5HT1a agonist, and vilazodone block reuptake of serotonin but have negligible effects on norepinephrine reuptake, although vortioxetine may increase norepinephrine levels through wide effects on serotonergic receptors, as a 5HT1a agonist, 5HT1b partial agonist, and a 5HT1d, 5HT3, and 5HT7 antagonist. Unlike the SSRIs, venlafaxine and vortioxetine have relatively linear dose-response curves. Patients on immediate-release venlafaxine should be monitored for a possible increase in diastolic blood pressure, and multiple daily dosing is required because of the drug's short half-life. An extended-release form is available and has a somewhat lower incidence of gastrointestinal side effects. Mirtazapine is a tetracyclic that has a unique spectrum of activity, as it increases noradrenergic and serotonergic neurotransmission through a blockade of central α₂-adrenergic receptors and postsynaptic 5-HT₂ and 5-HT₃ receptors. It is also strongly antihistaminic and, as such, may produce sedation. Levomilnacipran is the most noradrenergic of the SNRIs and theoretically may be appropriate for patients with more severe fatigue and anergia.

With the exception of citalopram and escitalopram, each of the SSRIs may inhibit one or more cytochrome P450 enzymes. Depending on the specific isoenzyme involved, the metabolism of a number of concomitantly administered medications can be dramatically affected. Fluoxetine and paroxetine, for example, by inhibiting 2D6, can cause dramatic increases in the blood level of type 1C antiarrhythmics, whereas sertraline, by acting on 3A4, may alter blood levels of carbamazepine or digoxin. Depending on drug specificity for a particular CYP enzyme for its own metabolism, concomitant medications or dietary factors, such as grapefruit juice, may in turn affect the efficacy or toxicity of the SSRI.

The MAOIs are highly effective, particularly in atypical depression, but the risk of hypertensive crisis following intake of tyramine-containing food or sympathomimetic drugs makes them inappropriate as first-line agents. Transdermal selegiline may avert this risk at low dose. Common side effects include orthostatic hypotension, weight gain, insomnia, and sexual dysfunction. MAOIs should not be used concomitantly with SSRIs, because of the risk of serotonin syndrome, or with TCAs, because of possible hyperadrenergic effects.

Electroconvulsive therapy is at least as effective as medication, but its use is reserved for treatment-resistant cases and delusional

depressions. Repetitive transcranial magnetic stimulation (rTMS) is approved for treatment-resistant depression and has been shown to have efficacy in several controlled trials. Vagus nerve stimulation (VNS) has also recently been approved for treatment-resistant depression, but its degree of efficacy is controversial. Some meta-analyses of low-intensity transcranial current stimulation (tCS) have shown a positive benefit over sham treatment, but whether this is comparable to or synergistic with antidepressant treatment is unclear. In off-label usage, intravenous ketamine, a dissociative anesthetic, and intranasal esketamine (an isomer that has FDA approval in treatment-resistant cases) have been shown to have short-term antidepressant efficacy, often after a single administration, suggesting a possible utility in addressing suicidality. Questions remain, however, about the risk/benefit ratio over the longer term. Psilocybin, a hallucinogen, has also shown some potential benefit in controlled administration. Lastly, deep brain stimulation of the ventral anterior limb of the internal capsule and of the subcallosal cingulate region have demonstrable efficacy in randomized experimental trials of treatment-resistant depression.

Postpartum depression may respond to any of the above interventions, but the FDA has recently approved the specific usage of brexanolone (Zulresso), administered in a continuous intravenous infusion over 60 h and found to result in symptomatic relief for at least 30 days. Sedation and loss of consciousness are possible adverse effects.

Regardless of the treatment undertaken, the response should be evaluated after ~2 months. Three-quarters of patients show improvement by this time, but if remission is inadequate, the patient should be questioned about compliance, and an increase in medication dose should be considered if side effects are not troublesome. If this approach is unsuccessful, referral to a mental health specialist is advised. Strategies for treatment resistance include selection of an alternative drug, combinations of antidepressants, and/or adjunctive treatment with other classes of drugs, including lithium, thyroid hormone, l-methylfolate, s-adenosylmethionine, n-acetyl cysteine, atypical antipsychotic agents, and dopamine agonists. In switching to a different monotherapy, other drugs from the same class appear to be as likely to be efficacious as choosing a drug from a different class. A large randomized trial (STAR-D) was unable to show preferential efficacy, but the addition of certain atypical antipsychotic drugs (quetiapine extended-release; aripiprazole; brexpiprazole) has received FDA approval, as has usage of a combined medication, olanzapine and fluoxetine (Symbyax). Patients whose response to an SSRI wanes over time may benefit from the addition of buspirone (10 mg tid) or pindolol (2–5 mg tid) or small amounts of a TCA such as nortriptyline (25 mg bid or tid). Most patients will show some degree of response, but aggressive treatment should be pursued until remission is achieved, and drug treatment should be continued for at least 6–9 months to prevent relapse. In patients who have had two or more episodes of depression, indefinite maintenance treatment should be considered. Pharmacogenomic testing focusing on cytochrome p450 allelic variation may sometimes be helpful in identifying individuals who are poor or rapid metabolizers, but assessing pharmacodynamic gene variants has not been shown to be cost-effective or affect clinical outcomes.

It is essential to educate patients both about depression and the benefits and side effects of medications they are receiving. Advice about stress reduction and cautions that alcohol may exacerbate depressive symptoms and impair drug response are helpful. Patients should be given time to describe their experience, their outlook, and the impact of the depression on them and their families. Occasional empathetic silence may be as helpful for the treatment alliance as verbal reassurance. Controlled trials have shown that cognitive-behavioral and interpersonal therapies are effective in improving psychological and social adjustment and that a combined treatment approach is more successful than medication alone for many patients.

BIPOLAR DISORDER

Clinical Manifestations Bipolar disorder is characterized by unpredictable swings in mood from mania (or hypomania) to depression. Some patients suffer only from recurrent attacks of *mania*, which in its pure form is associated with increased psychomotor activity; excessive social extroversion; decreased need for sleep; impulsivity and impaired judgment; and expansive, elated, grandiose, and sometimes irritable mood (Table 452-8). In severe mania, patients may experience delusions and paranoid thinking indistinguishable from schizophrenia. One-half of patients with bipolar disorder present not with euphoria but with a mixture of psychomotor agitation and activation, accompanied by dysphoria, anxiety, and irritability. It may be difficult to distinguish such a mixed state from agitated depression. In some bipolar patients (*bipolar II disorder*), the full criteria for mania are lacking, and the requisite recurrent depressions are separated by periods of mild activation and increased energy (hypomania). In *cyclothymic disorder*, there are numerous hypomanic periods, usually of relatively short duration, alternating with clusters of depressive symptoms that fail, either in severity or duration, to meet the criteria of major depression. The mood fluctuations are chronic and should be present for at least 2 years before the diagnosis is made.

Manic episodes typically emerge over a period of days to weeks, but onset within hours is possible, usually in the early-morning hours. An untreated episode of either depression or mania can be as short as several weeks or last as long as 8–12 months, and rare patients have an unremitting chronic course. The term *rapid cycling* is used for patients who have four or more episodes of either depression or mania in a given year. This pattern occurs in 15% of all patients, most of whom are women. In some cases, rapid cycling is linked to an underlying thyroid dysfunction, and in others, it is iatrogenically triggered by prolonged antidepressant treatment. Approximately one-half of patients have sustained difficulties in work performance and psychosocial functioning, with depressive phases being more responsible for impairment than mania.

Bipolar disorder is common, affecting ~1.5% of the population in the United States. Onset is typically between 20–30 years of age, but many individuals report premorbid symptoms in late childhood or early adolescence. The prevalence is similar for men and women; women are likely to have more depressive and men more manic

TABLE 452-8 Criteria for a Manic Episode

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
- B. During the period of the mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
 - 1. Inflated self-esteem or grandiosity.
 - 2. Decreased need for sleep (e.g., feels rested after only 3 h of sleep).
 - 3. More talkative than usual or pressure to keep talking.
 - 4. Flight of ideas or subjective experience that thoughts are racing.
 - 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
 - 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
 - 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
- C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- D. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or another medical condition.

Source: Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (Copyright © 2013). American Psychiatric Association. All Rights Reserved.

episodes over a lifetime. Recognizing a bipolar diathesis in an individual who presents with a depressive episode but no history of mania is difficult but essential in optimizing treatment planning, because antidepressants may be contraindicated and result in symptom worsening and cycle acceleration. Suggestive features of bipolarity include a childhood onset, a history of antidepressant treatment failure, atypical features of hypersomnolence and weight gain, and marked irritability or impulsivity.

Differential Diagnosis The differential diagnosis of mania includes secondary mania induced by stimulant or sympathomimetic drugs, hyperthyroidism, AIDS, neurologic disorders such as Huntington's or Wilson's disease, frontotemporal dementia, and cerebrovascular accidents. Comorbidity with alcohol and substance abuse is common, either because of poor judgment and increased impulsivity or because of an attempt to self-treat the underlying mood symptoms and sleep disturbances.

Etiology and Pathophysiology Genetic predisposition to bipolar disorder is evident from family studies; the concordance rate for monozygotic twins approaches 80%. A number of risk genes that have been identified to date overlap with those conveying risk for other psychiatric disorders, such as schizophrenia and autism, implying some degree of shared pathophysiology. Replicated loci include the alpha subunit of the L-type calcium channel (*CACNA1C*), teneurin transmembrane protein 4 (*ODZ4*), ankyrin 3 (*ANK3*), neurocan (NCAN), and tetratricopeptide repeat and ankyrin repeat containing 1 (*TRANK1*). Common variants convey little individual risk, but collectively account for 25% of heritability. A few rarer, more penetrant variants have also been reported, but no causative mutations have as yet been confirmed. Similarly, no clear biomarkers have been identified, but there is evidence for circadian rhythm dysregulation and oxidative stress, mitochondrial, and endoplasmic reticulum abnormalities. Reported MRI findings include grey matter thinning in frontal, temporal, and parietal cortex.

TREATMENT

Bipolar Disorder

(Table 452-9) Lithium carbonate is the mainstay of treatment in bipolar disorder, although sodium valproate and carbamazepine, as well as a number of second-generation antipsychotic agents (aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, ziprasidone), also have FDA approval for the treatment of acute mania. Oxcarbazepine is not FDA approved, but appears to enjoy carbamazepine's spectrum of efficacy. The response rate to lithium carbonate is 70–80% in acute mania, with beneficial effects appearing in 1–2 weeks. Lithium also has a prophylactic effect in prevention of recurrent mania and, to a lesser extent, in the prevention of recurrent depression, which is more difficult to treat than unipolar depression. A simple cation, lithium is rapidly absorbed from the gastrointestinal tract and remains unbound to plasma or tissue proteins. Some 95% of a given dose is excreted unchanged through the kidneys within 24 h.

Serious side effects from lithium are rare, but minor complaints such as gastrointestinal discomfort, nausea, diarrhea, polyuria, weight gain, skin eruptions, alopecia, and edema are common. Over time, urine-concentrating ability may be decreased, but significant nephrotoxicity is relatively rare. Lithium exerts an antithyroid effect by interfering with the synthesis and release of thyroid hormones. More serious side effects include tremor, poor concentration and memory, ataxia, dysarthria, and incoordination.

In the treatment of acute mania, lithium is initiated at 300 mg bid or tid, and the dose is then increased by 300 mg every 2–3 days to achieve blood levels of 0.8–1.2 meq/L. Because the therapeutic effect of lithium may not appear until after 7–10 days of treatment, adjunctive usage of lorazepam (1–2 mg every 4 h) or clonazepam (0.5–1 mg every 4 h) may be beneficial to control agitation. Antipsychotics are indicated in patients with severe agitation who respond only partially to benzodiazepines. Patients using lithium should be

TABLE 452-9 Clinical Pharmacology of Mood Stabilizers

AGENT AND DOSING	SIDE EFFECTS AND OTHER EFFECTS
Lithium	<p>Common Side Effects</p> <p>Starting dose: 300 mg bid or tid Therapeutic blood level: 0.8–1.2 meq/L</p> <p>Nausea/anorexia/diarrhea, fine tremor, thirst, polyuria, fatigue, weight gain, acne, folliculitis, neutrophilia, hypothyroidism Blood level is increased by thiazides, tetracyclines, and NSAIDs</p> <p>Blood level is decreased by bronchodilators, verapamil, and carbonic anhydrase inhibitors</p> <p><i>Rare side effects:</i> Neurotoxicity, renal toxicity, hypercalcemia, ECG changes</p>
Valproic Acid	<p>Common Side Effects</p> <p>Starting dose: 250 mg tid Therapeutic blood level: 50–125 µg/mL</p> <p>Nausea/anorexia, weight gain, sedation, tremor, rash, alopecia Inhibits hepatic metabolism of other medications</p> <p><i>Rare side effects:</i> Pancreatitis, hepatotoxicity, Stevens-Johnson syndrome</p>
Carbamazepine/Oxcarbazepine	<p>Common Side Effects</p> <p>Starting dose: 200 mg bid for carbamazepine, 150 mg bid for oxcarbazepine Therapeutic blood level: 4–12 µg/mL for carbamazepine</p> <p>Nausea/anorexia, sedation, rash, dizziness/ataxia Carbamazepine, but not oxcarbazepine, induces hepatic metabolism of other medications</p> <p><i>Rare side effects:</i> Hyponatremia, agranulocytosis, Stevens-Johnson syndrome</p>
Lamotrigine	<p>Common Side Effects</p> <p>Starting dose: 25 mg/d</p> <p>Rash, dizziness, headache, tremor, sedation, nausea <i>Rare side effect:</i> Stevens-Johnson syndrome</p>

Abbreviations: ECG, electrocardiogram; NSAIDs, nonsteroidal anti-inflammatory drugs.

monitored closely, because the blood levels required to achieve a therapeutic benefit are close to those associated with toxicity.

Valproic acid may be more effective than lithium for patients who experience rapid cycling (i.e., more than four episodes a year) or who present with a mixed or dysphoric mania. Tremor and weight gain are the most common side effects; hepatotoxicity and pancreatitis are rare toxicities.

The recurrent nature of bipolar mood disorder necessitates maintenance treatment. A sustained blood lithium level of at least 0.8 meq/L is important for optimal prophylaxis and has been shown to reduce the risk of suicide, a finding not yet apparent for other mood stabilizers. Combinations of mood stabilizers together or with atypical antipsychotic drugs are sometimes required to maintain mood stability. Quetiapine extended release, olanzapine, risperidone, and lamotrigine have been approved for maintenance treatment as sole agents, in combination with lithium and with aripiprazole and ziprasidone as adjunctive drugs. Lurasidone, olanzapine/fluoxetine, and quetiapine are also approved to treat acute depressive episodes in bipolar disorder. Compliance is frequently an issue and often requires enlistment and education of concerned family members. Efforts to identify and modify psychosocial factors that may trigger episodes are important, as is an emphasis on lifestyle regularity (social rhythm therapy). Mobile apps for smartphones that alert the individual and clinician to changes in activity and speech are proving useful in early detection of behavioral change and in delivering clinical interventions and education. Antidepressant medications are sometimes required for the treatment of severe breakthrough depressions, but their use should generally be avoided during maintenance treatment because of the risk of precipitating mania or accelerating the cycle frequency. Alternative off-label agents for bipolar depression include pramipexole, modafinil, omega-3 fatty acids, and *N*-acetyl cysteine; interventions such as ECT, light therapy,

and rTMS may also be effective. Loss of efficacy over time may be observed with any of the mood-stabilizing agents. In such situations, an alternative agent or combination therapy is usually helpful.

SOMATIC SYMPTOM DISORDER

Many patients presenting in general medical practice, perhaps as many as 5–7%, will experience a somatic symptom(s) as particularly distressing and preoccupying, to the point that it comes to dominate their thoughts, feelings, and beliefs and interferes to a varying degree with everyday functioning. Although the absence of a medical explanation for these complaints was historically emphasized as a diagnostic element, it has been recognized that the patient's interpretation and elaboration of the experience is the critical defining factor and that patients with well-established medical causation may qualify for the diagnosis. Multiple complaints are typical, but severe single symptoms can occur as well. Comorbidity with depressive and anxiety disorders is common and may affect the severity of the experience and its functional consequences. Personality factors may be a significant risk factor, as may a low level of educational or socioeconomic status or a history of recent stressful life events. Cultural factors are relevant as well and should be incorporated into the evaluation. Individuals who have persistent preoccupations about having or acquiring a serious illness, but who do not have a specific somatic complaint, may qualify for a related diagnosis—illness anxiety disorder. The diagnosis of conversion disorder (functional neurologic symptom disorder) is used to specifically identify those individuals whose somatic complaints involve one or more symptoms of altered voluntary motor or sensory function that cannot be medically explained and that cause significant distress or impairment or require medical evaluation.

In *factitious illnesses*, the patient consciously and voluntarily produces physical symptoms of illness. The term *Munchausen's syndrome* is reserved for individuals with particularly dramatic, chronic, or severe factitious illness. In true factitious illness, the sick role itself is gratifying. A variety of signs, symptoms, and diseases have been either simulated or caused by factitious behavior, the most common including chronic diarrhea, fever of unknown origin, intestinal bleeding or hematuria, seizures, and hypoglycemia. Factitious disorder is usually not diagnosed until 5–10 years after its onset, and it can produce significant social and medical costs. In *malingering*, the fabrication derives from a desire for some external reward such as a narcotic medication or disability reimbursement.

TREATMENT

Somatic Symptom Disorder and Related Disorders

Patients with somatic symptom disorder are frequently subjected to many diagnostic tests and exploratory surgeries in an attempt to find their "real" illness. Such an approach is doomed to failure and does not address the core issue. Successful treatment is best achieved through behavior modification, in which access to the physician is tightly regulated and adjusted to provide a sustained and predictable level of support that is less clearly contingent on the patient's level of presenting distress. Visits can be brief and should not be associated with a need for a diagnostic or treatment action. Although the literature is limited, some patients may benefit from antidepressant treatment.

Any attempt to confront the patient usually creates a sense of humiliation and causes the patient to abandon treatment from that caregiver. A better strategy is to introduce psychological causation as one of a number of possible explanations in the differential diagnoses that are discussed. Without directly linking psychotherapeutic intervention to the diagnosis, the patient can be offered a face-saving means by which the pathologic relationship with the health care system can be examined and alternative approaches to life stressors developed. Specific medical treatments also may be indicated and effective in treating some of the functional consequences of conversion disorder.

FEEDING AND EATING DISORDERS

■ CLINICAL MANIFESTATIONS

Feeding and eating disorders constitute a group of conditions in which there is a persistent disturbance of eating or associated behaviors that significantly impair an individual's physical health or psychosocial functioning. In DSM-5 the described categories (with the exception of pica) are defined to be mutually exclusive in a given episode, based on the understanding that although they are phenotypically similar in some ways, they differ in course, prognosis, and effective treatment interventions. Compared with DSM-IV-TR, three disorders (i.e., avoidant/restrictive food intake disorder, rumination disorder, pica) that were previously classified as disorders of infancy or childhood have been grouped together with the disorders of anorexia and bulimia nervosa. Binge-eating disorder is also now included as a formal diagnosis; the intent of each of these modifications is to encourage clinicians to be more specific in their codification of eating and feeding pathology.

■ PICA

Pica is diagnosed when the individual, aged >2 years, eats one or more nonnutritive, nonfood substances for a month or more and requires medical attention as a result. There is usually no specific aversion to food in general but a preferential choice to ingest substances such as clay, starch, soap, paper, or ash. The diagnosis requires the exclusion of specific culturally approved practices and has not been commonly found to be caused by a specific nutritional deficiency. Onset is most common in childhood, but the disorder can occur in association with other major psychiatric conditions in adults. An association with pregnancy has been observed, but the condition is only diagnosed when medical risks are increased by the behavior.

■ RUMINATION DISORDER

In this condition, individuals who have no demonstrable associated gastrointestinal or other medical condition repeatedly regurgitate their food after eating and then either rechew or swallow it or spit it out. The behavior typically occurs on a daily basis and must persist for at least 1 month. Weight loss and malnutrition are common sequelae, and individuals may attempt to conceal their behavior, either by covering their mouth or through social avoidance while eating. In infancy, the onset is typically between 3 and 12 months of age, and the behavior may remit spontaneously, although in some it appears to be recurrent.

■ AVOIDANT/RESTRICTIVE FOOD INTAKE DISORDER

The cardinal feature of this disorder is avoidance or restriction of food intake, usually stemming from a lack of interest in or distaste of food and associated with weight loss, nutritional deficiency, dependency on nutritional supplementation, or marked impairment in psychosocial functioning, either alone or in combination. Culturally approved practices, such as fasting or a lack of available food, must be excluded as possible causes. The disorder is distinguished from anorexia nervosa by the presence of emotional factors, such as a fear of gaining weight and distortion of body image in the latter condition. Onset is usually in infancy or early childhood, but avoidant behaviors may persist into adulthood. The disorder is equally prevalent in males and females and is frequently comorbid with anxiety and cognitive and attention-deficit disorders and situations of familial stress. Developmental delay and functional deficits may be significant if the disorder is long-standing and unrecognized.

■ ANOREXIA NERVOSA

Individuals are diagnosed with anorexia nervosa if they restrict their caloric intake to a degree that their body weight deviates significantly from age, gender, health, and developmental norms and if they also exhibit a fear of gaining weight and an associated disturbance in body image. The condition is further characterized by differentiating those who achieve their weight loss predominantly through restricting intake or by excessive exercise (restricting type) from those who engage in recurrent binge eating and/or subsequent purging, self-induced vomiting, and usage of enemas, laxatives, or diuretics (binge-eating/purging

type). Such subtyping is more state- than trait-specific, as individuals may transition from one profile to the other over time. Determination of whether an individual satisfies the primary criterion of significant low weight is complex and must be individualized, using all available historical information and comparison of body habitus to international body-mass norms and guidelines.

Individuals with anorexia nervosa frequently lack insight into their condition and are in denial about possible medical consequences; they often are not comforted by their achieved weight loss and persist in their behaviors despite having met previously self-designated weight goals. Alterations in the circuitry of reward sensitivity and executive function have been reported in anorexia, implicating disturbances in frontal cortex and anterior insula regulation of interoceptive awareness of satiety and hunger. Neurochemical findings, including the role of ghrelin, remain controversial.

Onset is most common in adolescence, although onset in later life can occur. Many more females than males are affected, with a lifetime prevalence in women of up to 4%. The disorder appears most prevalent in post-industrialized and urbanized countries and is frequently comorbid with preexisting anxiety disorders. The medical consequences of prolonged anorexia nervosa are multisystemic and can be life-threatening in severe presentations. Changes in laboratory values may be present, including leukopenia with lymphocytosis, elevations in blood urea nitrogen, and metabolic alkalosis and hypokalemia when purging is present. History and physical examination may reveal amenorrhea in females, skin abnormalities (petechiae, lanugo hair, dryness), and signs of hypometabolic function, including hypotension, hypothermia, and sinus bradycardia. Endocrine effects include hypogonadism, growth hormone resistance, and hypercortisolism. Osteoporosis is a longer-term concern.

