403

APPROACH TO THE PATIENT WITH NEUROLOGIC DISEASE

ROBERT C. GRIGGS, RALPH F. JÓZEFOWICZ, AND MICHAEL J. AMINOFF

CLINICAL MANIFESTATIONS

The symptoms of nervous system diseases are a part of everyday experience for most normal people. Slips of the tongue, headaches, backache and other pains, dizziness, lightheadedness, numbness, muscle twitches, jerks, cramps, and tremors all occur in totally healthy persons. Mood swings with feelings of elation and depression, paranoia, and displays of temper are equally a part of the behavior of completely normal people. The rapid increase in information about neurologic diseases coupled with the intense interest of people in all walks of life in medical matters has focused public attention on both common and rare neurologic conditions.

Most older people are concerned that they or their spouse have or are developing Alzheimer's disease or stroke. The almost ubiquitous tremor of the elderly prompts concern about Parkinson's disease. Many younger patients are concerned about multiple sclerosis or brain tumor, and few normal people lack one or more symptoms suggesting the diagnosis of a serious neurologic disease. For most of these and other common diagnoses, the results of imaging and other tests are typically normal when symptoms first appear, and such tests should not be performed to reassure the patient or physician. Moreover, the widespread availability of neurodiagnostic imaging and electrophysiologic, biochemical, and genetic testing has led to the detection of "abnormalities" in many young and most elderly persons. In evaluating a patient's symptoms, it is imperative that a clinical diagnosis be reached without reference to a neurodiagnostic laboratory finding. Patients with disorders such as headache, anxiety, and depression do not usually have abnormal laboratory results. Abnormalities noted on various neurodiagnostic studies are often incidental findings whose treatment may be justified and necessary, but they do not improve the patient's symptoms. Abnormalities detected incidentally that are not accompanied by signs or symptoms may, as for disorders such as hypertension, require aggressive evaluation and treatment, but in general, the adage that it is difficult to improve an asymptomatic patient should be kept in mind. Thus, in elderly patients, few imaging or electrophysiologic studies are interpreted as "normal," but in the absence of specific complaints consistent with the findings, treatment and even further evaluation should reflect an estimate of the specificity and sensitivity of the test as well as the likelihood that the patient will require and benefit from treatment. It is a good rule of thumb that one should never perform (or refer to the result of) a neurodiagnostic procedure without a specific diagnosis or at least a differential diagnosis in mind.

It is important to allow patients to describe any symptoms in their own words. Direct questions are often necessary to fully characterize the problem, but suggested terms or descriptors for symptoms are frequently grasped by a patient unfamiliar with medical terminology and then parroted to subsequent interviewers. The patient's terms should always be used in recording symptoms. Terms such as *lameness, weakness, numbness, heaviness, cramps*, and *tiredness* may each mean pain, weakness, or alteration of sensation to some patients.

DIAGNOSIS

History

In neurologic diagnosis, the history usually indicates the nature of the disease or the diagnosis, whereas the neurologic examination localizes it and quantitates its severity. For many diseases, the history is almost the only avenue to explore. Examples of such disorders include headaches, seizures, developmental disorders, memory disorders, and behavioral diseases. In arriving at a diagnosis, the following points are useful. Consider the entire medical history of the patient. Early life events or long-standing processes such as head or spine trauma, unilateral hearing or visual loss, poor prowess in sports, poor performance in school, spinal curvature, and bone anomalies are easily overlooked but may point to the underlying disease process.

Consider the tempo and duration of the symptoms. Have the symptoms been progressive without remission, or have there been plateaus or periods of return to normal? Cerebral mass lesions (tumor, subdural) tend to have a progressive but fluctuating course; seizures and migraine, an episodic course; and strokes, an abrupt, ictal onset with worsening for 3 to 5 days, followed by partial or complete recovery.

Can one disease account for all of the symptoms and signs? The clinician should formulate a diagnostic opinion in anatomic terms. Is the history suggestive of a single (e.g., stroke or tumor) focus or multiple sites of nervous system involvement (e.g., multiple sclerosis), or is the process a disease of a system (vitamin B_{12} deficiency, myopathy, or polyneuropathy)?

The neurologic history is the most important component of neurologic diagnosis. A careful history frequently determines the cause and allows one to begin localizing the lesions, which aids in establishing whether the disease is diffuse or focal. Symptoms of acute onset suggest a vascular cause or seizure; symptoms that are subacute in onset suggest a mass lesion, such as a tumor or abscess; symptoms that have a waxing and waning course with exacerbations and remissions suggest a demyelinating cause; and symptoms that are chronic and progressive suggest a degenerative disorder.

The history is often the only way of diagnosing neurologic illnesses that typically have normal or nonfocal findings on neurologic examination. These illnesses include many seizure disorders, narcolepsy, migraine and most other headache syndromes, the various causes of dizziness, and most types of dementia. The neurologic history may often provide the first clues that a symptom is psychological in origin. The following are points to consider in obtaining a neurologic history.

- *Carefully identify the chief complaint or problem.* Not only is the chief complaint important in providing the first clue to the physician about the differential diagnosis, but it is also the reason that the patient is seeking medical advice and treatment. If the chief complaint is not properly identified and addressed, the proper diagnosis may be missed and an inappropriate diagnostic work-up may be undertaken. Establishing a diagnosis that does not incorporate the chief complaint frequently focuses attention on a coincidental process irrelevant to the patient's concerns.
- *Listen carefully to the patient for as long as necessary.* A good rule of thumb is to listen initially for at least 5 minutes without interrupting the patient. The patient often volunteers the most important information at the start of the history. During this time, the examiner can also assess mental status, including speech, language, fund of knowledge, and affect, and observe the patient for facial asymmetry, abnormalities in ocular movements, and an increase or a paucity of spontaneous movements as seen with movement disorders.
- *Steer the patient away from discussions of previous diagnostic test results and the opinions of previous caregivers.* Abnormal results of laboratory studies may be incidental to the patient's primary problem or may simply represent a normal variant.
- *Take a careful medical history, medication history, psychiatric history, family history, and social and occupational history.* Many neurologic illnesses are complications of underlying medical disorders or are due to adverse effects of drugs. For example, parkinsonism is a frequent complication of the use of metoclopramide and most neuroleptic agents. A large number of neurologic disorders are hereditary, and a positive family history may establish the diagnosis in many instances. Occupation plays a major role in various neurologic disorders, such as carpal tunnel syndrome (in machine operators and people who use computer keyboards) and peripheral neuropathy (caused by exposure to lead or other toxins).
- *Interview surrogate historians.* Because patients with dementia or altered mental status are generally unable to provide exact details of the history, a family member may need to provide the key details required to make an accurate diagnosis. This situation is especially common with patients who have dementia and certain right hemispheric lesions with various agnosias (lack of awareness of disease) that may interfere with their ability to provide a cogent history. Surrogate historians also provide missing historical details for patients with episodic loss of consciousness, such as syncope and epilepsy.
- *Summarize the history for the patient.* Summarizing the history is an effective way to ensure that all details were covered sufficiently for a tentative diagnosis to be made. Summarizing also allows the physician to fill in historical gaps that may not have been apparent when the history was initially taken. In addition, the patient or surrogate may correct any historical misinformation at this time.
- *End by asking what the patient thinks is wrong.* This question allows the physician to evaluate the patient's concerns about and insight into the

condition. Some patients have a specific diagnosis in mind that spurs them to seek medical attention. Multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, and brain tumors are diseases that patients often suspect may be the cause of their neurologic symptoms.

Diagnostic Challenges

Two common situations provide special challenges to the diagnostic skills of the physician.

Physical Abuse as a Cause of Neurologic Symptoms

Traumatic injury inflicted by family members or others is usually difficult to detect by the medical history and examination. Physically battered babies, abused children, battered women, and traumatized seniors are often unable or unwilling to complain of this cause or contribution to symptoms. The only method to prevent overlooking of this frequent cause of common problems is systematic consideration of the possibility in every patient and awareness of the often subtle signs that suggest physical trauma: ecchymoses or fractures (often attributed to a logical cause), denial of expected symptoms, failure to keep appointments, and unexplained intensification of neurologic symptoms (headache, dizziness, ringing in the ears, blackouts).