The course of the disorder is variable, with some individuals recovering after a single episode, while others exhibit recurrent episodes or a chronic course. Untreated anorexia has a mortality of 5.1/1000, the highest among psychiatric conditions. Maudsley Anorexia Nervosa Treatment for Adults (MANTRA) and eating disorder-focused cognitive behavior therapy have proven to be effective therapies, with strict behavioral contingencies used when weight loss becomes critical. No pharmacologic intervention has proven to be specifically beneficial, but comorbid depression and anxiety should be treated. Weight gain should be undertaken gradually with a goal of 0.5–1 pound per week to prevent refeeding syndrome. Most individuals are able to achieve remission within 5 years of the original diagnosis.

BULIMIA NERVOSA

Bulimia nervosa describes individuals who engage in recurrent and frequent (at least once a week for 3 months) periods of binge eating and who then resort to compensatory behaviors, such as self-induced purging, enemas, use of laxatives, or excessive exercise, to avoid weight gain. Binge eating itself is defined as excessive food intake in a prescribed period of time, usually <2 h. As in anorexia nervosa, disturbances in body image occur and promote the behavior, but unlike in anorexia, individuals are of normal weight or even somewhat overweight. Subjects typically describe a loss of control and express shame about their actions, and often relate that their episodes are triggered by feelings of negative self-esteem or social stresses. The lifetime prevalence in women is ~2%, with a 10:1 female-to-male ratio. The disorder typically begins in adolescence and may be persistent over a number of years. Transition to anorexia occurs in only 10–15% of cases. Many of the medical risks associated with bulimia nervosa parallel those of anorexia nervosa and are a direct consequence of purging, including fluid and electrolyte disturbances and cardiac conduction abnormalities. Physical examination often results in no specific findings, but dental erosion and parotid gland enlargement may be present. Effective treatment approaches include SSRI antidepressants, usually in combination with cognitive-behavioral, emotion regulation, or interpersonal-based psychotherapies.

BINGE EATING DISORDER

Binge-eating disorder is distinguished from bulimia nervosa by the absence of compensatory behaviors to prevent weight gain after an

episode and by a lack of effort to restrict weight gain between episodes. Other features are similar, including distress over the behavior and the experience of loss of control, resulting in eating more rapidly or in greater amounts than intended or eating when not hungry. The 12-month prevalence in females is 1.6%, with a much lower female-to-male ratio than bulimia nervosa. Little is known about the course of the disorder, given its recent categorization, but its prognosis is markedly better than for other eating disorders, both in terms of its natural course and response to treatment. Transition to other eating disorder conditions is thought to be rare.

PERSONALITY DISORDERS

CLINICAL MANIFESTATIONS

Personality disorders are characteristic patterns of thinking, feeling, and interpersonal behavior that are relatively inflexible and cause significant functional impairment or subjective distress for the individual. The observed behaviors are not secondary to another mental disorder, nor are they precipitated by substance abuse or a general medical condition. This distinction is often difficult to make in clinical practice, because personality change may be the first sign of serious neurologic, endocrine, or other medical illness. Patients with frontal-lobe tumors, for example, can present with changes in motivation and personality while the results of the neurologic examination remain within normal limits. Individuals with personality disorders are often regarded as “difficult patients” in clinical medical practice because they are seen as excessively demanding and/or unwilling to follow recommended treatment plans. Although DSM-5 portrays personality disorders as qualitatively distinct categories, there is an alternative and emerging perspective that personality characteristics vary as a continuum between normal functioning and formal mental disorder, the essential features being moderate or greater impairment in self/interpersonal functioning and one or more pathological personality traits.

Personality disorders have been grouped into three overlapping clusters. *Cluster A* includes paranoid, schizoid, and schizotypal personality disorders. It includes individuals who are odd and eccentric and who maintain an emotional distance from others. Individuals have a restricted emotional range and remain socially isolated. Patients with schizotypal personality disorder frequently have unusual perceptual experiences and express magical beliefs about the external world. The essential feature of paranoid personality disorder is a pervasive mistrust and suspiciousness of others to an extent that is unjustified by available evidence. *Cluster B* disorders include antisocial, borderline, histrionic, and narcissistic types and describe individuals whose behavior is impulsive, excessively emotional, and erratic. *Cluster C* incorporates avoidant, dependent, and obsessive-compulsive personality types; enduring traits are anxiety and fear. The boundaries between cluster types are to some extent artificial, and many patients who meet criteria for one personality disorder also meet criteria for aspects of another. The risk of a comorbid major mental disorder is increased in patients who qualify for a diagnosis of personality disorder.

ETIOLOGY AND PATHOPHYSIOLOGY

Genetic studies have increasingly suggested a genetic contribution to the development of personality disorders. One study of 106,000 subjects identified nine loci significantly linked to aspects of neuroticism.

TREATMENT

Personality Disorders

Dialectical behavior therapy (DBT) is a cognitive-behavioral approach that focuses on behavioral change while providing acceptance, compassion, and validation of the patient. Several randomized trials have demonstrated the efficacy of DBT in the treatment of personality disorders. Antidepressant medications and low-dose

antipsychotic drugs have some efficacy in cluster A personality disorders, whereas anticonvulsant mood-stabilizing agents and MAOIs may be considered for patients with cluster B diagnoses who show marked mood reactivity, behavioral dyscontrol, and/or rejection hypersensitivity. Anxious or fearful cluster C patients often respond to medications used for axis I anxiety disorders (see above). It is important that the physician and the patient have reasonable expectations vis-à-vis the possible benefit of any medication used and its side effects. Improvement may be subtle and observable only over time.

SCHIZOPHRENIA

■ CLINICAL MANIFESTATIONS

Schizophrenia is a heterogeneous syndrome characterized by perturbations of language, perception, thinking, social activity, affect, and volition. There are no pathognomonic features. The syndrome commonly begins in late adolescence, has an insidious (and less commonly, acute) onset, and, often, a poor outcome, progressing from social withdrawal and perceptual distortions to recurrent delusions and hallucinations. Patients may present with positive symptoms (such as conceptual disorganization, delusions, or hallucinations) or negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement) and must have at least two of these for a 1-month period and continuous signs for at least 6 months to meet formal diagnostic criteria. Disorganized thinking or speech and grossly disorganized motor behavior, including catatonia, may also be present. As individuals age, positive psychotic symptoms tend to attenuate, and some measure of social and occupational function may be regained. “Negative” symptoms predominate in one-third of the schizophrenic population and are associated with a poor long-term outcome and a poor response to drug treatment. However, marked variability in the course and individual character of symptoms is typical.

The term *schizophreniform disorder* describes patients who meet the symptom requirements but not the duration requirements for schizophrenia, and *schizoaffective disorder* is used for those who manifest symptoms of schizophrenia and independent periods of mood disturbance. The terms *schizotypal* and *schizoid* refer to specific personality disorders and are discussed in that section. The diagnosis of delusional disorder is used for individuals who have delusions of various content for at least 1 month but who otherwise do not meet criteria for schizophrenia. Patients who experience a sudden onset of a brief (<1 month) alteration in thought processing, characterized by delusions, hallucinations, disorganized speech, or gross motor behavior, are most appropriately designated as having a brief psychotic disorder. Catatonia is recognized as a nonspecific syndrome that can occur as a consequence of other severe psychiatric/medical disorders and is diagnosed by the documentation of three or more of a cluster of motor and behavioral symptoms, including stupor, cataplexy, mutism, waxy flexibility, and stereotypy, among others. Prognosis depends not on symptom severity but on the response to antipsychotic medication. A permanent remission without recurrence does occasionally occur. About 10% of schizophrenic patients commit suicide.

Schizophrenia is present in 0.85% of individuals worldwide, with a lifetime prevalence of ~1–1.5%. An estimated 300,000 episodes of acute schizophrenia occur annually in the United States, resulting in direct and indirect costs of \$155.7 billion.

■ DIFFERENTIAL DIAGNOSIS

The diagnosis is principally one of exclusion, requiring the absence of significant associated mood symptoms, any relevant medical condition, and substance abuse. Drug reactions that cause hallucinations, paranoia, confusion, or bizarre behavior may be dose-related or idiosyncratic; parkinsonian medications, clonidine, quinacrine, and procaine derivatives are the most common prescription medications associated with these symptoms. Drug causes should be ruled out in any case of newly emergent psychosis. The general neurologic examination in patients with schizophrenia is usually normal, but motor rigidity, tremor, and dyskinesias are noted in one-quarter of untreated patients.

■ EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Epidemiologic surveys identify several risk factors for schizophrenia, including genetic susceptibility, early developmental insults, winter birth, and increasing parental age. Genetic factors are involved in at least a subset of individuals who develop schizophrenia. Schizophrenia is observed in ~6.6% of all first-degree relatives of an affected proband. If both parents are affected, the risk for offspring is 40%. The concordance rate for monozygotic twins is 50%, compared to 10% for dizygotic twins. Schizophrenia-prone families are also at risk for other psychiatric disorders, including schizoaffective disorder and *schizotypal* and *schizoid personality disorders*, the latter terms designating individuals who show a lifetime pattern of social and interpersonal deficits characterized by an inability to form close interpersonal relationships, eccentric behavior, and mild perceptual distortions. Large-scale genome-wide association studies have identified >100 small effect risk loci and a few larger effect copy number variants, along with epigenetic effects and have led to initial exploration in the clinical use of polygenic risk scores in diagnosis and prognosis. Pathways identified include ones involved in immunity, inflammation, and cell signaling.

TREATMENT

Schizophrenia

Antipsychotic agents (Table 452-10) are the cornerstone of acute and maintenance treatment of schizophrenia and are effective in the treatment of hallucinations, delusions, and thought disorders, regardless of etiology. The mechanism of action involves, at least in part, binding to dopamine D₂/D₃ receptors in the ventral striatum; the clinical potencies of traditional antipsychotic drugs parallel their affinities for the D₂ receptor, and even the newer “atypical” agents exert some degree of D₂ receptor blockade. All neuroleptics induce expression of the immediate-early gene c-fos in the nucleus accumbens, a dopaminergic site connecting prefrontal and limbic cortices. The clinical efficacy of newer atypical neuroleptics, however, may involve N-methyl-D-aspartate (NMDA) receptor blockade, α₁- and α₂-noradrenergic activity, altering the relationship between 5-HT₂ and D₂ receptor activity, and faster dissociation of D₂ binding and effects on neuroplasticity.

Conventional neuroleptics differ in their potency and side-effect profile. Older agents, such as chlorpromazine and thioridazine, are more sedating and anticholinergic and more likely to cause orthostatic hypotension, whereas higher-potency antipsychotics, such as haloperidol, perphenazine, and thiothixene, are more likely to induce extrapyramidal side effects. The model “atypical” antipsychotic agent is clozapine, a dibenzodiazepine that has a greater potency in blocking the 5-HT₂ than the D₂ receptor and a much higher affinity for the D₄ than the D₂ receptor. Its principal disadvantage is a risk of blood dyscrasias. Risperidone is a metabolite of risperidone and shares many of its properties. Unlike other antipsychotics, clozapine does not cause a rise in prolactin levels. Approximately 30% of patients who do not benefit from conventional antipsychotic agents will have a better response to this drug, which also has a demonstrated superiority to other antipsychotic agents in preventing suicide; however, its side-effect profile makes it most appropriate for treatment-resistant cases. Risperidone, a benzisoxazole derivative, is more potent at 5-HT₂ than D₂ receptor sites, like clozapine, but it also exerts significant α₂ antagonism, a property that may contribute to its perceived ability to improve mood and increase motor activity. Risperidone is not as effective as clozapine in treatment-resistant cases but does not carry a risk of blood dyscrasias. Olanzapine is similar neurochemically to clozapine but has a significant risk of inducing weight gain. Quetiapine is distinct in having a weak D₂ effect but potent α₁ and histamine blockade. Ziprasidone causes minimal weight gain and is unlikely to increase prolactin but may increase QT prolongation. Aripiprazole also has little risk of weight gain or prolactin increase but may increase anxiety, nausea, and insomnia as a result of its partial

TABLE 452-10 Antipsychotic Agents

Name	Usual PO Daily Dose (mg)	Side Effects	Sedation	Comments
First-Generation Antipsychotics				
Low potency				
Chlorpromazine (Thorazine)	100–1000	Anticholinergic effects; orthostasis; photosensitivity; cholestasis; QT prolongation	+++	EPSEs usually not prominent; can cause anticholinergic delirium in elderly patients
Thioridazine (Mellaril)	100–600			
Midpotency				
Trifluoperazine (Stelazine)	2–50	Fewer anticholinergic side effects	++	Well tolerated by most patients
Perphenazine (Trilafon)	4–64	Fewer EPSEs than with higher-potency agents	++	
Loxapine (Loxitane)	30–100	Frequent EPSEs	++	
Molindone (Molan)	30–100	Frequent EPSEs	0	Little weight gain
High potency				
Haloperidol (Haldol)	5–20	No anticholinergic side effects; EPSEs often prominent	0/+	Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available
Fluphenazine (Prolixin)	1–20	Frequent EPSEs	0/+	
Thiothixene (Navane)	2–50	Frequent EPSEs	0/+	
Second-Generation Antipsychotics				
Clozapine (Clozaril)	150–600	Agranulocytosis (1%); weight gain; seizures; drooling; hyperthermia	++	Requires weekly WBC count for first 6 months, then biweekly if stable
Risperidone (Risperdal)	2–8	Orthostasis	+	Requires slow titration; EPSEs observed with doses >6 mg qd
Olanzapine (Zyprexa)	10–30	Weight gain	++	Mild prolactin elevation
Quetiapine (Seroquel)	350–800	Sedation; weight gain; anxiety	+++	Bid dosing
Ziprasidone (Geodon)	120–200	Orthostatic hypotension	+//+	Minimal weight gain; increases QT interval
Aripiprazole (Abilify)	10–30	Nausea, anxiety, insomnia	0/+	Mixed agonist/antagonist; ER available
Paliperidone (Invega)	3–12	Restlessness, EPSEs, increased prolactin, headache	+	Active metabolite of risperidone
Iloperidone (Fanapt)	12–24	Dizziness, hypotension	0/+	Requires dose titration; long-acting injectable available
Asenapine (Saphris)	10–20	Dizziness, anxiety, EPSEs, minimal weight gain	++	Sublingual tablets; bid dosing
Lurasidone (Latuda)	40–80	Nausea, EPSEs	++	Uses CYP3A4
Brexpiprazole (Rexulti)	1–4	Anxiety, dizziness, fatigue	++	CYP3A4 and 2D6 interactions
Pimavanserin (Nuplazid)	34	Edema, confusion, sedation	++	Approved for Parkinson's disease psychosis
Cariprazine (Vraylar)	1.5–6	EPSEs, vomiting	++	Preferential D3 receptor affinity
Lumateperone (Caplyta)	42	Fatigue, dry mouth; no apparent metabolic/motor effects	++	5HT ₂ >D2 receptor affinity

Abbreviations: EPSEs, extrapyramidal side effects; WBC, white blood cell.

agonist properties. Asenapine is associated with minimal weight gain and anticholinergic effect but may have a higher than expected risk of extrapyramidal symptoms (EPSs). Cariprazine, a D2/D3 partial agonist, has no QT or prolactin elevation risk, but can result in EPS as well.

Antipsychotic agents are effective in 70% of patients presenting with a first episode. Improvement may be observed within hours or days, but full remission usually requires 6–8 weeks. The choice of agent depends principally on the side-effect profile and cost of treatment or on a past personal or family history of a favorable response to the drug in question. Atypical agents appear to be more effective in treating negative symptoms and improving cognitive function. An equivalent treatment response can usually be achieved with relatively low doses of any drug selected (i.e., 4–6 mg/d of haloperidol, 10–15 mg of olanzapine, or 4–6 mg/d of risperidone). Doses in this range result in >80% D₂ receptor blockade, and there is little evidence that higher doses increase either the rapidity or degree of response. Maintenance treatment requires careful attention to the possibility of relapse and monitoring for the development of a movement disorder. Intermittent drug treatment is less effective than regular dosing, but gradual dose reduction is likely

to improve social functioning in many schizophrenic patients who have been maintained at high doses. If medications are completely discontinued, however, the relapse rate is 60% within 6 months. Long-acting injectable preparations (risperidone, paliperidone, olanzapine, aripiprazole) are considered when noncompliance with oral therapy leads to relapses but should not be considered interchangeable, because the agents differ in their indications, injection intervals and sites/volumes, and possible adverse reactions, among other factors. In treatment-resistant patients, a transition to clozapine usually results in rapid improvement, but a prolonged delay in response in some cases necessitates a 6- to 9-month trial for maximal benefit to occur.

Antipsychotic medications can cause a broad range of side effects, including lethargy, weight gain, postural hypotension, constipation, and dry mouth. Extrapyramidal symptoms such as dystonia, akathisia, and akinesia are also frequent with first-generation agents and may contribute to poor adherence if not specifically addressed. Anticholinergic and parkinsonian symptoms respond well to trihexyphenidyl, 2 mg bid, or benztropine mesylate, 1–2 mg bid. Akathisia may respond to beta blockers. In rare cases, more serious and occasionally life-threatening side effects may emerge,

including hyperprolactinemia, ventricular arrhythmias, gastrointestinal obstruction, retinal pigmentation, obstructive jaundice, and neuroleptic malignant syndrome (characterized by hyperthermia, autonomic dysfunction, muscular rigidity, and elevated creatine phosphokinase levels). The most serious adverse effects of clozapine are agranulocytosis, which has an incidence of 1%, and induction of seizures, which has an incidence of 10%. Weekly white blood cell counts are required, particularly during the first 3 months of treatment.

The risk of type 2 diabetes mellitus appears to be increased in schizophrenia, and second-generation agents as a group, with the exception of lumateperone, produce greater adverse effects on glucose regulation, independent of effects on obesity, than traditional agents. Clozapine, olanzapine, and quetiapine seem more likely to cause hyperglycemia, weight gain, and hypertriglyceridemia than other atypical antipsychotic drugs. Close monitoring of plasma glucose and lipid levels is indicated with the use of these agents.

A serious side effect of long-term use of first-generation and, to a lesser extent, second-generation antipsychotic agents is tardive dyskinesia, characterized by repetitive, involuntary, and potentially irreversible movements of the tongue and lips (bucco-linguo-masticatory triad) and, in approximately half of cases, choreoathetosis. Tardive dyskinesia has an incidence of 2–4% per year of exposure and a prevalence of 20% in chronically treated patients. The prevalence increases with age, total dose, and duration of drug administration and may involve formation of free radicals and perhaps mitochondrial energy failure. Valbenazine, a vesicular monoamine transporter 2 inhibitor that depletes presynaptic dopamine, has recently received FDA approval for treatment of tardive dyskinesia.

The CATIE study, a large-scale investigation of the effectiveness of antipsychotic agents in “real-world” patients, revealed a high rate of discontinuation of treatment >18 months. Olanzapine showed greater effectiveness than quetiapine, risperidone, perphenazine, or ziprasidone but also a higher discontinuation rate due to weight gain and metabolic effects. Surprisingly, perphenazine, a first-generation agent, showed little evidence of inferiority to newer drugs.

Drug treatment of schizophrenia is by itself insufficient. Educational efforts directed toward families and relevant community resources have proved to be necessary to maintain stability and optimize outcome. A treatment model using social cognition interventions and involving a multidisciplinary case-management team that seeks out and closely follows the patient in the community has proved particularly effective. Attempts to prevent schizophrenia through early identification and treatment (both psychosocial and psychopharmacologic) of high-risk children and adolescents are currently being evaluated.

ASSESSMENT AND EVALUATION OF VIOLENCE

Primary care physicians may encounter situations in which family, domestic, or societal violence is discovered or suspected. Such an awareness can carry legal and moral obligations; many state laws mandate reporting of child, spousal, and elder abuse. Physicians are frequently the first point of contact for both victim and abuser. Approximately 2 million older Americans and 1.5 million U.S. children are thought to experience some form of physical maltreatment each year. Spousal abuse is thought to be even more prevalent. An interview study of 24,000 women in 10 countries found a lifetime prevalence of physical or sexual violence that ranged from 15–71%; these individuals are more likely to suffer from depression, anxiety, and substance abuse and to have attempted suicide. In addition, abused individuals frequently express low self-esteem, vague somatic symptomatology, social isolation, and a passive feeling of loss of control. Although it is essential to treat these elements in the victim, the first obligation is to ensure that the perpetrator has taken responsibility for preventing any further violence. Substance abuse and/or dependence and serious mental illness in the abuser may contribute to the risk of harm and require direct intervention. Depending on the situation, law enforcement

agencies, community resources such as support groups and shelters, and individual and family counseling can be appropriate components of a treatment plan. A safety plan should be formulated with the victim, in addition to providing information about abuse, its likelihood of recurrence, and its tendency to increase in severity and frequency. Antianxiety and antidepressant medications may sometimes be useful in treating the acute symptoms, but only if independent evidence for an appropriate psychiatric diagnosis exists.

FURTHER READING

- B J et al: Benzodiazepines versus placebo for panic disorder in adults. *Cochrane Database Syst Rev* 3:CD010677, 2019.
- C A et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391:1357, 2018.
- C -F B et al: The burden of disease in early schizophrenia—a systematic literature review. *Curr Med Res Opin* 37:109, 2020.
- C S et al: Posttraumatic stress disorder prevalence in medical populations: A systematic review and meta-analysis. *Gen Hosp Psychiatry* 69:81, 2021.
- G J, F G: Sequential combination of pharmacotherapy and psychotherapy in major depressive disorder: A systematic review and meta-analysis. *JAMA Psychiatry* 78:261, 2021.
- H H et al: Pharmacological treatment of eating disorders, comorbid mental health problems, malnutrition and physical consequences. *Pharmacol Ther* 217:107667, 2021.
- H M et al: Comparative efficacy and tolerability of 32 antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *Lancet* 394:939, 2019.
- H S: Personality disorders in the ICD-11: Opportunities and challenges for advancing the diagnosis of personality disorders. *Curr Psychiatry* 22:40, 2020.
- L Y et al: Development and implementation of guidelines for the management of depression: A systematic review. *Bull World Health Organ* 98:683, 2020.
- M R et al: Bipolar disorders. *Lancet* 396:10265, 2020.
- P B et al: Anxiety disorders. *Lancet* 397:914, 2021.

453

Alcohol and Alcohol Use Disorders

Marc A. Schuckit



Alcohol (beverage ethanol) has diverse and widespread effects on the body and impacts directly or indirectly on almost every neurochemical system in the brain. A large majority of patients in most clinical settings consume alcohol, with the highest proportions of drinkers of at least modest levels of alcohol seen in more educated and affluent patient groups. At even relatively low doses, this drug can exacerbate most medical problems and affect medications metabolized in the liver, and at higher doses, it can temporarily mimic many medical (e.g., diabetes) and psychiatric (e.g., depression) conditions. The lifetime risk for repetitive serious alcohol problems (e.g., alcohol use disorders as described below) in patients is at least 20% for men and 10% for women, regardless of a person's education or income, and U.S. yearly costs for these disorders exceed \$249 billion. Although low doses of alcohol might have healthful benefits, drinking more than three standard drinks per day enhances the risk for cancer and vascular disease, and alcohol use disorders decrease the life span by ~10 years. Unfortunately, most clinicians have had only limited

training regarding identifying and treating alcohol-related disorders. This chapter presents a brief overview of clinically useful information about alcohol use and associated problems.

■ PHARMACOLOGY AND NUTRITIONAL IMPACT OF ETHANOL

Ethanol blood levels are expressed as milligrams or grams of ethanol per deciliter (e.g., 100 mg/dL = 0.10 g/dL), with values of ~0.02 g/dL resulting from the ingestion of one typical drink. In round figures, a standard drink is 10–12 g of ethanol, as seen in 340 mL (12 oz) of beer, 115 mL (4 oz) of nonfortified wine, and 43 mL (1.5 oz) (a shot) of 80-proof (40% ethanol by volume) beverage (e.g., whisky); 0.5 L (1 pint) of 80-proof beverage contains ~160 g of ethanol (~16 standard drinks), and 750 mL of wine contains ~60 g of ethanol. These beverages also have additional components (*congeners*) that affect the drink's taste and might contribute to adverse effects on the body. Congeners include methanol, butanol, acetaldehyde, histamine, tannins, iron, and lead. As a depressant drug, alcohol acutely decreases neuronal activity and has similar behavioral effects and cross-tolerance with other depressants, including benzodiazepines, barbiturates, and some anticonvulsants.

Alcohol is absorbed from mucous membranes of the mouth and esophagus (in small amounts), from the stomach and large bowel (in modest amounts), and from the proximal portion of the small intestine (the major site). The rate of absorption is increased by rapid gastric emptying (as seen with carbonation); by the absence of proteins, fats, or carbohydrates (which interfere with absorption); and by dilution to a modest percentage of ethanol (maximum at ~20% by volume).

Between 2% (at low blood alcohol concentrations) and 10% (at high blood alcohol concentrations) of ethanol is excreted directly through the lungs, urine, or sweat, but most is metabolized to acetaldehyde, primarily in the liver. The most important pathway occurs in the cell cytosol where alcohol dehydrogenase (ADH) produces acetaldehyde, which is then rapidly destroyed by aldehyde dehydrogenase (ALDH) in the cytosol and mitochondria (Fig. 453-1). A second pathway occurs in the microsomes of the smooth endoplasmic reticulum (the microsomal ethanol-oxidizing system [MEOS]) that is responsible for ≥10% of ethanol oxidation at high blood alcohol concentrations.

Although a standard drink contains ~300 kJ, or 70–100 kcal, these are devoid of minerals, proteins, and vitamins. In addition, alcohol interferes with absorption of vitamins in the small intestine and decreases their storage in the liver with modest effects on folate (folacin or folic acid), pyridoxine (B₆), thiamine (B₁), nicotinic acid (niacin, B₃), and vitamin A.

Heavy drinking in a fasting, healthy individual can produce transient hypoglycemia within 6–36 h, secondary to the acute actions of ethanol that decrease gluconeogenesis. This can result in temporary abnormal glucose tolerance tests (with a resulting erroneous diagnosis of diabetes mellitus) until the heavy drinker has abstained for

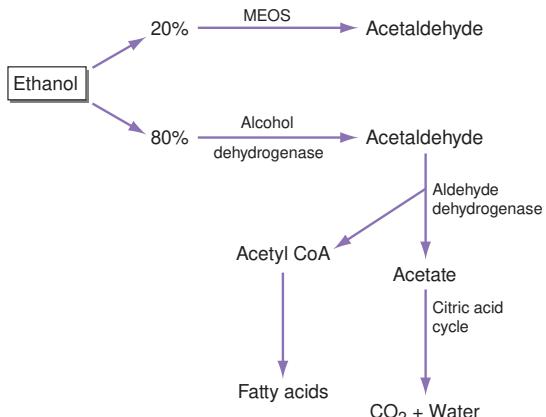


FIGURE 453-1 The metabolism of alcohol. CoA, coenzyme A; MEOS, microsomal ethanol oxidizing system.

2–4 weeks. Alcohol ketoacidosis, probably reflecting a decrease in fatty acid oxidation coupled with poor diet or persistent vomiting, can be misdiagnosed as diabetic ketosis. With alcohol-related ketoacidosis, patients show an increase in serum ketones along with a mild increase in glucose but a large anion gap, a mild to moderate increase in serum lactate, and a β-hydroxybutyrate/lactate ratio of between 2:1 and 9:1 (with normal being 1:1).

In the brain, alcohol affects almost all neurotransmitter systems, with acute effects that are often the opposite of those seen following desistance after a period of heavy drinking. The most prominent acute actions relate to boosting γ-aminobutyric acid (GABA) activity, especially at GABA_A receptors. Enhancement of this complex chloride channel system contributes to anticonvulsant, sleep-inducing, anti-anxiety, and muscle relaxation effects of all GABA-boosting drugs. Acutely administered alcohol produces a release of GABA, and continued use increases density of GABA_A receptors, whereas alcohol withdrawal states are characterized by decreases in GABA-related activity. Equally important is the ability of acute alcohol to inhibit postsynaptic N-methyl-D-aspartate (NMDA) excitatory glutamate receptors, whereas chronic drinking and desistance are associated with an upregulation of these excitatory receptor subunits. The relationships between greater GABA and diminished NMDA receptor activity during acute intoxication and diminished GABA with enhanced NMDA actions during alcohol withdrawal explain much of intoxication and withdrawal phenomena.

As with all pleasurable activities, alcohol acutely increases dopamine levels in the ventral tegmentum and related brain regions, and this effect plays an important role in continued alcohol use, craving, and relapse. The changes in dopamine pathways are also linked to increases in "stress hormones," including cortisol and adrenocorticotropic hormone (ACTH), during intoxication and in the context of the stresses of withdrawal. Such alterations are likely to contribute to both feelings of reward during intoxication and depression during falling blood alcohol concentrations. Also closely linked to alterations in dopamine (especially in the nucleus accumbens) are alcohol-induced changes in opioid receptors, with acute alcohol causing release of β-endorphins.

Additional neurochemical changes include increases in synaptic levels of serotonin during acute intoxication and subsequent upregulation of serotonin receptors. Acute increases in nicotinic acetylcholine systems contribute to the impact of alcohol in the ventral tegmental region, which occurs in concert with enhanced dopamine activity. In the same regions, alcohol impacts on cannabinol receptors, with resulting release of dopamine, GABA, and glutamate as well as subsequent effects on brain reward circuits.

■ BEHAVIORAL EFFECTS, TOLERANCE, AND WITHDRAWAL

The acute effects of a drug depend on the dose, the rate of increase in plasma, the concomitant presence of other drugs, and past experience with the agent. "Legal intoxication" with alcohol in most states is based on a blood alcohol concentration of 0.08 g/dL, some states are considering lowering acceptable levels to <0.05 g/dL, and levels of 0.04 g/dL are cited for pilots in the United States and automobile drivers in some other countries. However, behavioral, psychomotor, and cognitive changes are seen at 0.02–0.04 g/dL (i.e., after one to two drinks) (Table 453-1). Deep but disturbed sleep can be seen at 0.15 g/dL in individuals who have not developed tolerance, and death can occur with levels between 0.30 and 0.40 g/dL. Beverage alcohol is probably responsible for more overdose deaths than any other drug.

Repeated use of alcohol contributes to the need for a greater number of standard drinks to produce effects originally observed with fewer drinks (acquired tolerance), a phenomenon involving at least three compensatory mechanisms. (1) After 1–2 weeks of daily drinking, *metabolic* or *pharmacokinetic tolerance* can be seen, with up to 30% increases in the rate of hepatic ethanol metabolism. This alteration disappears almost as rapidly as it develops. (2) *Cellular* or *pharmacodynamic tolerance* develops through neurochemical changes that maintain relatively normal physiologic functioning despite the presence of alcohol. Subsequent decreases in blood levels contribute to symptoms

TABLE 453-1 Effects of Blood Alcohol Levels in the Absence of Tolerance

BLOOD LEVEL, g/dL	USUAL EFFECT
0.02	Decreased inhibitions, a slight feeling of intoxication
0.08	Decrease in complex cognitive functions and motor performance
0.20	Obvious slurred speech, motor incoordination, irritability, and poor judgment
0.30	Light coma and depressed vital signs
0.40	Death

of withdrawal. (3) Individuals learn to adapt their behavior so that they can function better than expected under the influence of the drug (*learned or behavioral tolerance*).

The cellular changes caused by chronic ethanol exposure may not resolve for several weeks or longer following cessation of drinking. Rapid decreases in blood alcohol levels before that time can produce a withdrawal syndrome, which is most intense during the first 5 days, but with some symptoms (e.g., disturbed sleep and anxiety) lasting up to 4–6 months as part of a “protracted withdrawal” syndrome.

THE EFFECTS OF ETHANOL ON ORGAN SYSTEMS

Relatively low doses of alcohol (one or two drinks per day) may have potential beneficial effects of increasing high-density lipoprotein cholesterol and decreasing aggregation of platelets, with a resulting possible decrease in risk for occlusive coronary disease and embolic strokes. Red wine has additional potential health-promoting qualities at relatively low doses due to flavinols and related substances. Such modest drinking might also decrease the risk for vascular dementia and, possibly, Alzheimer’s disease. However, any potential healthful effects disappear with the regular consumption of three or more drinks per day, and knowledge about the deleterious effects of alcohol can both help the physician to identify patients with alcohol use disorders and supply them with information that might help motivate changes in behavior.

NERVOUS SYSTEM

Approximately 35% of drinkers overall, including as many as 50% of drinking college students and a much higher proportion of individuals with alcohol use disorders, ever experience a *blackout*. This is an episode of temporary anterograde amnesia, in which the person was awake but forgot all (en bloc blackouts at blood alcohol levels >0.20 mg/dL) or part (fragmentary blackouts at >0.12 mg/dL) of what occurred during a drinking period.

Another common problem, one seen after as few as one or two drinks shortly before bedtime, is disturbed sleep. Although alcohol might initially help a person fall asleep, it disrupts sleep throughout the rest of the night. The stages of sleep are altered, and times spent in rapid eye movement (REM) and deep sleep early in the night are reduced. Alcohol relaxes muscles in the pharynx, which can cause snoring and exacerbate sleep apnea; symptoms of the latter occur in 75% of men with alcohol use disorders aged ≥60 years. Patients may also experience prominent and sometimes disturbing dreams later in the night. All these sleep impairments can contribute to relapses to drinking in persons with alcohol use disorders.

Other common consequences of alcohol use even at relatively low alcohol levels are impaired judgment and coordination, which increase the risk of injuries. In the United States, ~40% of drinkers have at some time driven while intoxicated. Heavy drinking can also be associated with headache, thirst, nausea, vomiting, and fatigue the following day, a hangover syndrome that is responsible for much missed work and school time and temporary cognitive deficits.

Chronic high alcohol doses cause *peripheral neuropathy* in ~10% of individuals with alcohol use disorders: similar to diabetes, patients experience bilateral limb numbness, tingling, and paresthesias, all of which are more pronounced distally. Approximately 1% of those

with alcohol use disorders develop *cerebellar degeneration* or *atrophy*, producing a syndrome of progressive unsteady stance and gait often accompanied by mild nystagmus; neuroimaging studies reveal atrophy of the cerebellar vermis. Perhaps 1 in 500 individuals with alcohol use disorders develop full *Wernicke’s* (ophthalmoparesis, ataxia, and encephalopathy) and *Korsakoff’s* (severe retrograde and anterograde amnesia) syndromes, although a higher proportion has one or more neuropathologic findings related to these conditions. These result from low levels of thiamine, especially in predisposed individuals with transketolase deficiencies. Repeated heavy drinking can contribute to *cognitive problems* and temporary memory impairment lasting for weeks to months after abstinence. Brain atrophy, evident as ventricular enlargement and widened cortical sulci on magnetic resonance imaging (MRI) and computed tomography (CT) scans, occurs in ~50% of individuals with long-term alcohol use disorders; these changes are usually reversible if abstinence is maintained. Adolescents may be especially vulnerable to alcohol-related brain changes, as indicated by preclinical studies and prospective investigations in humans suggesting that alcohol exposure in the developing brain may adversely impact future cognitive processes related to cognition, reward recognition, and cue processing. There is no single “alcoholic dementia” syndrome; rather, this label describes patients who have irreversible cognitive changes (possibly from diverse causes) in the context of chronic alcohol use disorders.

Psychiatric Comorbidity As many as two-thirds of individuals with alcohol use disorders meet criteria for another independent or temporary substance-induced psychiatric syndrome as defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) of the American Psychiatric Association (Chap. 452). A substantial proportion of those with independent psychiatric conditions (i.e., not just temporary symptoms only seen during intoxication or withdrawal) relate to a preexisting antisocial personality disorder (ASPD) manifesting as severe impulsivity and disinhibition that contribute to both alcohol and drug use disorders. The lifetime ASPD risk is 3% in males, and >80% of such individuals demonstrate alcohol- and/or drug-related conditions. Another common psychiatric comorbidity occurs with problems regarding other substances of abuse. The remainder of individuals with alcohol use disorders who have an independent psychiatric syndrome relate to preexisting conditions such as schizophrenia, manic-depressive disease, posttraumatic stress disorder, or anxiety syndromes such as panic disorder. The comorbidities of alcohol use disorders with independent psychiatric disorders might represent an overlap in genetic vulnerabilities, impaired judgment regarding the use of alcohol from the independent psychiatric condition, or an attempt to use alcohol to alleviate symptoms of the disorder or side effects of medications.

Many alcohol-related psychiatric syndromes can be seen *temporarily* during heavy drinking and subsequent withdrawal. These alcohol-induced conditions include an intense *sadness* lasting for days to weeks in the midst of heavy drinking seen in 40% of individuals with alcohol use disorders, which tends to disappear over several weeks of abstinence (alcohol-induced mood disorder); 10–30% have temporary severe *anxiety*, often beginning during alcohol withdrawal, which can persist for a month or more after cessation of drinking (alcohol-induced anxiety disorder); and 3–5% have auditory *hallucinations* and/or paranoid delusions while they are otherwise alert and oriented (alcohol-induced psychotic disorder).

Treatment of all forms of alcohol-induced psychopathology includes helping patients achieve abstinence and offering supportive care, as well as reassurance and “talk therapy” such as cognitive-behavioral approaches. However, with the exception of short-term antipsychotic medications for substance-induced psychoses, substance-induced psychiatric conditions only rarely require medications. Recovery is likely within several days to 4 weeks of abstinence. Conversely, because alcohol-induced conditions are temporary and do not indicate a need for long-term pharmacotherapy, a history of heavy alcohol intake is an important part of the workup for any patient who presents with any of these psychiatric symptoms.

■ THE GASTROINTESTINAL SYSTEM

Esophagus and Stomach Alcohol can cause inflammation of the esophagus and stomach causing epigastric distress and gastrointestinal bleeding, making alcohol one of the most common causes of hemorrhagic gastritis. Violent vomiting can produce severe bleeding through a Mallory-Weiss lesion, a longitudinal tear in the mucosa at the gastoesophageal junction.

Pancreas and Liver The incidence of acute pancreatitis (~25 per 1000 per year) is almost threefold higher in individuals with alcohol use disorders than in the general population, accounting for an estimated 10% or more of the total cases. Alcohol impairs gluconeogenesis in the liver, resulting in a fall in the amount of glucose produced from glycogen, increased lactate production, and decreased oxidation of fatty acids. These contribute to an increase in fat accumulation in liver cells. In healthy individuals, these changes are reversible, but with repeated exposure to ethanol, especially daily heavy drinking, more severe changes in the liver occur, including alcohol-induced hepatitis, perivenular sclerosis, and cirrhosis, with the latter observed in an estimated 15% of individuals with alcohol use disorders (Chap. 342). Perhaps through an enhanced vulnerability to infections, individuals with alcohol use disorders have an elevated rate of hepatitis C, and drinking in the context of that disease is associated with more severe liver deterioration.

■ CANCER

As few as 1.5 drinks per day increases a woman's risk of breast cancer 1.4-fold. For both sexes, four drinks per day increases the risk for oral and esophageal cancers approximately threefold and rectal cancers by a factor of 1.5; seven to eight or more drinks per day produces an approximately fivefold increased risk for many other cancers. These consequences may result directly from cancer-promoting effects of alcohol and acetaldehyde or indirectly by interfering with immune homeostasis.

■ HEMATOPOIETIC SYSTEM

Ethanol causes an increase in red blood cell size (mean corpuscular volume [MCV]), which reflects its effects on stem cells. If heavy drinking is accompanied by folic acid deficiency, there can also be hypersegmented neutrophils, reticulocytopenia, and a hyperplastic bone marrow; if malnutrition is present, sideroblastic changes can be observed. Chronic heavy drinking can decrease production of white blood cells, decrease granulocyte mobility and adherence, and impair delayed-hypersensitivity responses to novel antigens (with a possible false-negative tuberculin skin test). Associated immune deficiencies can contribute to vulnerability toward infections, including hepatitis and HIV, and interfere with their treatment. Finally, many individuals with alcohol use disorders have mild thrombocytopenia, which usually resolves within a week of abstinence unless there is hepatic cirrhosis or congestive splenomegaly.

■ CARDIOVASCULAR SYSTEM

Acutely, ethanol decreases myocardial contractility and causes peripheral vasodilation, with a resulting mild decrease in blood pressure and a compensatory increase in cardiac output. Exercise-induced increases in cardiac oxygen consumption are higher after alcohol intake. These acute effects have little clinical significance for the average healthy drinker but can be problematic when persisting cardiac disease is present.

The consumption of three or more drinks per day results in a dose-dependent increase in blood pressure, which returns to normal within weeks of abstinence. Thus, heavy drinking is an important factor in mild to moderate hypertension. Chronic heavy drinkers also have a sixfold increased risk for coronary artery disease, related, in part, to increased low-density lipoprotein cholesterol, and carry an increased risk for cardiomyopathy through direct effects of alcohol on heart muscle. Symptoms of the latter include unexplained arrhythmias in the presence of left ventricular impairment, heart failure, hypocontractility of heart muscle, and dilation of all four heart chambers with associated

potential mural thrombi and mitral valve regurgitation. Atrial or ventricular arrhythmias, especially paroxysmal tachycardia, can also occur temporarily after heavy drinking in individuals showing no other evidence of heart disease—a syndrome known as the "holiday heart."

■ GENITOURINARY SYSTEM CHANGES, SEXUAL FUNCTIONING, AND FETAL DEVELOPMENT

Heavy drinking in adolescence can affect normal sexual development and reproductive onset. At any age, modest ethanol doses (e.g., blood alcohol concentrations of 0.06 g/dL) can increase sexual drive but also decrease erectile capacity in men. Even in the absence of liver impairment, a significant minority of chronic heavy drinking men show irreversible testicular atrophy with shrinkage of the seminiferous tubules, decreases in ejaculate volume, and a lower sperm count (Chap. 391).

The repeated ingestion of high doses of ethanol by women can result in amenorrhea, a decrease in ovarian size, absence of corpora lutea with associated infertility, and an increased risk of spontaneous abortion. Drinking during pregnancy results in the rapid placental transfer of both ethanol and acetaldehyde, which may contribute to a range of consequences known as fetal alcohol spectrum disorder (FASD). One severe result is the *fetal alcohol syndrome* (FAS), seen in ~5% of children born to heavy-drinking mothers, which can include any of the following: facial changes with epicanthal eye folds; poorly formed ear concha; small teeth with faulty enamel; cardiac atrial or ventricular septal defects; an aberrant palmar crease and limitation in joint movement; and microcephaly with intellectual impairment. Less pervasive FASD conditions include combinations of low birth weight, a lower intelligence quotient (IQ), hyperactive behavior, and some modest cognitive deficits. The amount of ethanol required and the time of vulnerability during pregnancy have not been defined, making it advisable for pregnant women to abstain from alcohol completely.

■ OTHER EFFECTS

Between one-half and two-thirds of individuals with alcohol use disorders have skeletal muscle weakness caused by acute *alcoholic myopathy*, a condition that improves but that might not fully remit with abstinence. Effects of repeated heavy drinking on the *skeletal system* include changes in calcium metabolism, lower bone density, and decreased growth in the epiphyses, leading to an increased risk for fractures and osteonecrosis of the femoral head. *Hormonal changes* include an increase in cortisol levels, which can remain elevated during heavy drinking; inhibition of vasopressin secretion at rising blood alcohol concentrations and enhanced secretion at falling blood alcohol concentrations (with the final result that most individuals with alcohol use disorders are likely to be slightly overhydrated); a modest and reversible decrease in serum thyroxine (T_4); and a more marked decrease in serum triiodothyronine (T_3). Hormone irregularities may disappear after a month or more of abstinence.

■ ALCOHOL USE DISORDERS

Because many drinkers occasionally imbibe to excess, temporary alcohol-related problems are common, especially in the late teens to the late twenties. However, repeated problems in multiple life areas can indicate an alcohol use disorder as defined in DSM-5.

■ DEFINITIONS AND EPIDEMIOLOGY

An *alcohol use disorder* (also called *alcoholism* or *alcohol dependence* in prior diagnostic manuals) is defined as repeated alcohol-related difficulties in at least 2 of 11 life areas that cluster together in the same 12-month period (Table 453-2). Ten of the 11 items in DSM-5 (published in 2013) were taken directly from the 7 dependence and 4 abuse criteria in DSM-IV, after deleting legal problems and adding craving. Severity of an alcohol use disorder is based on the number of items endorsed: mild is two or three items; moderate is four or five; and severe is six or more of the criterion items. The 2013 diagnostic approach is similar enough to DSM-IV that the following descriptions of associated phenomena are still accurate.

The lifetime risk for an alcohol use disorder in most Western countries is ~10–20% for men and 5–10% for women; higher rates are seen in individuals who seek help from health care deliverers. Between 2001

TABLE 453-2 *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Classification of Alcohol Use Disorder (AUD)**Criteria**

- Two or more of the following items occurring in the same 12-month period must be endorsed for the diagnosis of an alcohol use disorder^a:
- Drinking resulting in recurrent failure to fulfill role obligations
 - Recurrent drinking in hazardous situations
 - Continued drinking despite alcohol-related social or interpersonal problems
 - Tolerance
 - Withdrawal, or substance use for relief/avoidance of withdrawal
 - Drinking in larger amounts or for longer than intended
 - Persistent desire/unsuccessful attempts to stop or reduce drinking
 - Great deal of time spent obtaining, using, or recovering from alcohol
 - Important activities given up/reduced because of drinking
 - Continued drinking despite knowledge of physical or psychological problems caused by alcohol
 - Alcohol craving

^aMild AUD: 2–3 criteria required; moderate AUD: 4–5 items endorsed; severe AUD: 6 or more items endorsed.

and 2013, the proportion of the U.S. population with a current (i.e., past 12 months) alcohol use disorder increased by 49% with increases of almost 100% in women, African Americans, and individuals aged ≥45. Rates are similar in the United States, Canada, Germany, Australia, and the United Kingdom; tend to be lower in most Mediterranean countries, such as Italy, Greece, and Israel; and may be higher in Ireland, France, Eastern Europe (e.g., Russia), and Scandinavia. An even higher lifetime prevalence has been reported for most native cultures, including Native Americans, Eskimos, Maori groups, and aboriginal tribes of Australia. These differences in prevalence reflect both cultural and genetic influences, as described below. In Western countries, the typical person with an alcohol use disorder is more often a blue- or white-collar worker or homemaker. The lifetime risk for this disorder among physicians is similar to that of the general population.