Alcoholism and Drug Abuse

See Chapters 32 and 33. A host of neurologic disorders can be the result of intentional ingestion of toxins (Chapter 110). Patients do not give an accurate account of their use of these agents. Consequently, physical signs and laboratory screening test results that give evidence of drug-related hepatic and other metabolic abnormalities may point to a major underlying problem.

ACUTE NEUROLOGIC DISORDERS REQUIRING IMMEDIATE DIAGNOSIS AND TREATMENT

Most neurologic diagnoses are arrived at by a careful, thorough history and an appropriately complete examination. However, the tempo of illness and the availability of life-saving treatment that is effective only if it is administered within minutes of first evaluating a patient dictate rapid action in several specific circumstances. Coma (Chapter 411), repetitive seizures (Chapter 410), acute stroke (Chapters 414 and 415), suspected meningitis and encephalitis (Chapters 420 and 422), head and spine trauma (Chapter 406), and acute spinal cord compression are diagnosed by clinical and laboratory assessment, and urgent treatment must be instituted as soon as ventilation and cardiac status are stabilized.

NEUROLOGIC EXAMINATION

The neurologic examination is always tailored to the clinical setting of the patient. A complete neurologic examination of a child is much different from that of an elderly adult, and the examination of a patient with specific complaints focuses on findings pertinent to that patient. Thus, more detailed testing of cognition is indicated in patients with behavioral or memory disturbance, and more detailed testing of sensation should be performed in patients with complaints of pain, numbness, or weakness.

However, many tests of neurologic function are routinely indicated in all patients because they provide a baseline for future examination and are frequently helpful in detecting unsuspected neurologic disease in apparently normal persons or in patients whose symptoms initially suggest disease outside the nervous system. It is particularly important to perform all routine tests in patients with abnormalities in one sphere of neurologic dysfunction; otherwise, erroneous localization of a lesion or disease process is likely. For deviations from normal to be recognized and quantitated, it is essential for a physician to have extensive experience in the routine assessment of normal persons.

The General Examination

Specific neurologic symptoms or signs should prompt attention to the assessment of general findings. Head circumference should be measured in patients with central nervous system (CNS) or spinal cord disease (normally 55 ± 5 cm in adults). Head enlargement is occasionally a normal, often hereditary variant but should suggest a long-standing anomaly of the brain or spinal cord. The skin should be inspected for cafe au lait maculae, adenoma sebaceum, vascular malformations, lipomas, neurofibromas, and other lesions (Chapter 426). Neck range of motion, straight leg raising, and spinal curvature (scoliosis) should be assessed. Carotid auscultation for bruits is indicated in all older adults; carotid palpation is seldom informative. In patients with bladder, bowel, or leg symptoms, a rectal sphincter examination for tone and ability to contract voluntarily is usually indicated. Limitation of joint range of motion or painless swelling of joints is often a sign of an unsuspected neurologic lesion.

Neurologic Examination

The various aspects of the detailed neurologic examination are considered in specific symptom and disease sections noted later. The five major divisions of the examination should be assessed in all patients. During a careful medical history, mental status is often adequately assessed: level of consciousness, orientation, memory, language function, affect, and judgment. If any of these functions are abnormal, more detailed testing is needed. Cranial nerve function that should be tested in all patients includes visual acuity (with and without correction); optic fundi; visual fields; pupils (size and reactivity to direct and consensual light); ocular motility; jaw, facial, palatal, neck, and tongue movement; and hearing.