GENETICS

 Approximately 60% of the risk for alcohol use disorders is attributed to genes, as indicated by the fourfold higher risk in children with an alcohol use disorder parent (even if adopted early in life and raised by nonalcoholics) and a higher risk in identical twins compared to fraternal twins of affected individuals. Like most medical and psychiatric conditions that are referred to as complex genetically influenced disorders, the risk for alcohol use disorders is related to hundreds of gene variations, each of which explains <1% of the vulnerability. These genetic variations operate primarily through intermediate characteristics that subsequently combine with environmental influences to alter the risk for heavy drinking and alcohol problems. These include genes relating to a high risk for all substance use disorders that operate through impulsivity, schizophrenia, and bipolar disorder. Another characteristic, an intense skin flushing response when drinking, decreases the risk for only alcohol use disorders through gene variations for several alcohol-metabolizing enzymes, especially ALDH (a mutation only seen in Japanese, Chinese, and Korean individuals), and to a lesser extent, variations in ADH.

An additional genetically influenced characteristic that increases the risk for heavy drinking, a low level of response or low sensitivity to alcohol, can be seen very early in the drinking career and before acquired tolerance or alcohol use disorders develop. The low response per drink operates, in part, through variations in genes relating to calcium and potassium channels, GABA, nicotinic, dopamine, and serotonin systems. Prospective studies have demonstrated that this need for higher doses of alcohol to achieve effects predicts future heavy drinking, alcohol problems, and alcohol use disorders, but not problems with drugs other than alcohol. The impact of a low response to alcohol on adverse drinking outcomes is partially mediated by a range of environmental and attitudinal influences, including the selection of heavier-drinking friends, more positive expectations of the effects of

high doses of alcohol, and using alcohol to cope with stress. Several studies of college freshmen demonstrated that helping students who have a low sensitivity to alcohol modify these influences was associated with lower drinking quantities and fewer alcohol-related problems over the subsequent year.

NATURAL HISTORY

Although the average age of the first drink (~15 years) is similar in individuals who do and do not go on to develop alcohol use disorders, an earlier onset of regular drinking and drunkenness, especially in the context of conduct problems, is associated with a higher risk for later alcohol-related diagnoses. By the mid-twenties, most nonalcoholic men and women begin to moderate their drinking (perhaps learning from negative consequences), whereas those with alcohol use disorders are likely to escalate their drinking despite difficulties. The first major life problem from alcohol often appears in the late teens to early twenties, and a pattern of multiple alcohol difficulties by the mid-twenties. Once established, the course is likely to include exacerbations and remissions, with little difficulty in temporarily stopping or controlling alcohol use when problems develop, but without help, desistance usually gives way to escalations in alcohol intake and subsequent problems. Following treatment, between half and two-thirds of those with alcohol use disorders maintain abstinence for at least a year and often permanently. Even without formal treatment or self-help groups, there is at least a 20% chance of spontaneous remission with long-term abstinence. However, should the individual continue to drink heavily, the life span is shortened by ~10 years on average, with the leading causes of early death being enhanced rates of heart disease, cancer, accidents, and suicide.

TREATMENT

The approach to treating alcohol-related conditions is relatively straightforward: (1) recognize that at least 20% of patients have an alcohol use disorder; (2) learn how to identify and treat acute alcohol-related conditions (e.g., severe intoxication); (3) know how to help patients begin to address their alcohol problems; and (4) know how to treat alcohol withdrawal symptoms and to appropriately refer patients for additional help.

IDENTIFICATION OF PATIENTS WITH ALCOHOL USE DISORDERS

Even in affluent locales, the ~20% of patients who have an alcohol use disorder can be identified by asking questions about *alcohol problems* and noting laboratory test results that can reflect regular consumption of six to eight or more drinks per day. The two blood tests with ≥60% sensitivity and specificity for heavy alcohol consumption are γ-glutamyl transferase (GGT) (>35 U) and carbohydrate-deficient transferrin (CDT) (>20 U/L or >2.6%); the combination of the two tests is likely to be more accurate than either alone. The values for these serologic markers are likely to return toward normal within several weeks of abstinence. Other useful blood tests include high-normal MCVs ($\geq 1 \mu\text{m}^3$) and serum uric acid (>416 mol/L, or 7 mg/dL).

The diagnosis of an alcohol use disorder ultimately rests on the documentation of a pattern of repeated difficulties associated with alcohol (Table 453-2). Thus, in screening, it is important to probe for marital or job problems, legal difficulties, histories of accidents, medical problems, evidence of tolerance, and so on, and then attempt to relate these issues to use of alcohol. Some standardized questionnaires can be helpful, including the 10-item Alcohol Use Disorders Identification Test (AUDIT) (Table 453-3), but these are only screening tools, and a face-to-face interview is still required for a meaningful diagnosis.

TREATMENT**Alcohol-Related Conditions****ACUTE INTOXICATION**

The first priority in treating severe intoxication is to assess vital signs and manage respiratory depression, cardiac arrhythmias, and blood pressure instability, if present. The possibility of intoxication

ITEM	5-POINT SCALE (LEAST TO MOST)
1. How often do you have a drink containing alcohol?	Never (0) to 4+ per week (4)
2. How many drinks containing alcohol do you have on a typical day?	1 or 2 (0) to 10+ (4)
3. How often do you have six or more drinks on one occasion?	Never (0) to daily or almost daily (4)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) to daily or almost daily (4)
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) to daily or almost daily (4)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) to daily or almost daily (4)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) to daily or almost daily (4)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) to daily or almost daily (4)
9. Have you or someone else been injured as a result of your drinking?	No (0) to yes, during the last year (4)
10. Has a relative, friend, doctor, or other health worker been concerned about your drinking or suggested that you should cut down?	No (0) to yes, during the last year (4)

^aThe AUDIT is scored by simply summing the values associated with the endorsed response. A score ≥8 may indicate harmful alcohol use.

with other drugs should be considered by obtaining, if needed, toxicology screens for other central nervous system (CNS) depressants such as benzodiazepines and for opioids. Aggressive behavior should be handled by offering reassurance but also by calling for help from an intervention team. If the aggressive behavior continues, relatively low doses of a short-acting benzodiazepine such as lorazepam (e.g., 1–2 mg PO or IV) may be used and can be repeated as needed, but care must be taken not to destabilize vital signs or worsen confusion. An alternative approach is to use an antipsychotic medication (e.g., olanzapine 2.5–10 mg IM repeated at 2 and 6 h, if needed).

INTERVENTION

There are two main elements to highlighting the need for compliance with treatment in a person with an alcohol use disorder: motivational interviewing and brief interventions. During motivational interviewing, the clinician helps the patient to think through the assets (e.g., comfort in social situations) and liabilities (e.g., health- and interpersonal-related problems) of the current pattern of drinking. The clinician should listen empathetically to the responses, help the patient weigh options, and encourage the taking of responsibility for needed changes. Patients should be reminded that only they can decide to avoid the consequences that will occur if heavy drinking continues. The process of brief intervention, a similar approach, has been summarized by the acronym FRAMES: *F*eedback to the patient; *R*esponsibility to be taken by the patient; *A*dvice, rather than orders, on what needs to be done; *M*enus of options that might be considered; *E*mpathy for understanding the patient's thoughts and feelings; and *S*elf-efficacy, i.e., offering support for the capacity of the patient to make changes.

Once the patient begins to consider change, the discussions can focus more on the consequences of high alcohol consumption, suggested approaches to stopping drinking, and help in recognizing and avoiding situations likely to lead to heavy drinking such as going to night clubs or associating with heavy drinking friends. Both motivational interviewing and brief interventions can be carried out in 15-min sessions, but because patients often do not change behavior immediately, multiple meetings are often required

to explore the problem and possible options, discuss optimal treatments, and explain the benefits of abstinence.

ALCOHOL WITHDRAWAL

If the patient agrees to stop drinking, sudden decreases in alcohol intake can produce withdrawal symptoms, most of which are the opposite of those produced by intoxication. Features include tremor of the hands (shakes); agitation and anxiety; autonomic nervous system overactivity including an increase in pulse, respiratory rate, sweating, and body temperature; and insomnia. These symptoms usually begin within 5–10 h of decreasing ethanol intake, peak on day 2 or 3, and improve by day 4 or 5, although mild levels of these problems may persist for 4–6 months as a protracted abstinence syndrome.

About 2% of individuals with alcohol use disorders experience a withdrawal seizure, with the risk increasing in the context of older age, concomitant medical problems, misuse of additional drugs, and higher alcohol quantities. The same risk factors also contribute to the ~1% rate of withdrawal delirium, also known as *delirium tremens* (DTs), where the withdrawal includes delirium (mental confusion, agitation, and fluctuating levels of consciousness) associated with a tremor and autonomic overactivity (e.g., marked increases in pulse, blood pressure, and respirations). The risks for seizures and DTs can be diminished by identifying and treating underlying medical conditions early in the course of withdrawal and by instituting adequate doses of depressant medications such as benzodiazepines.

Thus, the first step in dealing with possible withdrawal phenomena is a thorough physical examination in all heavy drinkers who are considering abstinence. This includes evaluation of possible liver impairment, gastrointestinal bleeding, cardiac arrhythmias, infection, and glucose or electrolyte imbalances. It is also important to offer adequate nutrition and oral multiple B vitamins, including 50–100 mg of oral thiamine daily for a week or more. Because most patients with alcohol use disorders who enter withdrawal are either normally hydrated or mildly overhydrated, IV fluids should be avoided unless there is a relevant medical problem or significant recent bleeding, vomiting, or diarrhea.

The next step is to recognize that because withdrawal symptoms reflect the rapid removal of a CNS depressant, alcohol, the symptoms can be controlled by administering any depressant in doses that decrease symptoms (e.g., a rapid pulse and tremor) and then tapering the dose over 3–5 days. Although most depressants are effective, benzodiazepines (Chap. 452) have the most supportive data for use in this situation, combining a high level of safety and low cost. Short-half-life benzodiazepines can be considered for patients with serious liver impairment or evidence of significant brain damage, but they must be given every 4 h to avoid abrupt blood-level fluctuations that may increase the risk for seizures. Therefore, most clinicians use drugs with longer half-lives (e.g., chlordiazepoxide), adjusting the dose if signs of withdrawal escalate and withholding the drug if the patient is sleeping or has orthostatic hypotension. The average patient requires 25–50 mg of chlordiazepoxide or 10 mg of diazepam given PO every 4–6 h on the first day, with doses then decreased to zero over the next 5 days. Although alcohol withdrawal can be treated in a hospital, patients in good physical condition who demonstrate mild signs of withdrawal despite low blood alcohol concentrations and who have no prior history of DTs or withdrawal seizures can be considered for outpatient detoxification. For the next 4 or 5 days, these patients should receive only 1 or 2 days of medications at a time and return daily for evaluation of vital signs. They can be hospitalized if signs and symptoms of withdrawal markedly escalate.

Treatment of patients with DTs can be challenging, and the condition is likely to run a course of 3–5 days regardless of the therapy used. However, conditions that meet the criteria for DTs outlined above represent medical emergencies that carry an estimated mortality as high as 5%, and treatment is best carried out in an intensive care unit by well-trained clinicians who closely monitor vital signs.

Medications can include high-dose benzodiazepines (e.g., as much as 800 mg/d of chlordiazepoxide has been reported) or, for those who do not respond to that regimen, closely monitored doses of propofol or dexmedetomidine. The focus of care is to identify and correct medical problems and to control behavior and prevent injuries. Antipsychotic medications are not recommended for treatment of alcohol withdrawal symptoms; although antipsychotics are less likely than benzodiazepines to exacerbate confusion, they may increase the risk of seizures.

Generalized withdrawal seizures rarely require more than the administration of an adequate dose of benzodiazepines. There is little evidence that anticonvulsants such as phenytoin or gabapentin are more effective than benzodiazepines for alcohol-withdrawal seizures, and the risk of seizures has usually passed by the time effective drug levels are reached. The rare patient with status epilepticus must be treated aggressively (Chap. 425).

HELPING INDIVIDUALS WITH ALCOHOL USE DISORDERS TO STOP DRINKING: THE REHABILITATION PHASE

An Overview After completing alcoholic rehabilitation, ≥60% of individuals with alcohol use disorders, especially highly functioning patients, maintain abstinence for at least a year; many also achieve long-term sobriety. The core components of the rehabilitation phase of treatment include cognitive-behavioral approaches to help patients recognize the need to change, while working with them to alter their behaviors to enhance compliance. A key step is to optimize motivation toward abstinence through education of patients and their significant others about alcohol use disorders and their likely course over time. It is important to recognize that contrary to what some physicians might think, the typical person with an alcohol use disorder is likely to have a job and a family and not fit the inaccurate “down and out” stereotype. However, after years of heavy drinking, some patients require vocational or avocational counseling to help to structure their days, and all patients should try self-help groups such as Alcoholics Anonymous (AA) to assist them in developing a sober peer group and to learn how to deal with life’s stresses while remaining sober. *Relapse prevention education* helps patients identify situations in which a return to drinking is likely (e.g., stopping in a bar to meet friends but planning to only have a nonalcoholic beverage), formulate ways to avoid the risky situation, and if not possible, mitigate the risks to which they are exposed. It is also important to develop coping strategies that increase the chances of a quick return to abstinence after an episode of drinking.

Although many patients can be treated as outpatients, more intense interventions are more effective, and some individuals with alcohol use disorders do not respond to just AA or outpatient groups. Whatever the setting, ongoing contact with outpatient treatment staff should be maintained for at least 6 months and preferably for a year after abstinence. Counseling focuses on areas of improved functioning in the absence of alcohol (i.e., why it is a good idea to continue abstinence), helping patients to manage free time without alcohol, encouraging them to develop a nondrinking peer group, and discussions of ways to handle stress without drinking.

The physician serves an important role in identifying the alcohol problem, diagnosing and treating associated medical and independent or substance-induced psychiatric syndromes, overseeing detoxification, referring the patient to outpatient or inpatient rehabilitation programs, providing counseling, and, if appropriate, selecting which (if any) medication might be needed. For insomnia, patients should be reassured that troubled sleep is temporary after alcohol withdrawal and will begin to improve over subsequent weeks. They should be taught the elements of “sleep hygiene” including maintaining consistent schedules for bedtime and awakening, avoiding exercise or consumption of large meals before bedtime, and keeping the bedroom cool, dark, and quiet at night (Chap. 31). Depressant sleep medications are not the optimal approach for this type of insomnia that often continues for several weeks or months. Patients are likely to develop rebound insomnia when the depressant dose is decreased or stopped. The

rebound increases the chance they will increase the dose and potentially develop problems controlling the prescribed depressant drug. Sedating antidepressants (e.g., trazodone) should not be used because they interfere with cognitive functioning the next morning and disturb the normal sleep architecture, but occasional use of over-the-counter sleeping medications (sedating antihistamines) can be considered. An additional problem, anxiety symptoms, can be addressed by increasing patients’ insights into the temporary nature of the symptoms and helping them develop strategies to achieve relaxation by using forms of cognitive therapy.

Medications for the Alcohol Rehabilitation Treatment Phase

Several medications have modest benefits when used in the first 6–12 months of recovery. The opioid antagonist naltrexone may shorten subsequent relapses, whether used in the oral form (50–150 mg/d) or as a once-per-month 380-mg injection. By blocking opioid receptors, naltrexone decreases activity in the dopamine-rich ventral tegmental reward system and decreases the feeling of pleasure if alcohol is imbibed. A second medication, acamprosate (Campral) (~2 g/d divided into three oral doses), has similar modest effects. Acamprosate inhibits NMDA receptors, decreasing mild symptoms of protracted withdrawal. Several trials of combined naltrexone and acamprosate have reported that the combination is well tolerated and the efficacy might be superior to either drug alone, although not all studies agree.

It is more difficult to establish the asset-to-liability ratio of a third drug, disulfiram, an ALDH inhibitor, used clinically at doses of 250 mg/d, a dose usually selected to avoid the side effects of the more effective 500 mg/d regimen. This drug produces vomiting and autonomic nervous system instability in the presence of alcohol as a result of rapidly rising blood levels of acetaldehyde. This reaction can be dangerous, especially for patients with heart disease, stroke, diabetes mellitus, or hypertension. The drug itself carries potential risks of temporary depressive or psychotic symptoms, peripheral neuropathy, and liver damage. Disulfiram is best given under supervision by someone (such as a spouse), especially during high-risk drinking situations (such as the Christmas holidays).

A 16-week, placebo-controlled trial in patients with relatively severe acute withdrawal reported better outcomes with use of a depressant medication (gabapentin 1200 mg/d), but those results have not yet been replicated. Additional drugs under investigation include another opioid antagonist, nalmefene; the nicotinic receptor agonist varenicline; the serotonin antagonist ondansetron; the α -adrenergic agonist prazosin; the GABA_B receptor agonist baclofen; the anticonvulsant topiramate; and cannabinol receptor antagonists. At present, there are insufficient data to determine the asset-to-liability ratio for these medications in treating alcohol use disorders, and therefore, few data yet offer solid support for their routine use in clinical settings.

■ GLOBAL CONSIDERATIONS

As described above, rates of alcohol use disorders differ across sex, age, ethnicity, and country. There are also differences across countries regarding the definition of a standard drink (e.g., 10–12 g of ethanol in the United States and 8 g in the United Kingdom) and the definition of being legally drunk. The preferred alcoholic beverage also varies across groups, even within countries. That said, regardless of sex, ethnicity, or country, the actual drug in the drink is still ethanol, and the risks for problems, course of alcohol use disorders, and approaches to treatment are similar across the world.

■ FURTHER READING

- A RF et al: Efficacy of gabapentin for the treatment of alcohol use disorder in patients with alcohol withdrawal symptoms: A randomized clinical trial. *JAMA Intern Med* 180:728, 2020.
- C KE et al: The effect of alcohol use on neuroimaging correlates of cognitive and emotional processing in human adolescents. *Neuropsychopharmacology* 33:781, 2019.

- G BF et al: Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001–2002 to 2012–2013: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry* 74:911, 2017.
- S MA: Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med* 371:2109, 2014.
- S MA: A critical review of methods and results in the search for genetic contributors to alcohol sensitivity. *Alcohol Clin Exp Res* 42:822, 2018.
- S MA et al: The low level of response to alcohol-based heavy drinking prevention program: One-year follow-up. *J Stud Alcohol Drugs* 77:25, 2016.
- S FP, G DH: Defining the genetic, genomic, cellular, and diagnostic architecture of psychiatric disorders. *Cell* 177:162, 2019.
- W K et al: Advances in the science and treatment of alcohol use disorder. *Sci Adv* 5:1, 2019.

genetic susceptibility can influence the probability that adolescent experimentation with tobacco will lead to addiction as an adult. Rates of smoking cessation have increased, and rates of nicotine addiction have decreased dramatically, since the mid-1950s, suggesting that factors other than genetics are more important influences for tobacco use.

Adult cigarette smoking prevalence has declined to below 14% in the United States, with only 75% of the cigarette smokers smoking every day. The rapidly rising smoking rate observed in the developing world is of concern, and the World Health Organization Framework Convention on Tobacco Control is encouraging effective tobacco control approaches in these countries with the hope of preventing a future epidemic of tobacco-related illness.

DISEASE MANIFESTATIONS OF CIGARETTE SMOKING

More than 480,000 individuals die prematurely each year in the United States from cigarette use; this represents almost one of every five deaths in the United States. Approximately 40% of cigarette smokers will die prematurely due to cigarette smoking unless they are able to quit.

The major diseases caused by cigarette smoking are listed in **Table 454-1**. The ratio of smoking-related disease rates in smokers compared to never smokers (relative risk) increases with advancing age for most cancers and for chronic obstructive pulmonary disease (COPD). However, relative risk declines with advancing age for cardiovascular diseases due to the increasing contribution of other risk factors as age advances. Nevertheless, even for cardiovascular disease, the absolute difference in mortality rate between smokers and never smokers, called excess death rate, continues to increase with advancing age, as one would expect from a process of cumulative injury.

454 Nicotine Addiction

David M. Burns



The use of tobacco leaf to create and satisfy nicotine addiction was introduced to Columbus by Native Americans and spread rapidly to Europe. Use of tobacco as cigarettes, however, only became popular in the twentieth century and so is a modern phenomenon, as is the epidemic of disease caused by this form of tobacco use.

Nicotine is the principal constituent of tobacco responsible for its addictive character, but other smoke constituents and behavioral associations contribute to the strength of the addiction. Addicted smokers regulate their nicotine intake by adjusting the frequency and intensity of their tobacco use both to obtain the desired psychoactive effects and avoid withdrawal.

Unburned cured tobacco used orally contains nicotine, carcinogens, and other toxicants capable of causing gum disease, oral and pancreatic cancers, and an increase in the risk of heart disease. When tobacco is burned, the resultant smoke contains, in addition to nicotine, >7000 other compounds that result from volatilization, pyrolysis, and pyro-synthesis of tobacco leaf and various chemical additives used in making different tobacco products. Tobacco smoke is composed of a fine aerosol and a vapor phase; the aerosol is of a size range that results in deposition in the airways and alveolar surfaces of the lungs. The aggregate of particulate matter, after subtracting nicotine and moisture, is referred to as tar.

The alkaline pH of smoke from blends of tobacco used for pipes and cigars allows sufficient absorption of nicotine across the oral mucosa to satisfy the smoker's need for this drug. Therefore, those who smoke pipes and cigars exclusively tend not to inhale the smoke into the lung, confining the toxic and carcinogenic exposure (and the increased rates of disease) largely to the upper airway. The acidic pH of smoke generated by the tobacco used in cigarettes dramatically reduces absorption of nicotine in the mouth, necessitating inhalation of the smoke into the larger surface of the lungs in order to absorb quantities of nicotine sufficient to satisfy the smoker's addiction. The shift to using tobacco as cigarettes, with resultant increased deposition and absorption of smoke in the lung, has created the epidemic of heart disease, lung disease, and lung cancer that dominates the current disease manifestations of tobacco use.

Several genes have been associated with nicotine addiction. Some reduce the clearance of nicotine, and others have been associated with an increased likelihood of becoming dependent on tobacco and other drugs as well as a higher incidence of depression. It is likely that

TABLE 454-1 Relative Risks for Current Smokers of Cigarettes

AGE	35–44	45–64	65–74	≥75
Males				
Lung cancer	14.33	19.03	28.29	22.51
Coronary heart disease	3.88	2.99	2.76	1.98
Cerebrovascular disease	2.17	1.48	1.23	1.12
Other vascular diseases			7.25	4.93
Chronic obstructive pulmonary disease (COPD)			29.69	23.01
All causes	2.55	2.97	3.02	2.40
Females				
Lung cancer	13.30	18.95	23.65	23.08
Other tobacco-related cancers	1.28	2.08	2.06	1.93
Coronary heart disease	4.98	3.25	3.29	2.25
Cerebrovascular disease	2.27	1.70	1.24	1.10
Other vascular diseases			6.81	5.77
COPD			38.89	20.96
All causes	1.79	2.63	2.87	2.47
Relative Risks for Selected Other Cancers				
Other cancers	Male	Female		
Larynx	14.6	13		
Lip, oral cavity, pharynx	10.9	5.1		
Esophagus	6.8	7.8		
Bladder	3.3	2.2		
Kidney	2.7	1.3		
Pancreas	2.3	2.3		
Stomach	2	1.4		
Liver	1.7	1.7		
Colorectal	1.2	1.2		
Cervix		1.6		
Acute myeloid leukemia	1.4	1.4		

Cigarette smokers are more likely than nonsmokers to develop both large-vessel atherosclerosis and small-vessel disease. Approximately 90% of peripheral vascular disease in the nondiabetic population can be attributed to cigarette smoking, as can ~50% of aortic aneurysms. In contrast, 24% of coronary artery disease and ~11% of ischemic and hemorrhagic strokes are caused by cigarette smoking. There is a multiplicative interaction between cigarette smoking and other cardiac risk factors such that the increment in risk produced by smoking among individuals with hypertension or elevated serum lipids is substantially greater than the increment in risk produced by smoking for individuals without these risk factors.

In addition to its role in promoting atherosclerosis, cigarette smoking also increases the likelihood of myocardial infarction and sudden cardiac death by promoting platelet aggregation and vascular occlusion. Reversal of these effects on coagulation may explain the rapid benefit of smoking cessation for a new coronary event demonstrable among those who have survived a first myocardial infarction. This effect may also explain the substantially higher rates of graft occlusion among continuing smokers following vascular bypass surgery for cardiac or peripheral vascular disease.

Cessation of cigarette smoking reduces the risk of a second coronary event within 6–12 months. Rates of first myocardial infarction and death from coronary heart disease decline within 2–4 years following cessation among those with no prior cardiovascular history. After 15 years of abstinence, the risk of a new myocardial infarction or death from coronary heart disease in former smokers is similar to that for those who have never smoked.

■ CANCER

Tobacco smoking causes cancer of the lung; lip; oral cavity; naso-, oro-, and hypopharynx; nasal cavity and paranasal sinuses; larynx; esophagus; stomach; pancreas; liver (hepatocellular); colon and rectum; kidney (body and pelvis); ureter; urinary bladder; uterine cervix; and acute myeloid leukemia. There is evidence suggesting that cigarette smoking may play a role in increasing the risk of breast cancer, particularly for premenopausal women. There does not appear to be a causal link between cigarette smoking and cancer of the endometrium, and there is a lower risk of uterine cancer among postmenopausal women who smoke. The risks of cancer increase with the increasing number of cigarettes smoked per day and with increasing duration of smoking. Additionally, there are synergistic interactions between cigarette smoking and alcohol use for cancer of the oral cavity and esophagus. Several occupational exposures synergistically increase lung cancer risk among cigarette smokers, most notably occupational asbestos and radon exposure.

Cessation of cigarette smoking reduces the risk of developing cancer relative to continuing smoking after about 4 years of abstinence, but even 20 years after cessation, there is a persistent two- to threefold increased risk of developing lung cancer.

■ RESPIRATORY DISEASE

Cigarette smoking is responsible for 80% of COPD. Within 1–2 years of beginning to smoke regularly, many young smokers will develop inflammatory changes in their small airways, although lung function measures of these changes do not predict development of chronic airflow obstruction. Pathophysiologic changes in the lungs manifest and progress over longer durations of smoking proportional to smoking intensity and duration. Chronic mucous hyperplasia of the larger airways results in a chronic productive cough in as many as 80% of smokers >60 years of age. Chronic inflammation and narrowing of the small airways and/or enzymatic digestion of alveolar walls resulting in pulmonary emphysema can reduce expiratory airflow sufficiently to produce clinical symptoms of respiratory limitation in ~15–25% of smokers.

Changes in the small airways of young smokers will reverse after 1–2 years of cessation. There is also a small increase in measures of expiratory airflow following cessation among many individuals who have developed chronic airflow obstruction, but the major change

following cessation is a slowing of the rate of decline in lung function with advancing age rather than a return of lung function toward normal.

■ PREGNANCY

Cigarette smoking is associated with several maternal complications of pregnancy: premature rupture of membranes, abruptio placentae, and placenta previa; there is also a small increase in the risk of spontaneous abortion among smokers. Infants of smoking mothers are more likely to experience preterm delivery, have a higher perinatal mortality rate, be small for their gestational age, and have higher rates of infant respiratory distress syndrome. They are more likely to die of sudden infant death syndrome and appear to have a developmental lag for at least the first several years of life.

■ OTHER CONDITIONS

Smoking delays healing of peptic ulcers; increases the risk of developing periodontal disease, diabetes, active tuberculosis, rheumatoid arthritis, osteoporosis, senile cataracts, and neovascular and atrophic forms of macular degeneration; and results in premature menopause, wrinkling of the skin, gallstones, and cholecystitis in women, and male impotence. Patients who continue to smoke during treatment for cancer with chemotherapy or radiation have poorer outcomes and reduced survival.

■ ENVIRONMENTAL TOBACCO SMOKE

Long-term exposure to environmental tobacco smoke increases the risk of lung cancer and coronary artery disease among nonsmokers. It also increases the incidence of respiratory infections, chronic otitis media, and asthma in children and causes exacerbation of asthma in children. Some evidence suggests that environmental tobacco smoke exposure may increase the risk of premenopausal breast cancer.

■ PHARMACOLOGIC INTERACTIONS

Cigarette smoking may interact with a variety of other drugs (**Table 454-2**). Cigarette smoking induces the cytochrome P450 system, which may alter the metabolic clearance of drugs such as warfarin. This may result in inadequate serum levels in smokers as outpatients when the dosage is established in the hospital under nonsmoking conditions. Correspondingly, serum levels may rise when smokers are hospitalized and not allowed to smoke. Smokers may also have higher first-pass clearance for drugs such as lidocaine, and the stimulant effects of nicotine may reduce the effect of benzodiazepines or beta blockers.

■ OTHER FORMS OF TOBACCO USE

Other major forms of tobacco use are moist snuff deposited between the cheek and gum, chewing tobacco, pipes and cigars, and recently bidi (tobacco wrapped in tendu or temburni leaf; commonly used in India), clove cigarettes, and water pipes. Oral tobacco use leads to gum disease and can result in oral and pancreatic cancer as well as heart disease. There are dramatic differences in the risks evident for products used in Africa or Asia as compared to those in the United States and Europe.

The risk of upper airway cancers is similar among cigarette, pipe, and cigar smokers, whereas those who have smoked only pipes and cigars have a much lower risk of lung cancer, heart disease, and COPD. Cigarette smokers who switch to pipes or cigars do tend to inhale the smoke, increasing their risk. Use of combusted tobacco in forms resembling and smoking like a cigarette, but classified as a cigar, represents a growing fraction of combusted tobacco use and likely has disease risks similar to those of cigarette smoking.

A resurgence of cigar, bidi, and water pipe use among adolescents of both genders has raised concerns that these older forms of tobacco use are once again causing a public health problem.

■ ELECTRONIC CIGARETTES

Electronic cigarettes (e-cigarettes) are devices with a heating element that produces an inhalable aerosol from a liquid usually containing nicotine. Multiple different designs exist, but there are three general categories. Disposable devices that look like cigarettes or ball point

TABLE 454-2 Interactions of Smoking and Prescription Drugs

DRUG	INTERACTION
Cardiovascular and Pulmonary Drugs	
β blockers	Reduced lowering of heart rate and blood pressure
Flecainide	Increased first-pass clearance
Heparin	Faster clearance
Lidocaine	Increased first-pass clearance
Mexiletine	Increased first-pass clearance
Propranolol	Increased first-pass clearance
Theophylline	Faster metabolic clearance
Verapamil	Increased clearance
Warfarin	Increased metabolism lowers serum levels
Neuropsychiatric Drugs	
Amitriptyline	Increased clearance
Benzodiazepines	Less sedation
Clomipramine, Imipramine	Decreased serum concentrations
Chlorpromazine	Decreased serum concentrations
Clozapine	Decreased serum concentrations
Duloxetine	Decreased serum concentrations
Fluphenazine	Decreased serum concentrations
Fluvoxamine	Decreased serum concentrations
Haloperidol	Decreased serum concentrations
Naratriptan	Increased clearance
Olanzapine	Faster clearance
Trazodone	Decreased serum concentrations
Anticancer Drugs	
Erlotinib	Increased clearance, higher response rate, and improved survival in nonsmokers
Gefitinib	Higher response rate and improved survival in nonsmokers
Irinotecan	Increased clearance
Other Drugs	
Dextropropoxyphene	Less analgesia
Estrogens (oral)	Increased hepatic clearance
Fentanyl	Increased clearance
Insulin	Delayed absorption due to skin vasoconstriction
Rivastigmine	Increased clearance

pens are the oldest products, but they generally do not deliver levels of nicotine comparable to a cigarette. Later vaping devices utilize a larger power source and a bulky refillable tank to store the nicotine-containing liquid. These devices deliver aerosolized nicotine at levels comparable to cigarette smoking. Liquids to refill the tanks come in different concentrations of nicotine, but liquids with high concentrations of nicotine create throat irritation, deterring their use. More recent designs include smaller devices that resemble computer USB flash drives and deliver nicotine as the salt of a mild acid. The nicotine salt aerosol leaving the device is mildly acidic, markedly lowering the percentage of the nicotine that is in the free base form. This reduces the irritation in the upper airway. However, as the aerosol moves down the airway, its pH rapidly converts to the lung tissue pH of ~7.4, releasing substantial amounts of free base nicotine, which is readily absorbed across the alveolar capillary wall. As the absorbed nicotine is carried away by the pulmonary blood flow, the remaining nicotine salt converts to the free base form, further enhancing the amount of nicotine that can be delivered to the brain. Limited data suggest that the nicotine intake is higher for users of devices delivering nicotine salts. It is likely that the transition to use of nicotine salts substantially contributed to the rise in use of e-cigarettes and addiction to nicotine among adolescents.

The role of e-cigarettes in smoking cessation remains conflicted. There is convincing randomized controlled evidence that the use of refillable-tank e-cigarettes is twice as effective as nicotine-replacement

medications in achieving sustained abstinence from conventional cigarettes. However, 80% of those who achieved abstinence were still using e-cigarettes at 12 months, suggesting continued nicotine addiction. Evidence on exposure to toxicants in smoke demonstrates markedly lower exposures among those using e-cigarettes exclusively, but evidence on e-cigarette use in the United States shows that approximately one-half of adult e-cigarette users continue to also smoke conventional cigarettes, negating the benefits of reduced toxicant exposure. Rates of relapse back to smoking among those with persistent nicotine addiction and the effectiveness of devices containing nicotine salts remain to be demonstrated.

E-cigarette use among U.S. adolescents has risen dramatically over recent years, becoming the most common form of nicotine delivery among adolescents. Adolescents who ever use an inhaled nicotine product are more likely to be a conventional cigarette smoker 1 year later (three times more likely with ever e-cigarette use and four times as likely with ever conventional cigarette use). These data show that adolescents who experiment with nicotine in any form are likely to become continuing users; nevertheless, the steeply rising level of adolescent e-cigarette prevalence has been accompanied by an independently driven dramatic fall in adolescent conventional cigarette prevalence. Concerns about e-cigarette use becoming a meaningful gateway to conventional cigarette use among adolescents and young adults are thus far not borne out by prevalence data for both product types.

Refillable or reloadable e-cigarette devices can be used to aerosolize a variety of liquids other than those provided by the manufacturer. Disposable “pods” and liquids for these devices can be purchased from the manufacturer but are also available from other sources that may use poor-quality manufacturing practices and control of contaminants. They may also contain marijuana oils, other drugs, and flavors not evaluated for potential lung injury with inhalation. Many of these liquids are provided on the black market with little oversight of the production process. Beginning in the spring of 2019, a rapidly accelerating epidemic of severe hypoxic lung injury was associated with e-cigarette use. The lung pathology includes diffuse alveolar damage, acute fibrinous pneumonitis, and organizing pneumonia. The closest associations were for cannabinoid products and vitamin E in the aerosolized liquid, but ~15% of those affected reported using only nicotine-containing liquids. Following widespread publicity of this toxicity and its association with irregular product sources, there has been a reduction in the incidence of this form of lung injury. Given the capacity of e-cigarettes to produce small particles that readily penetrate to the alveolar level, multiple toxicants may contribute to the epidemic. Nevertheless, vitamin E has the strongest evidence to support its role as a major contributor. Vitamin E is sometimes used as a thickening agent in tetrahydrocannabinol (THC)-containing products. Given the difficulty in controlling the illicit market for e-liquids, it is likely that episodic exposure to pulmonary toxicants will continue to occur. Regulatory control may need to focus on the delivery devices.

LOWER TAR AND NICOTINE CIGARETTES

Filtered cigarettes with lower machine-measured yields of tar and nicotine commonly use ventilation holes in the filters and other engineering designs to artificially lower the machine measurements. Smokers compensate for the lowered nicotine delivery resulting from these design changes by changing the manner in which they puff on the cigarette or the number of cigarettes smoked per day. Actual tar and nicotine deliveries are not reduced with use of these products, negating any reduction in disease risks with their use.

The amount of carcinogenic tobacco-specific nitrosamines in the tobacco used in cigarettes has increased over time, and cigarette design changes that reduce machine-measured tar and nicotine also led to deeper inhalation of the smoke. Presentation of more carcinogenic smoke to the alveolar portions of the lung increases the risk of adenocarcinoma of the lung. The increased adenocarcinoma risk produces a substantively greater overall risk for lung cancer among current smokers compared with smokers of cigarettes manufactured prior to the 1960s. This increased risk may also be present for COPD. It is the changes in cigarette design and composition of cigarettes over the past

3566 six decades that caused the dramatic rise in rates of adenocarcinoma of the lung observed over the past half century. There has been no increase in risk of lung cancer or adenocarcinoma of the lung over the same period among never smokers.

CESSATION

The process of stopping smoking is commonly a cyclical one, with the smoker sometimes making multiple attempts to quit and failing before finally being successful. Approximately 70–80% of smokers would like to quit smoking. More than one-half of current smokers attempted to quit in the last year, but only 6% quit for 6 months, and only 3% remain abstinent for 2 years. Clinician-based smoking interventions should repeatedly encourage smokers to try to quit and to use different forms of cessation assistance with each new cessation attempt, rather than focusing exclusively on immediate cessation at the time of the first visit.

Advice from a physician to quit smoking, particularly at the time of an acute illness, is a powerful trigger for cessation attempts, with up to half of patients who are advised to quit making a cessation effort. Other triggers that may be enhanced by timely physician advice to quit include increases in the tax on cigarettes, media campaigns, and changes in rules to restrict smoking in the workplace.

PHYSICIAN INTERVENTION TABLE 454 3

All patients should be asked whether they smoke, how much they smoke, how long they have smoked, their past experience with quitting, and whether they are currently interested in quitting. The number of cigarettes smoked per day and smoking within 30 min of waking are useful measures of the intensity of nicotine addiction. Even those who are not interested in quitting should be encouraged and motivated to quit; provided a clear, strong, and personalized message by the clinician that smoking is an important health concern; and offered assistance if they become interested in quitting in the future. Many of those not currently expressing an interest in quitting may nevertheless make an

attempt to quit in the subsequent year. For those interested in quitting, a quit date should be negotiated, usually not the day of the visit but within the next few weeks, and a follow-up contact by office staff around the time of the quit date should be provided. There is a relationship between the amount of assistance a patient is willing to accept and the success of the cessation attempt.

There are a variety of nicotine-replacement products, including over-the-counter nicotine patches, gum, and lozenges, as well as nicotine nasal and oral inhalers available by prescription. These products can be used for up to 3–6 months, and some products are formulated to allow a gradual step-down in dosage with increasing duration of smoking abstinence. Antidepressants such as bupropion (300 mg in divided doses for up to 6 months) have also been shown to be effective, as has varenicline, a partial agonist for the nicotinic acetylcholine receptor (initial dose 0.5 mg daily increasing to 1 mg twice daily at day 8; treatment duration up to 6 months). Combined use of nicotine-replacement therapy (NRT) and antidepressants as well as the use of gum or lozenges for acute cravings in patients using patches can increase cessation outcomes. Pretreatment with antidepressants or varenicline is recommended for 1–2 weeks prior to the quit date. Pretreatment with nicotine-replacement products is also useful prior to a cessation date. Longer duration of nicotine replacement as a maintenance therapy for those who are unsuccessful in quitting with a shorter duration of use is a useful strategy. NRT is provided in different dosages, with higher doses being recommended for more intense smokers. Clonidine or the tricyclic antidepressant nortriptyline should be reserved for patients who have failed on first-line pharmacologic treatment or who are unable to use other therapies. Antidepressants are more effective among smokers with a history of depression symptoms.

Current recommendations are to offer pharmacologic treatment, usually with nicotine patches or varenicline, to all who will accept it and to provide counseling and other support as a part of the cessation attempt. Cessation advice alone by a physician or his or her staff is likely to increase success compared with no intervention; a more comprehensive approach with advice, pharmacologic assistance, and counseling can increase cessation success nearly threefold.

For adult addicted smokers, switching to exclusive use of e-cigarettes, but not dual use with combusted cigarettes, can promote combusted cigarette cessation, particularly for those unlikely to try to quit with other proven cessation modalities.

Incorporation of cessation assistance into a practice requires a change of the care delivery infrastructure. Simple changes include (1) adding questions about smoking and interest in cessation on patient-intake questionnaires, (2) asking patients whether they smoke as part of the initial vital sign measurements made by office staff, (3) listing smoking as a problem in the medical record, and (4) automating follow-up contact with the patient on the quit date. These changes are essential to institutionalizing smoking intervention within the practice setting; without this institutionalization, the best intentions of physicians to intervene with their patients who smoke are often lost in the time crush of a busy practice.

PREVENTION

Approximately 85% of individuals who become cigarette smokers initiate the behavior during adolescence. Factors that promote adolescent initiation are parental or older-sibling cigarette smoking, tobacco advertising and promotional activities, the availability of cigarettes, and the social acceptability of smoking. The need for an enhanced self-image and to imitate adult behavior is greatest for those adolescents who have the least external validation of their self-worth, which may explain in part the enormous differences in adolescent smoking prevalence by socioeconomic and school performance strata.

Prevention of smoking initiation must begin early, preferably in the elementary school years. Physicians who treat adolescents should be sensitive to the prevalence of this problem even in the preteen population. Physicians should ask all adolescents whether they have experimented with nicotine or currently use nicotine products, reinforce the fact that most adolescents and adults do not smoke or use nicotine, and explain that all forms of nicotine intake are both addictive and harmful.

TABLE 454-3 Clinical Practice Guidelines

Physician Actions

- Ask: Systematically identify all tobacco users at every visit
- Advise: Strongly urge all smokers to quit
- Identify smokers willing to quit
- Assist the patient in quitting
- Arrange follow-up contact

Effective Pharmacologic Interventions^a

First-line therapies

- Nicotine gum (1.5)
- Nicotine patch (1.9)
- Nicotine nasal inhaler (2.3)
- Nicotine oral inhaler (2.1)
- Nicotine lozenge (2 mg: 2.0, 4 mg: 2.8)
- Bupropion (2.0)
- Varenicline (3.1)

Second-line therapies

- Clonidine (2.1)
- Nortriptyline (1.8)

Other Effective Interventions^a

- Physician or other medical personnel counseling (10 min) (1.84)
- Intensive group smoking cessation programs (at least 4–7 sessions of 20- to 30-min duration lasting at least 2 and preferably 8 weeks) (1.3)
- Intensive individual counseling (1.7)
- Clinic-based smoking status identification system (3.1)
- Telephone counseling (1.6)
- Exclusive E-cigarette use (3.0)

^aNumerical value following the intervention is the multiple for cessation success compared to no intervention.

FURTHER READING

- E MJ et al: Effect of e-cigarettes plus counseling vs counseling alone on smoking cessation: A randomized clinical trial. *JAMA* 324:1844, 2020.
- H P et al: A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med* 380:629, 2019.
- L FT et al: Initiating pharmacologic treatment in tobacco-dependent adults. An official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 202:e5, 2020.
- S HS et al: Evidence supporting the need for considering the effects of smoking on drug disposition and effectiveness in medication practices: A systematic narrative review. *Int J Clin Pharmacol Ther* 53:621, 2015.
- U.S. D H H S : *U.S. Department of Health and Human Services. Smoking Cessation. A Report of the Surgeon General.* Atlanta, GA, 2020. Available from <https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf>. Accessed May 2, 2020.
- U.S. D H H S : *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General.* Atlanta, GA, 2014. Available from https://www.ncbi.nlm.nih.gov/books/NBK179276/pdf/Bookshelf_NBK179276.pdf. Accessed May 2, 2020.

455

Marijuana and Marijuana Use Disorders

Nora D. Volkow, Aidan Hampson, Ruben Baler

Marijuana is the most widely used illicit drug, with ~192 million users worldwide and with >43 million Americans having used it in 2018. Cannabis strains fall into those grown for their euphorogenic and medical properties (i.e., for their Δ-9-tetrahydrocannabinol [THC] content), and “hemp,” which is grown for seed, fiber, and cannabidiol (CBD). As of August 2020, Canada and 43 U.S. states have decriminalized and/or “medicalized” marijuana or marijuana-derived products, which has increased the availability of cannabis strains and derived products. Between 2008 and 2017, the average THC content in marijuana increased from 8.9% to 17.1%. Today, THC concentrations in marijuana flowers found in dispensaries can exceed 25%, while oil extracts used for “vaping” can contain >95% THC. Similar high THC concentrations are found in solid cannabis concentrates (e.g., wax or shatter) used for “dabbing,” which involves vaporization with a propane torch. Vaping and dabbing both provide very high THC levels with a rapid absorption and speed of effect onset, a phenomenon that increases addiction risk. Cannabis-infused “edibles” (e.g., gummy bears, cookies, chocolates, and drinks) are also widely available and valued for their discreet administration and perception of reduced harm.

PHARMACOLOGIC EFFECTS

Cannabis is used recreationally because it enhances the subjective sense of well-being, provides rewarding sensations, and can decrease stress responses. However, consumption of high THC doses can induce anxiety, paranoia, and panic. THC is primarily an agonist (activator) of G protein-coupled cannabinoid receptors (CB1R and CB2R), with the euphoric effects mediated through CB1Rs located on excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABA)-ergic interneurons and glial cells in brain regions that process stress, mood, and reward. These receptors are the effectors of the endocannabinoid system (ECS), which is physiologically activated by 2-arachidonoylglycerol (2-AG, a full agonist) and anandamide (a partial agonist). According to current understanding, 2-AG modulates synaptic

signaling by inhibiting overstimulated synapses. Endocannabinoids are synthesized and eliminated on demand and thus provide a temporally and regionally specific control signal. In contrast, the effect of THC is not defined by synaptic necessity but by the dose taken and pharmacokinetics, and so it disrupts ECS neuroregulation. THC is a partial CB1/2R agonist (it produces less signal per receptor bound) and thus does not inhibit glutamate release as effectively as 2-AG but can out-compete endocannabinoids by mass action. However, GABA-releasing interneurons have more CB1R than they have connecting intracellular signaling components, and so THC and 2-AG inhibit GABA release to a similar degree. This may explain the subjective similarity of THC and GABA inhibitors such as benzodiazepines.

The rewarding effects of THC are thought to be mediated by modulation of glutamatergic and GABAergic activity in the ventral tegmental area in the midbrain, the nucleus that contains the dopaminergic neurons projecting into the nucleus accumbens, which integrates glutamate and dopamine signals to produce reward responses. The anxiety-reducing effects of THC are mediated by its effects in the amygdala, a region critical for threat perception and emotional reactivity.