Examination of the motor system (Chapter 429) is essential in all patients because incipient weakness is generally overlooked by the patient. Muscle tone (flaccid, spastic, or rigid), muscle size (atrophy or hypertrophy), and muscle strength can be assessed rapidly. Muscle strength testing should always assess specific functional activities, including the ability to walk on heel and toe, to sit up from a supine position, to rise from a deep knee bend or deep chair, to lift the arms over the head, and to make a tight fist. Gait, stance, and coordination are assessed. The patient should be observed for tremor and other abnormal movements and the muscles inspected for fasciculations.

Sensory testing (Chapter 428) need not be detailed unless there are sensory symptoms. However, vibration perception in the toes and the normality of perception of pain, temperature, and light touch in the hands and feet should be assessed.

Muscle stretch reflexes and plantar responses should always be assessed by evaluating right-left symmetry and disparity between proximal and distal reflexes or arm and leg reflexes. Biceps, triceps, brachioradialis, quadriceps, and ankle reflexes should be quantitated from 1 to 4 (4 = clonus; 3 = spread; 2 = brisk; 1 = hypoactive).

The Comatose Patient

The rapid examination required for a patient with an altered state of consciousness is much different from that of an alert, aware individual (Chapter 411). Many aspects of the neurologic examination cannot be tested: cognitive function, subtleties of sensory perception, specific motor functions, coordination, gait, and stance. Moreover, the muscle stretch reflexes are likely to fluctuate from one moment to the next, and minor asymmetries are much less important than in an awake patient. Instead, attention should focus on examination of the level of consciousness, respiratory pattern, eyelid position and eye movements, pupils, corneal reflexes, optic fundi, and motor responses. Particular elements of the general examination must also be assessed quickly: evidence of cranial and spine trauma, tenderness of the skull to percussion, nuchal rigidity (but not in patients with head or neck trauma), and evidence of physical abuse.

COMMON COMPLAINTS OF POSSIBLE NEUROLOGIC ORIGIN

Weakness

It is axiomatic that patients typically have motor signs before motor symptoms and, conversely, sensory symptoms before sensory signs. Thus, patients with even severe weakness may not report symptoms of weakness. Somewhat paradoxically, patients who complain of "weakness" often do not have confirmatory findings on examination that document the presence of weakness.

Weakness, when it is actually a symptom of neurologic disease, is frequently caused by diseases of the motor unit (Chapters 418, 429, and 430) and is usually reported by a patient in terms of loss of specific functions, for example, difficulty with tasks such as climbing stairs, rising from a chair, sitting up, lifting objects onto a high shelf, or opening jars. Symptoms may also reflect the consequences of weakness, such as frequent falls or tripping. Such symptoms can be remarkably quantitative. A patient with leg muscle weakness who is falling even as infrequently as once a month almost invariably has severe weakness of the knee extensor muscles and can be shown on examination to have a knee extension lag, an inability to lift the leg fully against gravity and to lock the knee.

The symptom of weakness without findings of weakness on examination is not generally the result of neuromuscular disease but can be a sign of neurologic disease outside the motor unit or, more commonly, a symptom of disease outside the nervous system altogether (Table 403-1).

TABLE 403-1 DISORDERS COMMONLY ACCOMPANIED BY WEAKNESS

- Disorders of the motor unit
- Upper motor neuron lesions—spasticity
- Basal ganglia disorders—rigidity
- General medical conditions
  - Heart failure
  - Respiratory insufficiency
  - Renal, hepatic, and other metabolic disease
  - Alcoholism and other toxin-related disease
- Psychiatric and behavioral disorders
  - Depression
  - Malingering

Fatigue

The complaints of "fatigue," "tiredness," and "lack of energy" are even less likely than the symptom of weakness to reflect definable neurologic disease. With the exception of neuromuscular junction disorders such as myasthenia gravis, fatigue is rarely a complaint of diseases of the motor unit. Fatigue can be a sign of upper motor neuron disease (corticospinal pathways) and is a common complaint of established multiple sclerosis and other multifocal CNS disease. Similarly, any process that produces bilateral corticospinal tract or extrapyramidal disease can cause fatigue. Examples include motor neuron disease (Chapter 418), spinal cord disease in the cervical cord region (Chapter 407), and Parkinson's disease (Chapter 416). In addition, disorders that impair sleep (Chapter 412) may include fatigue as a complaint.