CANNABIS PHARMACOKINETICS

Traditional smoking (e.g., joints and water pipes) is the main route of administration, but the rise of e-cigarette-derived vaping concentrates (vape pens) has led to a move to small dosing and more regular administration, also known as micro-dosing. Vape pens use concentrate liquids and offer both an easier dose control mechanism and more discreet consumption. The subjective effects of marijuana are affected by dose, route of administration, (smoked, vaped, ingested), and the subject's prior experience. Smoked THC exhibits a bioavailability of 10–35%, with interindividual differences stemming from individual variations in the capacity to hold smoke in the lungs long enough for maximal absorption. The pharmacokinetics (PKs) of heated (not burnt) marijuana is similar to that of the smoked flower, but no data are available to address the PKs of oils and solid concentrates. When smoked, THC is rapidly absorbed (T_{max} within 5–10 min) and displays three phases of elimination. After T_{max} , plasma levels drop rapidly (alpha half-life [$t_{1/2}$] ~6 min) due to redistribution from plasma to lipophilic tissues such as adipose and brain. As a result, the brain continues to accumulate THC while plasma levels decline, so subjective effects max out at ~20–30 min. This “hysteresis” phase continues for several hours, wherein subjective effects decline more slowly than plasma levels. Most of the pharmacologic effects (i.e., subjective, cardiovascular, and conjunctival reddening) occur during the initial 20–30 min and last for 4–8 h. Finally, there is a terminal elimination phase, during which relatively low concentrations of THC and metabolites (primarily THC 11-COOH) leach out from adipose tissues with a $t_{1/2}$ ranging from 20–35+ h. Generally, metabolite levels drop below 100 ng/mL within 3–5 days, although considerable variation exists, and in frequent marijuana users, urinary metabolites can remain detectable for weeks. High metabolite levels during long leach-out periods in frequent users typically do not indicate impairment, even when similar concentrations in occasional users might indicate recent marijuana use and substantial impairment. This difficulty in correlating THC levels in biological matrices with behavioral effect has hampered efforts to regulate marijuana-impaired driving.

PK studies using cannabis edibles have demonstrated only 6–12% bioavailability. Lipophilic cannabinoids are poorly absorbed in the water/mucus-rich intestinal environment and are rapidly metabolized by intestinal and hepatic systems, even before they reach the systemic circulation. Interestingly, cannabinoids consumed with fatty food display 200–400% improved bioavailability. Fatty foods stimulate bile release, which emulsifies fats (and dissolved cannabinoids) to increase the surface area for absorption. However, fats are not absorbed into hepatic portal blood but secreted as chylomicrons into lymphatic lacteals, which allows dissolved cannabinoids to bypass hepatic elimination. Since lymphatic flow is slower than portal blood transport, the higher cannabinoid bioavailability and slower effect onset in the presence of fat are overdose risks for the unwary who may consume additional doses when failing to perceive effects as quickly as expected.

The frequency and severity of marijuana's adverse effects are influenced by the user's age, dose, frequency of use, route of administration, underlying health status, and genetics. Especially concerning are the potential negative effects of marijuana on the brain during early life stages. Perturbation of ECS signaling during early fetal development affects neuronal development, migration, and connectivity. The relevant studies, which are few and confounded by the frequent use of other drugs, suggested an association between maternal marijuana use and fetal growth restriction and preterm delivery but yielded substantial evidence of lower birth weight. As a consequence, the American College of Obstetricians and Gynecologists recommends discouraging the use of marijuana by women who are pregnant or planning a pregnancy. Children and adolescents are also more vulnerable to the harmful effects of marijuana use, which increases markedly during adolescence and has been associated with lower grades, lower IQ, and higher risk of dropping out of school, although causality associations are hindered by poor control of confounding variables. Brain imaging studies have revealed that use of marijuana at this stage is associated with structural and functional brain changes often (but findings are not always replicated) in the form of reduced brain connectivity and cortical thickness. It is not clear whether these are caused by early exposure to marijuana, a question that the Adolescent Brain and Child Development study, a longitudinal neuroimaging, behavioral, and genetic study of close to 12,000 children in the United States, may be able to answer. Finally, there is increasing evidence of cardiovascular adverse effects, including higher risk of myocardial infarction among cannabis smokers.

Cannabis Use Disorder Repeated marijuana use, especially during adolescence, can result in cannabis use disorder (CUD), which the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) defines as "a problematic pattern of cannabis use leading to clinically significant impairment or distress." Use becomes problematic when at least two of the criteria (which include craving, failure to fulfill role obligations due to recurrent use, tolerance, and withdrawal) have manifested themselves in a 12-month period. In regular marijuana users, abstinence results in a withdrawal syndrome that manifests within 1–3 days of drug discontinuation as anxiety, restlessness, insomnia, depression, and reduced appetite. Many of the withdrawal symptoms resolve within approximately 2 weeks of discontinuation, but symptoms such as insomnia can persist longer and contribute to drug taking as a means to combat the symptoms of withdrawal. The risk of CUD increases with earlier age of initiation, frequency of use, and exposure to marijuana with high THC content.

PREVENTION Preventing marijuana use during adolescence reduces the risk for CUD and also the risk for other substance use disorders. There are several evidence-based prevention strategies focused in children and adolescents that have shown benefits in decreasing marijuana use during adolescence or in delaying its age of initiation. Evidence-based prevention interventions target the individual (e.g., Keepin' It Real, Life Skills, InShape), the family (e.g., Brief Strategic Family Therapy, Coping Power Program [CPP], Familia Adelante), and the community (e.g., The Abecedarian Project, Midwestern Prevention Project, Caring School Community). School-based prevention programs are the most widely implemented, and the cumulative evidence (from randomized controlled trials and prospective cohort and longitudinal studies) indicates that comprehensive interventions that include antidrug information with refusal skills, self-management skills, and social skills training appear to be the most effective approaches for long-term reduction of marijuana (and alcohol) use in adolescents.

TREATMENT The treatment of CUD is managed by tapering marijuana use and, in severe cases, by providing support to combat withdrawal symptoms. The treatment of severe CUD is much more challenging and requires continuous care. Although there are no U.S. Food and Drug Administration (FDA)-approved medications for the treatment of CUD, there are several behavioral interventions, including

contingency management and cognitive-behavioral and motivational enhancement therapies for which there is evidence of benefit. Several studies have found a broad reduction in cannabinoid receptors in the brain of cannabis users when compared to healthy controls, but receptors recover rapidly, returning to values similar to those of nonusers after 28 days of abstinence.

Mental Illness An area of major concern is the association between marijuana use and increased risk for mental illnesses, particularly psychosis, the risk of which increases with the frequent consumption of high-THC-content marijuana (>10% content). High-potency marijuana can trigger acute psychotic episodes, which is one of the main causes for emergency department (ED) visits associated with cannabis use that can occur even upon first exposure. While most of these psychotic episodes are transient, with regular marijuana use, they can become chronic, and in those who are vulnerable, they might trigger or exacerbate the presentation of schizophrenia. Multiple studies, although not all, have linked adolescent marijuana use with higher risk and earlier onset of chronic psychosis, particularly for those using marijuana at higher frequency or with higher THC content. Furthermore, recent evidence suggests that the difference in the prevalence of psychosis across different countries may be attributable in part to the differences in the prevalence of regular use of high-THC-content marijuana. Concerns have also been raised regarding an association between marijuana use during adolescence and a higher risk for depression and suicidality, although these associations have been much less studied.

Accidents Marijuana use increases the risk of injuries when driving under its influence. THC impairs judgment, motor coordination, and reaction time, all of which are necessary for safe driving. Laboratory studies have found a direct relationship between blood THC levels and impaired driving ability. Not surprisingly, marijuana use while driving increases the risk of fatal and nonfatal accidents, and its use while flying aircraft may have also contributed to increased fatalities among pilots. However, roadside surveillance of marijuana intoxication has been difficult to implement because circulating cannabinoid levels do not correlate with the degree of impairment.

Acute and Chronic Toxicity The increased availability of high-THC-content products over the past decade has been paralleled by increased marijuana-related ED visits and hospital admissions. Such illnesses can be caused by acute toxicity (inappropriate dosing) and chronic use syndromes. Cannabis edibles represent a significant portion of acute cannabis toxicity events. Patients include children accidentally consuming sweet treats and infrequent users such as "cannabis tourists" with limited experience with consumed products. As described in the PK section, edibles have a slow onset of effect, and THC bioavailability can differ greatly when taken on an empty stomach or with fatty foods. For a variety of reasons, actual dose is also more difficult to envisage, so naïve or infrequent users are at increased risk of overdosing. Cannabis toxicity is frequently manifested by severe anxiety, tachycardia, and even acute psychoses.

Chronic high-dose cannabis use can also induce a *cannabis hyperemesis syndrome* (CHS), a growing cause for ED and hospital admissions. CHS presents in the ED as severe cycles of nausea, vomiting, and abdominal pain, but has a prodromal phase of abdominal pain and nausea that can last several years. CHS does not respond to CB1R agonist medications such as dronabinol and nabilone that are FDA approved to treat nausea and vomiting. CHS treatment includes intravenous hydration and proton pump inhibitors for gastritis. Very hot showers and capsaicin creams are popularly used, but efficacy data are limited. Droperidol reduces hospital stay times and antiemetic use, but only cannabis abstinence leads to long-term recovery.

The widespread medicalization of marijuana and its dispensation outside of the pharmacy system is exposing patients to possible drug-drug interactions (DDIs), potentially without their physician's or pharmacist's knowledge. However, the long history of population exposure has not provided much evidence for cannabis (i.e., THC)-related DDIs, except for a couple of case studies where THC (metabolized by

cytochrome P450 [CYP3A, 2C9]) affected a patient's warfarin levels. In contrast, the legalization of hemp-derived CBD has made it available at doses never experienced with marijuana. CBD in the Epidiolex formulation has been FDA approved as a high-dosage (see below) add-on drug against childhood epilepsies. Recent reports of possible interactions between CBD and benzodiazepines, methadone, and the antirejection drug tacrolimus suggest more research is needed to ensure safety of CBD medications.

■ THERAPEUTIC POTENTIAL

Currently, no FDA-approved medications contain cannabis-derived THC, although synthetic THC (or dronabinol) is approved for treatment of chemotherapy-induced nausea and appetite stimulation. Several countries have approved the cannabis-derived THC:CBD formulation Sativex for treating chronic pain and multiple sclerosis (MS)-induced spasticity. However, evidence of Sativex efficacy in MS is largely based on patient reports, with little electromyographic evidence or physician-scored improvement. Chronic pain is one of the most frequent indications for which medical marijuana is used, although the effect is generally modest and possibly related to its mood-enhancement effects.

High-dose Epidiolex is an FDA-approved oil formulation of CBD for use as an add-on treatment for Dravet's and Lennox-Gastaut syndromes and tuberous sclerosis epilepsies. There is clinical evidence for CBD, at lower doses, as an anxiolytic for the treatment of posttraumatic stress, anxiety, and relapse of substance use disorders. Animal studies suggest that this effect of CBD may be mediated by the 5-hydroxytryptamine 1A receptor.

■ FURTHER READING

- A C O G
C O P : Committee Opinion No. 637: Marijuana use during pregnancy and lactation. *Obstet Gynecol* 126:234, 2015.
H DJ J et al: Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *Neuroimage* 202:116091, 2019.
M AA A et al: Acute illness associated with cannabis use, by route of exposure: An observational study. *Ann Intern Med* 170:531, 2019.
P J, M R: *Cannabis Use Disorder*. StatPearls. Treasure Island, FL, 2020.
V ND et al: Don't worry, be happy: Endocannabinoids and cannabis at the intersection of stress and reward. *Annu Rev Pharmacol Toxicol* 57:285, 2017.

and have accelerated due to mixing high-potency fentanyl derivatives with heroin. The accelerating death rates are partially because reversal of fentanyl overdoses can require severalfold larger doses of naloxone than the doses in the intranasal devices used for nonmedical street resuscitations. An additional spike in fentanyl-associated deaths has also been associated with the COVID-19 pandemic. According to the most recent World Drug Report, opioid misuse causes the greatest global burden of morbidity and mortality; disease transmission; increased health care, crime, and law enforcement costs; and less tangible costs of family distress and lost productivity.

The terms *dependence* and *addiction* are no longer used to describe substance use disorders. Opioid-related disorders encompass opioid use disorder, opioid intoxication, and opioid withdrawal. The diagnosis of opioid use disorder, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), requires the repeated use of the opiate while producing problems in two or more areas in a 12-month period. The areas include tolerance, withdrawal, use of greater amounts of opioids than intended, craving, and use despite adverse consequences. This new definition of opioid use disorder, reducing the criteria for diagnosis from three problem areas to two, is not expected to change the rates of these disorders because most individuals using these substances meet more than three criteria.

A striking recent aspect of illicit opioid use has been its marked increase as the gateway to illicit drugs in the United States. Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially use, although overall rates of opioid use are far lower than marijuana. The most commonly used opioids are diverted prescriptions for oxycodone and hydrocodone, followed by heroin and morphine, and—among health professionals—meperidine and fentanyl. Heroin is metabolized into 6-monoacetylmorphine and morphine thus acting as a prodrug that more readily penetrates the brain and is converted rapidly to morphine in the body. Two opioid maintenance treatment agents—methadone and buprenorphine—are also misused, but at substantially lower rates, and the partial opioid agonists such as butorphanol, tramadol, and pentazocine are misused even less frequently. Because the chemistry and general pharmacology of these agents are covered in major pharmacology texts, this chapter focuses on the neurobiology and pharmacology relevant to opioid use disorder and its treatments. Although the neurobiology of misuse involves all four of the known opioid receptors—mu, kappa, delta, and nociceptin/orphanin—this discussion focuses on the mu receptor targeted by most of the clinically used opioids.

■ NEUROBIOLOGY

The neurobiology of opioids and their effects not only include opioid receptors, but also downstream intracellular messenger systems and ion channels that the receptors regulate. The different functional activities of opioid receptors are summarized in Table 456-1. Abuse liability of opioids is primarily associated with the mu receptor. All opioid receptors are G protein-linked and coupled to the cyclic adenosine monophosphate (cAMP) second messenger system and to G protein-coupled, inwardly rectifying potassium channels (GIRKs). Opioids

456 Opioid-Related Disorders

Thomas R. Kosten, Colin N. Haile

Opioid analgesics have been used since at least 300 . . . Nepenthe (Greek for “free from sorrow”) helped the hero of the *Odyssey*, but widespread opium smoking in China and the Near East has caused harm for centuries. Since the first chemical isolation of opium and codeine 200 years ago, a wide range of synthetic opioids have been developed, and opioid receptors were cloned in the 1990s. Two of the most important adverse effects of all these agents are the development of opioid use disorder and overdose. Prescription opioids are primarily used for pain management, but due to ease of availability, individuals procure and misuse these drugs with dire consequences. In 2015, for example, 3.8 million individuals in the United States were current misusers of pain relievers. More concerning, during 2015, >20,000 overdose deaths involved opioids with an additional 12,990 overdose deaths related to heroin alone. These numbers continue to increase

TABLE 456-1 Actions of Opioid Receptors

RECEPTOR TYPE	ACTIONS
Mu (μ) (e.g., morphine, buprenorphine)	Analgesia, reinforcement euphoria, cough and appetite suppression, decreased respirations, decreased GI motility, sedation, hormone changes, dopamine and acetylcholine release
Kappa (κ) (e.g., butorphanol)	Dysphoria, decreased GI motility, decreased appetite, decreased respiration, psychotic symptoms, sedation, diuresis, analgesia
Delta (δ) (e.g., etorphine)	Analgesia, euphoria, physical dependence, hormone changes, appetite suppression, dopamine release
Nociceptin/orphanin (e.g., buprenorphine)	Analgesia, appetite, anxiety, tolerance to opioids, hypotension, decreased GI motility, 5-HT and NE release

Abbreviations: GI, gastrointestinal; 5-HT, serotonin; NE, norepinephrine.

activate GIRKs, increasing permeability to potassium ions to cause hyperpolarization, which inhibits the production of action potentials. Thus, opioids inhibit the activity of diverse and widely distributed neuronal types. The major effects of opioids, such as analgesia, sedation, and drug reinforcement, are produced through this inhibition of neurons that belong to specific brain pathways.

Many opioid actions are related to the specific neuroanatomic locations of mu receptors. Reinforcing and euphoric effects of opioids relate primarily to activation of the mesolimbic dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), where opioids increase synaptic levels of dopamine. This increase is due to inhibition of GABAergic neurons that inhibit the activity of neurons within both the VTA and the NAc. The positive subjective effects of opioid drugs also include mu receptor desensitization and internalization, potentially related to stimulation of β -arrestin signaling pathways. However, the “high” only occurs when the *rate of change* in dopamine is fast. Large, rapidly administered doses of opioids block γ -aminobutyric acid (GABA) inhibition and produce a burst of VTA dopamine neuron activity that is associated with a “high” in commonly misused substances. Therefore, routes of administration that slowly increase opioid blood and brain levels, such as oral and transdermal routes, are effective for analgesia and sedation but do not produce an opioid “high” that follows smoking and intravenous routes. Other acute effects such as analgesia and respiratory depression involve opioid receptors located in other brain areas such as the locus coeruleus (LC).

Opioid tolerance and withdrawal are chronic effects related to the cAMP-protein kinase A (PKA)-cAMP response-element binding protein (CREB) intracellular cascade (Fig. 456-1). These effects are also reflective of genetic risk factors for developing opioid use disorder, with estimates of up to 50% of the risk due to polygenic inheritance. Specific functional polymorphisms in the mu opiate receptor gene appear to be associated with this risk for opioid misuse, including one producing a threefold increase in this receptor’s affinity for opiates and the endogenous ligand β -endorphin. Epigenetic methylation changes also occur on DNA in the region of the mu receptor gene in individuals with opioid use disorder, inhibiting gene transcription. This molecular cascade links acute intoxication and sedation to opioid tolerance and withdrawal mediated by the LC. Noradrenergic (NE) neurons in the LC mediate activation of the cortical hemispheres. When large opioid doses saturate and activate all of its mu receptors, action potentials cease. When this direct inhibitory effect is sustained over weeks and months of opioid use, a secondary set of adaptive changes occur that lead to tolerance and withdrawal symptoms (Fig. 456-1). Withdrawal symptoms reflect, in part, overactivity of NE neurons in the LC. This

molecular model of NE neuronal activation during withdrawal has had important treatment implications, such as the use of the α_2 -agonist clonidine to treat opioid withdrawal. Other contributors to withdrawal include deficits within the dopamine reward system.

■ PHARMACOLOGY

Tolerance and withdrawal commonly occur with chronic daily use, developing as quickly as 6–8 weeks depending on dose concentration and dosing frequency. Tolerance appears to be primarily a pharmacodynamic rather than pharmacokinetic effect, with relatively limited induction of cytochrome P450 or other liver enzymes. The metabolism of opioids occurs in the liver, primarily through the cytochrome P450 systems of 2D6 and 3A4. They then are conjugated to glucuronic acid and excreted in small amounts in feces. The plasma half-lives generally range from 2.5 to 3 h for morphine and >22 h for methadone. The shortest half-lives of several minutes are for fentanyl-related opioids, and the longest are for buprenorphine and its active metabolites, which can block opioid withdrawal for up to 3 days after a single dose. Tolerance to opioids leads to the need for increasing amounts of drugs to sustain the desired euphoric effects—as well as to avoid the discomfort of withdrawal. This combination has the expected consequence of strongly reinforcing misuse once it has started. Methadone taken chronically at maintenance doses is stored in the liver, which may reduce the occurrence of withdrawal between daily doses. The role of endogenous opioid peptides in tolerance and withdrawal is uncertain.

The clinical features of opioid misuse are tied to route of administration and rapidity of the drug reaching the brain. Intravenous and smoked administration rapidly produces high drug concentrations in the brain. This produces a “rush,” followed by euphoria, a feeling of tranquility, and sleepiness (“the nod”). Heroin produces effects that last 3–5 h, and several doses a day are required to forestall manifestations of withdrawal in chronic users. Symptoms of opioid withdrawal begin 8–10 h after the last dose; lacrimation, rhinorrhea, yawning, and sweating appear first. Restless sleep followed by weakness, chills, gooseflesh (“cold turkey”), nausea and vomiting, muscle aches, involuntary movements (“kicking the habit”), hyperpnea, hyperthermia, and hypertension occur in later stages of the withdrawal syndrome. The acute course of withdrawal may last 7–10 days. A secondary phase of protracted abstinence lasts for 26–30 weeks and is characterized by hypotension, bradycardia, hypothermia, mydriasis, and decreased responsiveness of the respiratory center to carbon dioxide.

Besides the brain effects of opioids on sedation and euphoria and the combined brain and peripheral nervous system effects on analgesia, a wide range of other organs can be affected. The release of several

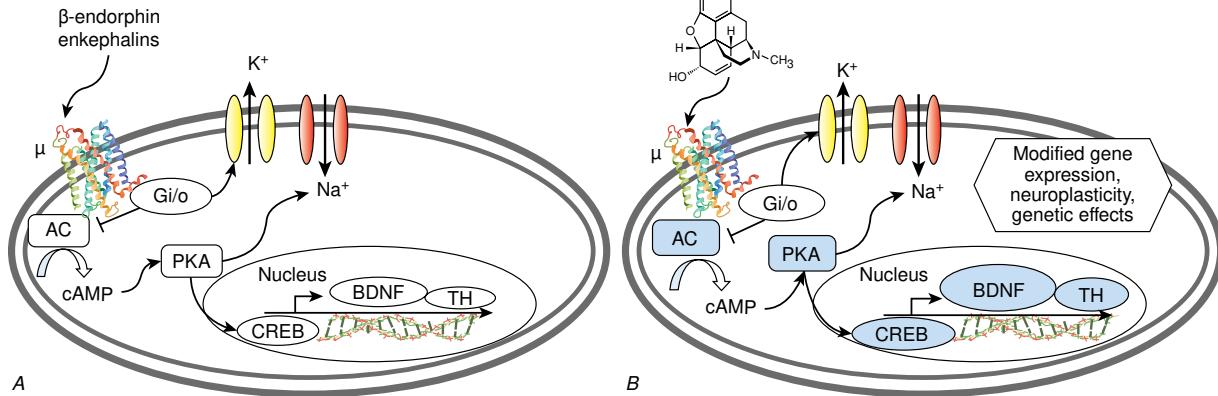


FIGURE 456-1 Normal mu-receptor activation by endogenous opioids inhibits the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP response-element binding protein (CREB) cascade in noradrenergic neurons within the locus coeruleus (*A*) through inhibitory Gi/o protein influence on adenylyl cyclase (AC). Similarly, acute exposure to opioids (e.g., morphine) inhibits this system, whereas chronic exposure to opiates (*B*) leads to upregulation of the cAMP pathway in an attempt to oppose opioid-induced inhibitory influence. Upregulation of this system is involved in opioid tolerance, and when the opioid is removed, unopposed noradrenergic neurotransmission is involved in opioid withdrawal. Upregulated PKA phosphorylates CREB, initiating the expression of various genes such as tyrosine hydroxylase (*TH*) and brain-derived neurotrophic factor (*BDNF*). *BDNF* is implicated in long-term neuroplastic changes in response to chronic opioids.

pituitary hormones is inhibited, including corticotropin-releasing factor (CRF) and luteinizing hormone, which reduces levels of cortisol and sex hormones and can lead to impaired stress responses and reduced libido. An increase in prolactin also contributes to the reduced sex drive in males. Two other hormones affected are thyrotropin, which is reduced, and growth hormone, which is increased. Respiratory depression results from opioid-induced insensitivity of brainstem neurons to increases in carbon dioxide, and in patients with pulmonary disease, this can result in clinically significant complications. In overdoses, aspiration pneumonia is common due to loss of the gag reflex. Opioids reduce gut motility, which is helpful for treating diarrhea, but can lead to nausea, constipation, and anorexia with weight loss. Deaths occurred in early methadone maintenance programs due to severe constipation and toxic megacolon. Opioids such as methadone may prolong QT intervals and lead to sudden death in some patients. Orthostatic hypotension may occur due to histamine release and peripheral blood vessel dilation, which is an opioid effect usefully applied to managing acute myocardial infarction. During opioid maintenance, interactions with other medications are of concern; these include inducers of the cytochrome P450 system (usually CYP3A4) such as rifampin and carbamazepine.

Heroin users in particular tend to use opioids intravenously and are likely to be polydrug users, also using alcohol, sedatives, cannabinoids, and stimulants. None of these other drugs are substitutes for opioids, but they have desired additive effects. Therefore, one needs to be sure that the person undergoing a withdrawal reaction is not also withdrawing from alcohol or sedatives, which might be more dangerous and more difficult to manage.

Intravenous opioid use carries with it the risk of serious complications. The common sharing of hypodermic syringes can lead to infections with hepatitis B and HIV/AIDS, among others. Bacterial infections can lead to septic complications such as meningitis, osteomyelitis, and abscesses in various organs. Off-target effects of opioids synthesized in illicit drug labs can lead to serious toxicity. For example, attempts to illicitly manufacture meperidine in the 1980s resulted in the production of a highly specific neurotoxin, MPTP, which produced parkinsonism in users (*Chap. 435*).

Lethal overdose is a relatively common complication of opioid use disorder. Rapid recognition and treatment with naloxone, a highly specific reversal agent that is relatively free of complications, are essential. The diagnosis is based on recognition of characteristic signs and symptoms, including shallow and slow respirations, pupillary miosis (mydriasis does not occur until significant brain anoxia supervenes), bradycardia, hypothermia, and stupor or coma. Blood or urine toxicology studies can confirm a suspected diagnosis, but immediate management must be based on clinical criteria. If naloxone is not administered, progression to respiratory and cardiovascular collapse leading to death occurs. At autopsy, cerebral edema and sometimes frothy pulmonary edema are generally found. Opioids generally do not produce seizures except for unusual cases of poly-drug use with the opioid meperidine, with high doses of tramadol, or in the newborn.

TREATMENT

Opioid Overdose

Beyond the acute treatment of opioid overdose with naloxone, clinicians have two general treatment options: opioid maintenance or detoxification. Opioid agonist and partial agonist medications are commonly used for both maintenance and detoxification purposes. α_2 -Adrenergic agonists are primarily used for detoxification. Antagonists are used to accelerate detoxification and then continued after detoxification to prevent relapse. Only the residential medication-free programs have had success that comes close to matching that of the medication-based programs. Success of the various treatment approaches is assessed as retention in treatment and reduced opioid and other drug use; secondary

TABLE 456-2 Management of Opioid Overdose

Establish airway. Intubation and mechanical ventilation may be necessary.

Naloxone 0.4–2.0 mg (IV, IM, or endotracheal tube). Onset of action with IV is ~1–2 min.

Repeat doses of naloxone if needed to restore adequate respiration or a continuous infusion of naloxone can be used.

One-half to two-thirds of the initial naloxone dose that reversed the respiratory depression is administered on an hourly basis (note: naloxone dosing is not necessary if the patient has been intubated).

outcomes, such as reduced HIV risk behaviors, crime, psychiatric symptoms, and medical comorbidity, also indicate successful treatment.

Stopping opioid use is much easier than preventing relapse. Long-term relapse prevention for individuals with opioid use disorder requires combined pharmacologic and psychosocial approaches. Chronic users tend to prefer pharmacologic approaches; those with shorter histories of drug use are more amenable to detoxification and psychosocial interventions.

OPIOID OVERDOSE

Managing overdose requires naloxone and support of vital functions, including intubation if needed (*Table 456-2*). If the overdose is due to buprenorphine, then naloxone might be required at total doses of 10 mg or greater, but primary buprenorphine overdose is nearly impossible because this agent is a partial opioid agonist, meaning that as the dose of buprenorphine is increased it has greater opioid antagonist than agonist activity. Thus, a 0.2-mg buprenorphine dose leads to analgesia and sedation, while a hundred times greater 20-mg dose produces profound opioid antagonism, precipitating opioid withdrawal in a person who had opioid use disorder on morphine or methadone. It is important to recognize that the goal is to reverse the respiratory depression and not to administer so much naloxone that it precipitates opiate withdrawal. Because naloxone only lasts a few hours and most opioids last considerably longer, an IV naloxone drip with close monitoring is frequently employed to provide a continuous level of antagonism for 24–72 h depending on the opioid used in the overdose (e.g., morphine vs methadone). Whenever naloxone has only a limited effect, other sedative drugs that produce significant overdoses must be considered. The most common are benzodiazepines, which have produced overdoses and deaths in combination with buprenorphine. A specific antagonist for benzodiazepines—flumazenil at 0.2 mg/min—can be given to a maximum of 3 g/h, but it may precipitate seizures and increase intracranial pressure. Like naloxone, administration for a prolonged period is usually required because most benzodiazepines remain active for considerably longer than flumazenil. Support of vital functions may include oxygen and positive-pressure breathing, IV fluids, pressor agents for hypotension, and cardiac monitoring to detect QT prolongation, which might require specific treatment. Activated charcoal and gastric lavage may be helpful for oral ingestions, but intubation will be needed if the patient is stuporous.

OPIOID WITHDRAWAL

The principles of detoxification are the same for all drugs: to substitute a longer-acting, orally active, pharmacologically equivalent medication for the substance being used, stabilize the patient on that medication, and then gradually withdraw the substituted medication. Methadone and buprenorphine are the two medications used to treat opioid use disorder. Clonidine, a centrally acting sympatholytic agent, has also been used for detoxification in the United States. By reducing central sympathetic outflow, clonidine mitigates many of the signs of sympathetic overactivity but typically requires augmentation with other agents. Clonidine has no narcotic action and is not addictive. Lofexidine, a clonidine analogue with less hypotensive effect, is not yet approved in the United States.

Methadone for Detoxification Dose-tapering regimens for detoxification using methadone range from 2–3 weeks to as long as 180 days, but this approach is controversial given the relative effectiveness of methadone maintenance and the low success rates of detoxification. Unfortunately, the vast majority of patients tend to relapse to heroin or other opioids during or after the detoxification period, indicative of the chronic and relapsing nature of opioid use disorder.

Buprenorphine for Detoxification Buprenorphine does not appear to lead to better outcomes than methadone but is superior to clonidine in reducing symptoms of withdrawal, in retaining patients in a withdrawal protocol, and in completing treatment.

α_2 -Adrenergic Agonists for Detoxification Several α_2 -adrenergic agonists have relieved opioid withdrawal by suppressing brain NE hyperactivity. Clonidine relieves some signs and symptoms of opioid withdrawal such as lacrimation, rhinorrhea, muscle pain, joint pain, restlessness, and gastrointestinal symptoms. Related agents are lofexidine, guanfacine, and guanabenz acetate. Lofexidine can be dosed up to ~2 mg/d and appears to be associated with fewer adverse effects. Clonidine or lofexidine is typically administered orally, in three or four doses per day, with dizziness, sedation, lethargy, and dry mouth as the primary adverse side effects. Outpatient-managed withdrawal will require close follow-up, often with naltrexone maintenance to prevent relapse.

Rapid and Ultrarapid Opioid Detoxification The opioid antagonist naltrexone typically combined with an α_2 -adrenergic agonist has been purported to shorten the duration of withdrawal without significantly increasing patient discomfort. Completion rates using naltrexone and clonidine range from 75 to 81% compared to 40 to 65% for methadone or clonidine alone. Ultrarapid opioid detoxification is an extension of this approach using anesthetics but is highly controversial due to the medical risks and mortality associated with it.

Opioid Agonist Medications For Maintenance Methadone maintenance substitutes a once-daily oral opioid dose for three to four times daily heroin. Methadone saturates the opioid receptors and, by inducing a high level of opioid tolerance, blocks the euphoria from additional opioids. Buprenorphine, a partial opioid agonist, also can be given once daily at sublingual doses of 4–32 mg daily, and in contrast to methadone, it can be given in an office-based primary care setting.

METHADONE MAINTENANCE Methadone's slow onset of action when taken orally, long elimination half-life (24–36 h), and production of cross-tolerance at doses from 80 to 150 mg are the basis for its efficacy in treatment retention and reductions in IV drug use, criminal activity, and HIV risk behaviors and mortality. Methadone can prolong the QT interval at rates as high as 16% above the rates in non-methadone-maintained, drug-injecting patients, but it has been used safely in the treatment of opioid use disorder for 40 years.

BUPRENORPHINE MAINTENANCE While France and Australia have had sublingual buprenorphine maintenance since 1996, it was first approved by the U.S. Food and Drug Administration (FDA) in 2002 as a Schedule III drug for managing opioid use disorder. Unlike the full agonist methadone, buprenorphine is a partial agonist of mu-opioid receptors with a slow onset and long duration of action. Its partial agonism reduces the risk of unintentional overdose but limits its efficacy to patients who need the equivalent of only 60–70 mg of methadone, and many patients in methadone maintenance require higher doses of up to 150 mg daily. Buprenorphine is combined with naloxone at a 4:1 ratio in order to reduce its abuse liability. Because of pediatric exposures and diversion of buprenorphine to illicit use, a new formulation, using mucosal films rather than sublingual pills that were crushed and snorted, is now marketed. A subcutaneous buprenorphine implant

that lasts up to 6 months has FDA approval as a formulation to prevent pediatric exposures and illicit diversion and to enhance compliance.

In the United States, the ability of primary care physicians to prescribe buprenorphine for opioid use disorder represents an important opportunity to improve access and quality of treatment as well as reduce social harm. Europe, Asia, and Australia have found reduced opioid-related deaths and drug-injection-related medical morbidity with buprenorphine available in primary care. Retention in office-based buprenorphine treatment has been as high as 70% at 6-month follow-ups.

Opioid Antagonist Medications The rationale for using narcotic antagonist therapy is that blocking the action of self-administered opioids should eventually extinguish the habit, but this therapy is poorly accepted by patients. Naltrexone, a long-acting orally active pure opioid antagonist, can be given three times a week at doses of 100–150 mg. Because it is an antagonist, the patient must first be detoxified from opioids before starting naltrexone. It is safe even when taken chronically for years, is associated with few side effects (headache, nausea, abdominal pain), and can be given to patients infected with hepatitis B or C without producing hepatotoxicity. However, most providers refrain from prescribing naltrexone if liver function tests are three times above normal levels. Naltrexone maintenance combined with psychosocial therapy is effective in reducing heroin use, but medication adherence is low. Depot injection formulations lasting up to 4 weeks markedly improve adherence, retention, and drug use. Subcutaneous naltrexone implants in Russia, China, and Australia have doubled treatment retention and reduced relapse to half that of oral naltrexone. In the United States, a depot naltrexone formulation is available for monthly use and maintains blood levels equivalent to 25 mg of daily oral use.

Medication-Free Treatment Most opioid users enter medication-free treatments in inpatient, residential, or outpatient settings, but 1- to 5-year outcomes are very poor compared to pharmacotherapy except for residential settings lasting 6–18 months. The residential programs require full immersion in a regimented system with progressively increasing levels of independence and responsibility within a controlled community of fellow drug users. These medication-free programs, as well as the pharmacotherapy programs, also include counseling and behavioral treatments designed to teach interpersonal and cognitive skills for coping with stress and for avoiding situations leading to easy access to drugs or to craving. Relapse is prevented by having the individual very gradually reintroduced to greater responsibilities and to the working environment outside of the protected therapeutic community.

■ PREVENTION

Preventing the development of opioid use disorder represents a critically important challenge for physicians. Opioid prescriptions are the most common source of drugs accessed by adolescents who begin a pattern of illicit drug use. The major sources of these drugs are family members, not drug dealers or the Internet. Pain management involves providing sufficient opioids to relieve the pain over as short a time as the pain warrants (Chap. 13). The patient then needs to dispose of any remaining opioids, not save them in the medicine cabinet, because this behavior leads to diversion by adolescents. Finally, physicians should never prescribe opioids for themselves.

■ FURTHER READING

- B C, V ND: Management of opioid use disorder in the USA: Present status and future directions. Lancet 393:1760, 2019.
- G PC et al: Medical use and misuse of prescription opioids in the US adult population: 2016–2017. Am J Public Health 109:1258, 2019.
- W SE et al: Comparative effectiveness of different treatment pathways for opioid use disorder. JAMA Netw Open 3:e1920622, 2020.

Karran A. Phillips, Wilson M. Compton



The use of cocaine, methamphetamine, other psychostimulants, and hallucinogens reflects a complex interaction between the pharmacology of the drug, the personality and expectations of the user, and the environmental context in which the drug is used. These substances cause significant harm, although they are less commonly used than other addictive substances such as alcohol (Chap. 453), nicotine (Chap. 454), cannabis (Chap. 455), and opioids (Chap. 456). It is also important to recognize that polydrug use, involving the concurrent use of several drugs with different pharmacologic effects, is common. Sometimes one drug is used to enhance the effects of another, as with the combined use of cocaine and nicotine, or cocaine and heroin in methadone-treated patients. Some forms of polydrug use, such as the combined use of intravenous (IV) heroin and cocaine, are especially dangerous and account for many hospital emergency department visits. Cocaine and psychostimulant use (especially chronic patterns of use) may cause adverse health consequences and exacerbate preexisting disorders such as hypertension and cardiac disease. In addition, the combined use of two or more drugs may accentuate medical complications associated with use of one drug. Chronic use is often associated with immune system dysfunction and increased vulnerability to infections, including risk for HIV infection. The concurrent use of cocaine and opiates ("speedball") is frequently associated with needle sharing by people using drugs intravenously. People who use IV drugs represent the largest single group of individuals with HIV infection in several major metropolitan areas in the United States as well as in many parts of Europe and Asia. Furthermore, several outbreaks of HIV in the United States since 2015 in rural and suburban areas have been attributed to clusters of injection drug use.

Psychostimulants and hallucinogens have been used for centuries to induce euphoria and alter consciousness. Hallucinogens have become popular recently, and new drugs are continually being developed. This chapter describes the subjective and adverse medical effects of cocaine, other psychostimulants including methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and cathinones; hallucinogens such as phencyclidine (PCP), -lysergic acid diethylamide (LSD), and *Salvia divinorum*; and emerging drugs.

PSYCHOSTIMULANTS

Psychostimulants include cocaine and methamphetamine, as well as drugs with stimulant-like properties such as MDMA and cathinones. In addition, prescribed psychostimulants such as methylphenidate, dextroamphetamine, and amphetamine are considered here.

■ COCAINE

Cocaine is a powerful psychostimulant drug made from the cocoa plant. It has local anesthetic, vasoconstrictor, and stimulant properties. Cocaine is a Schedule II drug, which means that it has high potential for abuse but can be administered by a physician for legitimate medical uses, such as local anesthesia for some eye, ear, and throat surgeries.

Pharmacology Cocaine comes in a variety of forms, the most-used being the hydrochloride salt, sulfate, and a base. The salt is an acidic, water-soluble powder with a high melting point, used by snorting or sniffing intranasally or by dissolving it in water and injecting it. When used intranasally the bioavailability of cocaine is about 60%. Cocaine sulfate ("paste") has a melting point of almost 200°C, so it has limited use, but is sometimes smoked with tobacco. The base form can be freebase or crystallized as crack. Cocaine freebase is made by adding a strong base to an aqueous solution of cocaine and extracting the alkaline freebase precipitate. It has a melting point of 98°C and can be

vaporized and inhaled. Freebase cocaine can also be crystallized and sold as crack or rock, which is also smoked or inhaled. Street dealers often dilute (or "cut") cocaine with nonpsychoactive substances such as cornstarch, talcum powder, flour, or baking soda, or adulterate it with other substances with similar effects (like procaine or amphetamine) to increase their profits. A recent concern has been the adulteration of cocaine (and other psychostimulants) with fentanyl-related opioids, resulting in overdose deaths due to opioid effects or polydrug use.

Given the extensive pulmonary vasculature, smoked or vaporized cocaine reaches the brain very quickly, similar in speed of onset to injected cocaine. The result is a rapid, intense, transient high, which enhances its addictive potential. Cocaine binds to the dopamine (DA) transporter and blocks DA reuptake, which increases synaptic levels of the monoamine neurotransmitters DA, norepinephrine (NE), and serotonin (5HT), in both the central nervous system (CNS) and the peripheral nervous system (PNS). Use of cocaine, like other drugs of abuse, induces long-term changes in the brain. Animal studies have shown adaptations in neurons that release the excitatory neurotransmitter glutamate after cocaine exposure.

Epidemiology According to the National Survey on Drug Use and Health (NSDUH), in 2019 an estimated 5.5 million people aged 12 years or older (2.0% of the population) were past-year consumers of cocaine, including about 778,000 (0.3% of the population) consumers of crack. Among those, 671,000 used cocaine for the first time (1800 cocaine initiates/day) including 59,000 adolescents aged 12–17 years. About 1 million people aged 12 years or older (0.4% of the population) in 2019 had a cocaine use disorder, but fewer than 1 in 5 received treatment, in the past year. According to the CDC National Center for Health Statistics, drug overdose deaths involving cocaine rose from 3822 in 1999 to 15,833 in 2019, with continued increases projected in 2020. Cocaine was involved in more than 1 in 5 overdose deaths in 2019. The number of deaths in combination with any opioid has been increasing steadily since 2014 and is mainly driven by the involvement of synthetic opioids including fentanyl and fentanyl analogs.

■ METHAMPHETAMINE

Methamphetamine is a psychostimulant drug usually used as a white, bitter-tasting powder or a pill. Crystal methamphetamine is a form of the drug that looks like glass fragments or shiny, bluish-white rocks. It can be inhaled/smoked, swallowed (pill), snorted, or injected (after being dissolved in water or alcohol).

Pharmacology When smoked, methamphetamine exhibits 90.3% bioavailability, compared to 67.2% for oral ingestion. Methamphetamine exists in two stereoisomers, the - and -forms. -Methamphetamine, or the dextrorotatory enantiomer, is a more powerful psychostimulant, with 3–5 times the CNS activity as compared with -methamphetamine. Methamphetamine is a cationic lipophilic molecule, which stimulates the release, and partially blocks the reuptake, of newly synthesized catecholamines in the CNS. Methamphetamine has a similar structure to the DA, NE, 5HT, and vesicular monoamine transporters and reverses their endogenous function, resulting in release of monoamines from storage vesicles into the synapse. Methamphetamine also attenuates the metabolism of monoamines by inhibiting monoamine oxidase.

Methamphetamine is more potent than amphetamine, resulting in much higher concentrations of synaptic DA and more toxic effects on nerve terminals. Outside the medical context, methamphetamine's pharmacokinetics and low cost often result in a chronic and continuous, high-dose self-administered use pattern.

Epidemiology According to the NSDUH, in 2019 approximately 2 million people aged 12 years or older (0.7% of the population) used methamphetamine in the past year, of those 184,000 used methamphetamine for the first time (510 people per day), and about 25% reported injecting methamphetamine. In 2019, an estimated 1 million people aged 12 years or older (0.4% of the population and 50% of those with past-year use) had a methamphetamine use disorder. High rates of co-occurring substance use or mental illness exist in adults who

use methamphetamine and only about one-third of adults with past-year methamphetamine use disorder received addiction treatment. Methamphetamine availability and methamphetamine-related harms (overdose deaths, treatment admissions, infectious disease transmission, etc.) continue to increase in the United States. According to CDC data, psychostimulants with abuse potential (primarily methamphetamine) caused 16,167 overdose deaths in 2019. These substances were the second leading cause of overdose death nationwide accounting for 23% of overdose deaths (compared to 49,860 deaths from an opioid in 2019). Of note there is significant geographic variation in the role of methamphetamine in overdose deaths; in four western regions methamphetamine was the #1 cause of overdose death accounting for 21–38% of all overdose deaths. Geographic variation is also apparent in overall psychostimulant-involved mortality rates; from 2015–2018 the highest increase was observed in West Virginia for psychostimulant use alone. Mortality associated with psychostimulants combined with opioids ranged from 15% in Hawaii to 91% in New Hampshire.

■ MDMA AND CATHINONES

MDMA Also known as Molly, ecstasy, or X, is an illegal synthetic drug that has stimulant and psychedelic effects. Khât is a plant found in East Africa and the Middle East; it has been used for centuries for its mild stimulant-like effect. Synthetic cathinones or “bath salts” are manufactured psychostimulants that are chemically similar to the naturally occurring substance cathinone found in the khât plant and are discussed under “Emerging Drugs” below.

MDMA Molly, slang for “molecular,” refers to the crystalline powder form of MDMA usually sold as powder or in capsules. The content of Molly varies and is often not MDMA at all but rather contains methylone or ethylone, which are synthetic substances commonly found in so-called bath salts and pose significant health risks. The clinician should always consider the possibility that the drug reported by the user may be incorrect or contaminated with other substances.

With MDMA use, individuals experience increased physical and mental energy, distortions in time and perception, emotional warmth, empathy toward others, a general sense of well-being, decreased anxiety, and an enhanced enjoyment of tactile experiences. MDMA is usually taken orally in a tablet, capsule, or liquid form with first effect at 45 min on average, peak effect at 1–2 h, and duration ~3–6 h. MDMA binds to serotonin transporters and increases the release of serotonin, NE, and DA. Research in animals has shown that MDMA in moderate to high doses can cause loss of serotonin-containing nerve endings and permanent damage. MDMA is a Schedule I drug, along with other substances with no proven therapeutic value. MDMA is currently in clinical trials as a possible treatment for posttraumatic stress disorder and anxiety and for patients with terminal illness including cancer. The evidence on MDMA’s therapeutic effects is quite limited to date, and research is ongoing.

Adulteration of MDMA tablets with methamphetamine, ketamine, caffeine, the over-the-counter cough suppressant dextromethorphan (DXM), the diet drug ephedrine, and cocaine is common. MDMA is rarely used alone and is often mixed with other substances, such as alcohol and marijuana, making the scope of its use difficult to ascertain. According to the NSDUH, >18 million people in the United States have tried MDMA at least once in their life. MDMA is predominantly used by men 18–25 years of age, with use typically beginning at age 21 years. There is evidence that gay or bisexual men and women are more likely than their heterosexual counterparts to have used MDMA in the last 30 days.

Cathinone Is an alkaloid psychostimulant structurally similar to amphetamine found in the khât (*Catha edulis*) plant, which grows at high altitudes in East Africa and the Middle East and whose leaves are chewed for their mild stimulant-like effect. The extraction of cathinone and other alkaloids from the leaves by chewing is very effective leaving little as unabsorbed residue. The leaves and twigs can also be smoked, infused in tea, or sprinkled on food. Cathinone increases dopamine release and reduces dopamine reuptake.

Originally limited to its area of cultivation, with advances in rapid transportation and postal delivery khât is now available in several continents including Europe and North America. Worldwide it is estimated that 10 million people chew khât, including up to 80% of all adults in some areas where the evergreen shrub is indigenous. In regions where the plant is indigenous, there have also been reports of khât use as a study aid among university students. Cathinone is a Schedule I drug in the United States, making its use illegal; however, the khât plant itself is not controlled.