Fatigue, like weakness, is much more often than not a sign of disease outside the central and peripheral nervous system. Depression and other psychiatric and behavioral disorders (Chapter 404) as well as the medical illnesses associated with a complaint of weakness are all frequent causes of fatigue.

Chronic fatigue syndrome and many cases of fibromyalgia (Chapter 282) have fatigue as a dominant, disabling symptom. These disorders are defined in part by the absence of consistent neurologic findings and lack of demonstrable disease in the nervous system.

Spontaneous Movements

Muscle tremors, jerks, twitches, cramps, and spasms (Chapter 417) are frequent symptoms. The cause of spontaneous movements can reside at any level of the nervous system. In general, movements that occur in an entire limb or in more than one muscle group concurrently are caused by CNS disease. Movements confined to a single muscle are likely to be a reflection of disease of the motor unit (including the motor neurons of the brain stem and spinal cord). When spontaneous movements of a muscle are associated with severe pain, patients often use the term *cramp.* Cramp is a medically defined disorder that reflects the intense contraction of a large group of motor units. Leg cramps are occasionally a sign of an underlying disease of the anterior horn cell, nerve roots, or peripheral nerve; however, cramps are frequent in normal persons and particularly common in older patients, and they are usually benign. When they are severe, cramps can produce such intense muscle contraction that muscle injury is caused and muscle enzyme (e.g., creatine kinase) levels are elevated in blood.

The rare muscle diseases in which an enzyme deficiency interferes with substrate use as fuel for exercise (e.g., McArdle's disease) are often associated with severe, exercise-provoked muscle *contractures.* These contractures are electrically silent on electromyography, in contrast to the intense motor unit activity seen with cramps. Contractures must not be confused with the limitation of joint range of motion resulting from long-standing joint disease or long-standing weakness—also termed contractures.

The intense muscle contractions of *tetany* are frequently painful. Although tetany is usually a reflection of hypocalcemia (Chapter 253), it can occasionally be seen without demonstrable electrolyte disturbance. Tetany results from hyperexcitability of peripheral nerves. Similarly, in the syndrome of *tetanus* produced by a clostridial toxin (Chapter 304), intensely painful, life-threatening muscle contractions arise from hyperexcitable peripheral nerves. A number of toxic disorders, such as strychnine poisoning and black widow spider envenomation, produce similar neurogenic spasms.

Muscle Pain

Acute muscle pain in the absence of abnormal muscle contractions is an extremely common symptom. When such pain occurs after strenuous exercise or in the context of an acute viral illness (e.g., influenza), it probably reflects muscle injury. In such patients, the serum creatine kinase level is often raised. It is uncommon for this frequent and essentially normal sign of muscle injury to be associated with weakness or demonstrable ongoing muscle disease. *Chronic* muscle pain is a common symptom but is seldom related to a definable disease of muscle.

TABLE 403-2 CHARACTERISTIC GAIT DISORDERS

SPECIFIC DISORDER	LOCATION OF LESION	CHARACTERISTICS
Spastic gait	Bilateral corticospinal pathways within the thoracic or cervical cord or in the brain	Legs stiff, feet turning inward, "scissoring"
Hemiparetic gait	Unilateral central nervous system, cervical cord, or brain	Affected leg circumducted, foot extended, arm flexed
Sensory ataxia	Posterior columns of the spinal cord or peripheral nerve	Wide-based, high steps; Romberg's sign present
Cerebellar ataxia	Brain stem or cerebellum	Wide-based steps; Romberg's sign absent
Parkinsonian gait	Basal ganglia	Shuffling, small steps
Dystonic gait	Basal ganglia; also corticospinal pathways	Abnormal posture of the arms, head, neck
Gait disorder of the elderly	Multifactorial: bihemispheric disease, spinal cord disease, impaired proprioception, muscle weakness	Stooped posture, wide-based steps; often retropulsion
Steppage gait	Distal muscle weakness	High steps ("steppage")
Waddling gait	Proximal muscle weakness	Both legs circumducted to allow locking of the knees
Antalgic gait	Non-neurologic; reflects disease of joints, bones, or soft tissue	Minimizes pain in the hip, spine, leg
Hysterical gait	Psychiatric or behavioral disorder	Reeling side to side, associated astasia-abasia, bizarre arm and trunk movements

Episodic and Intermittent Weakness

The complaint of attacks of severe weakness or paralysis occurring in a patient with baseline normal strength is an uncommon symptom. It is typical of the periodic paralyses and may also be seen with episodic ataxias and myotonic disorders (Chapter 429). All of these disorders are ion channelopathies. These channelopathies (e.g., the calcium channelopathy hypokalemic periodic paralysis) are rare but treatable disorders (Chapter 429). Episodic weakness is also seen in patients with neuromuscular junction disorders, such as myasthenia gravis and the myasthenic syndrome (Chapter 430). On occasion, patients with narcolepsy complain of intermittent paralysis as a reflection of *sleep paralysis* (Chapter 412).

Loss of Balance

Unsteadiness of gait is a common symptom. When it is associated with complaints of dizziness or vertigo (Chapter 436), disease of the labyrinth, the vestibular nerve, the brain stem, or the cerebellum is a probable cause. When unsteadiness and loss of balance are unassociated with dizziness, particularly if the unsteadiness appears to be out of proportion to other symptoms of the patient, a widespread disorder of sensation or motor function is likely.

Abnormal Gait and Posture

The ability to stand and to walk in a well-coordinated, effortless fashion requires the integrity of the entire nervous system. Relatively subtle deficits localized to one part of the central or peripheral nervous system produce characteristic abnormalities (Table 403-2).

Sensory Symptoms

Sensory symptoms can be negative or positive. Negative symptoms represent a loss of sensation, such as a feeling of numbness. Positive symptoms, by contrast, consist of sensory phenomena that occur without normal

stimulation of receptors and include paresthesias and dysesthesias. *Paresthesias* may include a feeling of tingling, crawling, itching, compression, tightness, cold, or heat and are sometimes associated with a feeling of heaviness. The term *dysesthesias* is used correctly to refer to abnormal sensations, often tingling, painful, or uncomfortable, that occur after innocuous stimuli, whereas *allodynia* refers to painful perception from a stimulus that is not normally painful. For some patients, it may be difficult to distinguish paresthesias and dysesthesias from pain. *Hypesthesia* and *hypalgesia* denote a loss or impairment of touch or pain sensibility, respectively. By comparison, *hyperesthesia* and *hyperalgesia* indicate a lowered threshold to tactile or painful stimuli, respectively, such that there is increased sensitivity to such stimuli.

With the use of a wisp of cotton, a pin, and a tuning fork, the trunk and extremities are examined for regions of abnormal or absent sensation. Certain instruments are available for quantifying sensory function, such as the computer-assisted sensory examination, which is based on the detection of touch, pressure, vibratory, and thermal sensation thresholds.

Alterations in pain and tactile sensibility can generally be detected by clinical examination. It is important to localize the distribution of any such sensory loss to distinguish between nerve, root, and central dysfunction. Similarly, abnormalities in proprioception can be detected by clinical examination when patients are unable to detect the direction in which a joint is moved. In severe cases, there may be pseudoathetoid movements of the outstretched hands, sensory ataxia, and sometimes postural and action tremors.

Disorders of peripheral nerves commonly lead to sensory disturbances that depend on the population of affected nerve fibers (Chapter 428). Some neuropathies are predominantly large-fiber neuropathies. Appreciation of movement and position is impaired, and paresthesias are common. Examination reveals that vibration, position, and movement sensations are impaired, and movement becomes clumsy and ataxic. Pain and temperature appreciation is relatively preserved. The tendon reflexes are lost early. In other neuropathies, it is the small fibers especially that are affected; spontaneous pain is common and may be burning, lancinating, or aching in quality. Pain and temperature appreciation is disproportionately affected in these neuropathies, and autonomic dysfunction may be present. Examples of small-fiber neuropathies include certain hereditary disorders, Tangier disease, and diabetes. Most sensory neuropathies are characterized by a distal distribution of sensory loss, whereas sensory neuronopathies are characterized by sensory loss that may also involve the trunk and face and tends to be particularly severe. Sensory changes in a radiculopathy conform to a root territory; in cauda equina syndromes, sensory deficits involve multiple roots and may lead to saddle anesthesia and loss of the normal sensation associated with the passage of urine or feces.