■ PRESCRIBED PSYCHOSTIMULANTS

Methylphenidate, dextroamphetamine, and dextroamphetamine/amphetamine combination products are psychostimulants approved in the United States for treatment of attention-deficit hyperactivity disorder (ADHD), weight control, and narcolepsy. Prescription psychostimulants increase alertness, attention, and energy. Phenylpropanolamine, a psychostimulant used primarily for weight control, was found to be related to hemorrhagic stroke in women and removed from the market in 2005. Nonprescribed amphetamines or methylphenidate is used quite frequently by college students, and as an energy and productivity booster by others. According to the 2019 NSDUH, past-year prescription stimulant misuse was reported by 4.9 million (1.8%) people aged 12 years or older. Past-year initiates of prescription stimulant misuse totaled 901,000, which averages to about 2500 people misusing prescription stimulants for the first time each day, including 1000 young adults each day. Among people aged 12 years or older, 0.2% (558,000 people) had a prescription stimulant use disorder in the past year.

■ PSYCHOSTIMULANT CLINICAL MANIFESTATIONS

Psychostimulants produce the same acute CNS effects: euphoria/elevated mood, increased energy/decreased fatigue, reduced need for sleep, decreased appetite, heightened sense of alertness, decreased distractibility, dosed-dependent effects on focus, attention, and curiosity, increased self-confidence, increased libido, and prolonged orgasm, independent of the specific psychostimulant or route of administration. Peripheral effects may include tremor, diaphoresis, hypertonia, tachypnea, hyperreflexia, and hyperthermia. Many of the effects are biphasic; for example, low doses improve psychomotor performance, while higher doses may cause tremors or convulsions. α -adrenergically mediated cardiovascular effects are also biphasic, with low doses resulting in increased vagal tone and decreased heart rate, and high doses causing increased heart rate and blood pressure. Psychostimulant use can result in restlessness, irritability, and insomnia and, at higher doses, suspiciousness, repetitive stereotyped behaviors, and bruxism. Endocrine effects resulting from chronic use may include impotence, gynecomastia, menstrual function disruptions, and persistent hyperprolactinemia (Table 457-1).

Overdose presents as sympathetic nervous system overactivity with psychomotor agitation, hypertension, tachycardia, headache, and mydriasis, and can lead to convulsions, cerebral hemorrhage or infarction, cardiac arrhythmias or ischemia, respiratory failure, or rhabdomyolysis. It is a medical emergency; treatment is largely symptomatic and should occur in an intensive care or telemetry unit. Inhalation of crack cocaine that is vaporized at high temperatures can cause airway burns, bronchospasm, and other symptoms of pulmonary disease. MDMA has also been shown to raise body temperature and can occasionally result in liver, kidney, or heart failure, or even death.

Psychostimulants are often used with other drugs, including opioids and alcohol, whose CNS-depressant effects tend to attenuate psychostimulant-induced CNS stimulation. These combinations often have additive deleterious effects, increasing the risk of morbidity and mortality. An example of this risk is the use of cocaine with alcohol, which results in the metabolite, cocaethylene. Cocaethylene’s effects on the cardiovascular system are additive to that of cocaine’s effects, resulting in intensified pathophysiologic consequences.

Adulteration of psychostimulants, particularly cocaine, with other drugs is common and can have additional potential health consequences. In addition to contamination with fentanyl-related compounds, potentially resulting in fatal overdose, multiple other

TABLE 457-1 Complications of Psychostimulant Use

Cardiovascular	Acute
	<ul style="list-style-type: none"> • Arterial vasoconstriction • Thrombosis • Tachycardia • Hypertension • Increased myocardial oxygen demand • Increased vascular shearing forces • Coronary vasoconstriction • Cardiac ischemia • Left ventricular dysfunction/heart failure (high blood concentrations) • Supraventricular and ventricular dysrhythmias • Aortic dissection/rupture
Chronic	<ul style="list-style-type: none"> • Accelerated atherogenesis • Left ventricular hypertrophy • Dilated cardiomyopathy
Central and Peripheral Nervous Systems	<ul style="list-style-type: none"> • Hyperthermia • Psychomotor agitation • Tremor • Hyperreflexia • Hypertonia • Headache • Seizures • Coma • Intracranial hemorrhage • Focal neurologic symptoms
Pulmonary	<ul style="list-style-type: none"> • Angioedema (inhaled) • Pharyngeal burns (inhaled) • Pneumothorax • Pneumomediastinum • Pneumopericardium • Reversible airway disease exacerbations • Bronchospasm • Shortness of breath ("crack lung") • Tachypnea • Pulmonary infarction
Gastrointestinal	<ul style="list-style-type: none"> • Perforated ulcers • Ischemic colitis • Bowel infarction • Impaction (body packing) • Hepatic enzyme elevation
Renal	<ul style="list-style-type: none"> • Metabolic acidosis • Renal infarction • Rhabdomyolysis
Endocrine	<ul style="list-style-type: none"> • Impotence • Gynecomastia • Menstrual function disruptions • Hyperprolactinemia
Other	<ul style="list-style-type: none"> • Diaphoresis • Irritability • Insomnia • Bruxism • Stereotypy • Splenic infarction • Acute angle-closure glaucoma • Vasospasm of the retinal vessels (unilateral or bilateral vision loss) • Mydriasis • Madarosis • Abruptio placenta

substances have been noted as contaminants of psychostimulants. Levamisole, an anthelmintic and immunomodulator used primarily in veterinary medicine, has been found in cocaine and can cause agranulocytosis, leukoencephalopathy, and cutaneous vasculitis, which has resulted in cutaneous necrosis. Clenbuterol, a sympathomimetic amine used clinically as a bronchodilator, has also been found in cocaine and can result in tachycardia, hyperglycemia, palpitations, and hypokalemia. Studies in Europe have found that, in addition to levamisole, some of the most common adulterants in cocaine include phenacetin, lidocaine, caffeine, diltiazem, hydroxyzine, procaine, tetracaine, paracetamol, creatine, and benzocaine.

Withdrawal from psychostimulants often includes hypersomnia, increased appetite, and depressed mood. Acute withdrawal typically lasts 7–10 days, but residual symptoms, possibly associated with neurotoxicity, may persist for several months. Debate remains whether psychostimulant withdrawal symptoms decline monotonically or occur in discrete phases, becoming worse before they improve. Psychostimulant withdrawal is not thought to be a major driver of ongoing use. Most current theories of psychostimulant addiction emphasize the primary role of conditioned craving, which can persist long after physiological withdrawal has abated. Conditioned craving includes the urge to use drugs in response to cues in the environment associated with drug use, such as drug-using associates, drug paraphernalia, drug-using locations, etc.

Injection of psychostimulants places people at increased risk of contracting infectious diseases from exposure to HIV and hepatitis B or C in blood or other bodily fluids, as well as with skin abscesses and endocarditis. Psychostimulant use can also increase risk for infection by causing altered judgment and decision-making, leading to risky behaviors, such as unprotected sex. There is some evidence that psychostimulant use may worsen the progression of HIV/AIDS via increased injury to nerve cells exacerbating cognitive problems.

The actions and effects of khât are like those of other psychostimulants. Short-term effects include euphoria, increased alertness and arousal, loss of appetite, insomnia, headaches, and tremors. Long-term use may result in gastrointestinal disorders such as constipation, ulcers, and stomach inflammation as well as increased risk for acute myocardial infarction and stroke, due to inotropic and chronotropic effects on the heart, vasospasm of coronary arteries, and catecholamine-induced platelet aggregation. There is evidence that, rarely, heavy khât use may cause mild to moderate psychological dependence. Compulsive use has been described, with resulting grandiose delusions, paranoia, and hallucinations. Mild withdrawal from khât has been described and can include depression, nightmares, low blood pressure, and lack of energy.

■ DIAGNOSIS

The *Diagnostic and Statistical Manual of Psychiatric Disorders*, 5th edition (*DSM-5*) defines a stimulant use disorder (SUD) as a pattern of use of amphetamine-type substances, cocaine, or other stimulants leading to clinically significant impairment or distress, as manifested by at least 2 of the following 11 problems within a 12-month period: taking larger amounts, or over a longer period of time, than intended; persistent desire or unsuccessful efforts to reduce or control use; a great deal of time spent in activities necessary to obtain, use, or recover; craving; use resulting in failure to fulfill major role obligations; continued use, despite recurrent social or interpersonal problems; giving up social, occupational, or recreational activities; recurrent use in physically hazardous situations; continued use despite persistent or recurrent physical or psychological problems; tolerance; and withdrawal symptoms, or avoidance of withdrawal symptoms, by continued use.

The International Classification of Diseases (ICD) 10th Revision (ICD-10) recognizes "stimulant dependence syndrome" and "stimulant withdrawal state" and the ICD 11th Revision (ICD-11) further specifies the definition to "stimulant dependence including amphetamines, methamphetamines, or methcathinone."

TREATMENT

Acute Intoxication

As with all emergency situations the first task is to check a patient's airway, breathing, and circulation. With cocaine use, succinylcholine is relatively contraindicated in rapid-sequence intubation; consider rocuronium (1 mg/kg IV) or another nondepolarizing agent as an alternative. If psychomotor agitation occurs, rule out hypoglycemia and hypoxemia first, and then administer benzodiazepines (e.g., diazepam 10 mg IV and then 5–10 mg IV every 3–5 min until agitation controlled). Benzodiazepines are usually sufficient to address cardiovascular side effects. Severe or symptomatic hypertension can be treated with phentolamine, nitroglycerin, or nitroprusside. Hyperthermic patients should be cooled within ≤30 min with the goal to achieve a core body temperature of <39°C (102°F). Evaluation of chest pain in someone using cocaine should include an electrocardiogram, chest radiograph, and biomarkers to exclude myocardial infarction. The treatment approach is similar to nonstimulant-induced chest pain; however, it is recommended that whenever possible beta blockers not be used in people who use cocaine. The concern arises from the potential unopposed alpha-adrenergic stimulation that results from beta blockade possibly causing coronary arterial vasoconstriction, ischemia, and infarction and limited data supporting the benefit of beta blockers in cocaine-related cardiovascular complications. If beta blockers are to be given, it is suggested that mixed alpha/beta blockers, e.g., labetalol and carvedilol, be used rather than nonselective beta blockers, and only in situations where the benefits outweigh the risks. Because many instances of psychostimulant-related mortality have been associated with concurrent use of other illicit drugs (particularly opioids), the physician must be prepared to institute effective emergency treatment for multiple drug toxicities.

Psychostimulant Use Disorders

Treatment of stimulant use disorders requires the combined efforts of primary care physicians, psychiatrists, and psychosocial care providers. Early abstinence from psychostimulant use is often complicated by symptoms of depression and guilt, insomnia, and anorexia, which may be as severe as those observed in major affective disorders and can last for months and even years after use has stopped.

Behavioral therapies, including cognitive-behavioral therapy (CBT), the community reinforcement approach (CRA), contingency management (CM; providing rewards to patients who remain substance free), motivational enhancement therapy (MET), combinations of these, and others remain the mainstay of treatment for stimulant use disorders and show modest benefit. These behavioral therapies are designed to help modify the patient's thinking, expectancies, and behaviors, and to increase life-coping skills, with behavioral interventions to support long-term, drug-free recovery. Based on systematic reviews, contingency management has been noted to be particularly effective. However, the effect of these behavioral therapies is often not sustained, and they may be less effective in individuals with severe use disorder.

There are no U.S. Food and Drug Administration (FDA)-approved medications for psychostimulant addiction. Current research includes several neurotransmitter-based strategies, including DA agonist-, serotonin-, γ-aminobutyric acid (GABA)-, and glutamate-based approaches. Trials of agonist therapy with longer-acting psychostimulant medications such as dexamphetamine and methylphenidate have not been conclusive. Studies with the antidepressants mirtazapine, bupropion, sertraline, imipramine, and atomoxetine have been equivocal as have studies with the atypical antipsychotic, aripiprazole, and the anticonvulsant, topiramate. Other therapies being studied for the treatment of psychostimulant use disorder include: acamprosate (possibly via a role in Ca^{2+} supply), galantamine (reversible acetylcholine esterase inhibitor, which may strengthen impulse control, as well as cognitive and social

abilities depleted by long-term psychostimulant use), naltrexone (opiate receptor antagonist), doxazosin (alpha-adrenergic antagonist), and varenicline (partial agonist at the $\alpha 4\beta 2$ nicotinic acetylcholine receptors and DA neurotransmission enhancer). Overall, it is promising that some of the medications studied showed statistically significant outcome improvement over placebo, but many of these studies were underpowered due to issues of small sample size, sample bias, low participant retention, and low treatment adherence rates. Ongoing studies are investigating lisdexamfetamine (a dexamphetamine pro-drug), a combination of extended-release naltrexone with bupropion, pomaglumetad (a glutamate agonist), and monoclonal antibodies. Special attention needs to be paid to the inclusion of underrepresented populations including women in future stimulant use disorder medication trials. Vaccines for cocaine and methamphetamine use disorders are also being developed. Finally, recent preliminary studies have brought attention to the potential use of brain stimulation techniques such as transcranial magnetic stimulation (TMS), theta-burst stimulation (TBS), and transcranial direct current stimulation (tDCS) to treat psychostimulant use disorders, although further studies will be required to determine their value, if any, in this situation.

HALLUCINOGENS

Hallucinogens are a diverse group of drugs causing alteration of thoughts, feelings, sensations, and perceptions. Some hallucinogens are found naturally in plants and mushrooms, while others are synthetic. They include: ayahuasca (a tea made from Amazonian plants containing dimethyltryptamine (DMT), the primary mind-altering ingredient); DMT (aka Dimitri, can also be synthesized in a lab); LSD (clear or white odorless material made from lysergic acid found in rye and other grain fungus); peyote (mescaline, derived from a small, spineless cactus or made synthetically); and 4-phosphoryloxy-N,N-dimethyltryptamine (psilocybin, comes from certain South and North American mushrooms).

A subgroup of hallucinogens produces the added sensation of feeling out of control or disconnected from one's body or surroundings. These dissociative drugs include: DXM (an over-the-counter cough suppressant, when used in high doses); ketamine (a human and veterinary anesthetic as well as an antidepressant medication recently approved by the FDA); phencyclidine (PCP; a cyclohexylamine derivative and dissociative anesthetic); and *Salvia divinorum* (salvia, a Mexican, Central, and South American plant). Dissociative drugs distort the way the user perceives time, motion, color, sound, and self, and their use can lead to bizarre and dangerous behavior and cause respiratory depression, heart rate abnormalities, and a withdrawal syndrome including drug craving, confusion, headache, and sweating.

Use of hallucinogens in religious and spiritual rituals goes back centuries, and they are ingested in a wide variety of ways, including orally, by smoking, intranasally, and transmucosally. Especially when taken orally, the onset of action of hallucinogens is within 20–90 min and the duration of action can be as long as 6–12 h, except for salvia, whose effects generally last about 30 min. Hallucinogens specifically disrupt the neurotransmitters serotonin and glutamate. Effects on the serotonin system can disturb mood, sensory perception, sleep, appetite, body temperature, sexual behavior, and muscle control. Glutamate system effects include perturbations in pain perception, responses to the environment, emotion, and learning and memory.

According to the NSDUH, in 2019 1.9 million adults reported past-month hallucinogen use and 6 million (2.2% of the population) reported past-year hallucinogen use, an increase from 4.7 million (1.8%) in 2015. Of these, 1.2 million used hallucinogens for the first time. These estimates are similar to 2015 and 2018 estimates for those aged 12–17 years but reflect an increase in past-year use among those aged 26 years and older. Of note, these statistics include ecstasy (MDMA or "Molly") in the overall hallucinogen use as well as LSD, PCP, peyote, mescaline, psilocybin mushrooms, ketamine, DMT/AMT/"Foxy", and *Salvia divinorum*. New initiates to drug use per day

among people age 12 years and older include 2421 for LSD, 83 for PCP, and 2039 for ecstasy. According to 2019 Monitoring the Future Data, the annual prevalence of use among 12th graders was 1.1% for PCP, 2.2% for ecstasy, and 0.7% for salvia, which was similar to 2018.

Clinical manifestations of hallucinogen use include false sensory experiences (i.e., hallucinations), intensified feelings, heightened sensory experiences, and time perturbations. Additional physiologic responses include nausea; increased heart rate, blood pressure, respiratory rate, or body temperature; loss of appetite; xerostomia; sleep problems; synesthesia; impaired coordination; and hyperhidrosis. Extremely negative experiences with hallucinogen use (the “bad trip”) can include panic, paranoia, and psychosis, which may persist for up to 24 h. Such experiences are best treated with supportive reassurance, but benzodiazepines (e.g., diazepam 10 mg or lorazepam, if liver damage is present) may be administered if agitation is severe. There is some evidence that chronic effects of hallucinogen use can occur, including persistent psychosis, memory loss, anxiety, depression, and flashbacks. Long-term effects of PCP and other dissociative drug use can include persistent speech difficulties, memory loss, depression, suicidal thoughts, anxiety, and social withdrawal that may persist for a year or more after chronic use stops.

Psilocybin is under active investigation for its possible benefit in treatment of depression and some anxiety disorders.

Hallucinogen addiction is atypical, as use patterns are generally not chronic, and there are currently no FDA-approved medications for the treatment of hallucinogen addiction. Research on behavioral treatments for hallucinogen addiction is underway.

EMERGING DRUGS

With the aid of the Internet, and some basic over-the-counter (and other) ingredients, the rise of the “kitchen chemist” is upon us. The production of new psychoactive substances (NPSs), such as synthetic cathinones (bath salts) and synthetic cannabinoids (spice), is on the rise and has resulted in the use of unregulated psychoactive substances that are intended to copy the effects of more expensive illegal drugs, such as methamphetamine and cocaine.

Synthetic cathinones (bath salts) are human-made drugs chemically similar to khât and are often stronger and more dangerous than the natural product. They usually take the form of a white or brown crystal-like powder, packaged in small plastic or foil bundles labeled “not for human consumption,” or as “plant food,” “jewelry cleaner,” or “phone screen cleaner,” and sold online and in drug paraphernalia stores. The popular nickname Molly (slang for “molecular”) often refers to the purported “pure” crystalline powder form of MDMA, usually sold in capsules. However, people who purchase powder or capsules sold as Molly often actually receive other drugs, such as synthetic cathinones. The uncertainty of what is actually in these synthetic products, whose components might change from batch to batch, makes them even more dangerous as anyone using them is unaware of what the products contain and how their bodies will react.

The three most common synthetic cathinones are mephedrone, methylone, and MDPV (*3,4-methylenedioxypyrovalerone*). With oral ingestion, these drugs have an onset of action from 15–45 min, and a duration that varies from 2–7 h. A recent study found that MDPV affects the brain in a manner similar to cocaine but is at least 10 times more potent. MDPV is the most common synthetic cathinone found in the blood and urine of patients admitted to EDs after taking “bath salts.” High doses, or chronic use, of synthetic cathinones can lead to dangerous medical consequences, including psychosis, violent behaviors, tachycardia, hyperthermia, and even death.

The ability to synthesize addictive and dangerous drugs relatively simply and rapidly, changing just a few molecules, yet retaining the effects, has allowed many of these emerging drugs to outpace efforts to regulate them, resulting in a developing global public health concern.

SUBSTANCE USE AND MENTAL HEALTH

According to the NSDUH, in 2019, among adults with no mental illness 16.6% consumed illicit drugs, compared to 49.4% with severe mental illness and 38.8% with any mental illness. In 2019, among adults 18 years

of age or older, 61.2 million people had either mental illness or a substance use disorder in the past year, 42 million had mental illness in the absence of a substance use disorder, 9.7 million had a substance use disorder and no mental illness, and 9.5 million (3.8% of the population) had both. Furthermore, based on 2018 NSDUH data it is estimated that more than 1 in 10 adults (27.5 million) in the United States reported ever having a substance use problem. Among those with a problem, nearly 75% (20.5 million) reported being in recovery, which was associated with lower prevalence of past-year substance use and having received substance use treatment. Self-reported prevalence of ever having a substance use problem was 31.9% among adults with a lifetime mental health problem but not in recovery, followed by 29.7% among adults in recovery, compared with 7.0% among adults without a lifetime mental health problem. Taken together, these data all point to the significant overlap of substance-related and other mental health problems.

GLOBAL CONSIDERATIONS

After nicotine, alcohol, and cannabis, stimulants are the next most commonly used drugs globally, accounting for 68 million past-year consumers. Past-year stimulant use worldwide for individuals aged 15–65 years approaches 29 million. Globally 7.4 million individuals have a stimulant use disorder and it is thought that 11% of all people who use stimulants develop such a disorder. The United Nations Office on Drugs and Crime (UNODC) estimates that 1 in 7 people with substance use disorders receives treatment, and this number is thought much lower in individuals with stimulant use disorder due to the lack of pharmacologic treatments. Cocaine use globally had remained stable until 2010 when it began to rise, driven by an increase in its use in South America. Amphetamine use in Western Europe is still well below 5% lifetime prevalence for most countries, and methamphetamine problems have been largely restricted to the Czech Republic; however, evidence indicates growing spread through Europe. Over three-quarters of the world’s production of amphetamine-type stimulants occurs in Southeast Asia and in recent years there has been a dramatic increase in use in this region, particularly Thailand. In Japan and the Philippines, methamphetamine use predominates. Lifetime experience with ecstasy among the general population is still well below 5% in most European countries, which is slightly lower than levels seen in Australia (6%). Ecstasy is more prevalent in the West; however, over the past decade use has increasingly become evident in other regions, including Africa, South and Central America, the Caribbean, and parts of Asia. Globally, psychostimulant use has been associated with elevated mortality, increased incidence of HIV and hepatitis C infection, poor mental health (suicidality, psychosis, depression, and violence), and increased risk of cardiovascular events. Globally, stigma and marginalization make treatment of drug use disorders difficult and hinder sustainable inclusive development incorporating gender and racial equity and the empowerment of women and underrepresented minorities.

FUTURE DIRECTIONS

Despite their prevalence and public health impact, psychostimulant and hallucinogen use disorders have no FDA-approved treatment medications. While behavioral therapies, such as contingency management and CBT, have been shown effective in psychostimulant use disorders, further research needs to be done regarding their utility for hallucinogen use disorders. Furthermore, based upon experience with opioid and alcohol use disorders, it is likely that the most efficacious treatments will employ a combination of behavioral and pharmacologic therapy.

Additionally, new approaches that utilize emerging technologies have considerable potential for future treatment of psychostimulant use disorders. These include neurostimulation/neuromodulation (TMS, TBS, tDCS), wearable biosensors, and mobile technology, including ecologic and geographic momentary assessment (EMA/GMA) as well as real-time interventions delivered via smartphone or other mobile devices.

A

The authors would like to acknowledge the contributions of Dr. Antonello Bonci to this chapter in previous editions.

- 3578 ■ FURTHER READING
- C WM: Polysubstance use in the U.S. Opioid Crisis. Mol Psychiatry 26:41, 2021.
- F M et al: Responding to global stimulant use: challenges and opportunities. Lancet 394:1652, 2019.
- T MH et al: Bupropion and naltrexone in methamphetamine use disorder. N Engl J Med 384:140, 2021.
- V ND et al: Neurobiologic advances from the brain disease model of addiction. N Engl J Med 374:363, 2016.

- WEBSITES
- A S : <https://www.asam.org/public-resources>
- N I : <https://www.drugabuse.gov/drugs-abuse>
- W H O : http://www.who.int/substance_abuse/en/