Lesions of the *posterolateral columns* of the cord, such as occur in multiple sclerosis (Chapter 419), vitamin B_{12} deficiency (Chapter 425), and cervical spondylosis (Chapter 407), often lead to a feeling of compression in the affected region and to a Lhermitte sign (paresthesias radiating down the back and legs on neck flexion). Examination reveals ipsilateral impairment of vibration and joint position senses, with preservation of pain and temperature appreciation. Conversely, lesions of the *anterolateral region* of the cord (as by cordotomy) or *central* lesions interrupting fibers crossing to join the spinothalamic pathways (as in syringomyelia; Chapter 426) lead to impairment in pain and temperature appreciation with relative preservation of vibration, joint position sense, and light touch. Motor deficits may also be present and help localize the lesion. Upper motor neuron dysfunction (Chapter 407) from cervical lesions leads to quadriplegia, whereas more caudal lesions lead to paraplegia; lesions below the level of the first lumbar vertebra may simply compress the cauda equina and result in lower motor neuron deficits from a polyradiculopathy as well as impairment of sphincter and sexual function.

NEUROLOGIC DIAGNOSTIC PROCEDURES

Lumbar Puncture

Sampling of cerebrospinal fluid (CSF) by lumbar puncture is crucial for accurate diagnosis of meningeal infections and carcinomatosis (Fig. 403-1). CSF analysis is also helpful in evaluating patients with central or peripheral nervous system demyelinating disorders and with intracranial hemorrhage, particularly when imaging studies are inconclusive.

The CSF formula often provides an important clue to the pathologic process involved (Table 403-3). An elevated white blood cell count is seen with infections and other inflammatory diseases as well as with carcinomatosis. The differential white blood cell count may point to a specific class of pathogen; polymorphonuclear leukocytes suggest a bacterial process, whereas mononuclear cells suggest a viral, fungal, or immunologic cause. The CSF glucose concentration is typically reduced in bacterial and fungal infections as well as with certain viral infections (e.g., mumps virus) and with sarcoidosis. The CSF protein concentration is elevated in a variety of disorders, including most infections and demyelinating neuropathies.

Specialized tests that can be performed on CSF include oligoclonal bands, a pathologic pattern of bands on CSF electrophoresis that is seen in up to 90% of patients with multiple sclerosis. The bands, which represent monoclonal immunoglobulins that are locally synthesized in the CNS, are not specific for multiple sclerosis and may be seen with other inflammatory and noninflammatory conditions, including systemic lupus erythematosus, human immunodeficiency virus infection, and stroke.

CSF polymerase chain reaction is a rapid, sensitive, and specific test for the diagnosis of herpes simplex encephalitis (Chapter 422), for which it has replaced brain biopsy as the diagnostic procedure of choice. The CSF VDRL (Venereal Disease Research Laboratory) assay is a specific although insensitive test for neurosyphilis (Chapter 327).

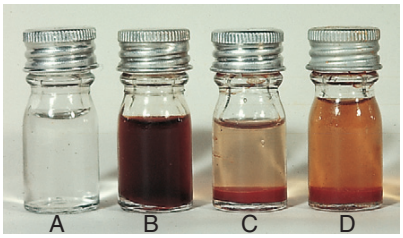


FIGURE 403-1. Cerebrospinal fluid examination. A, Normal crystal-clear CSF. **B**, Blood in the CSF, which could result from a traumatic (bloody) tap or from subarachnoid hemorrhage. In a traumatic tap, subsequent tubes of CSF are usually less bloody. **C**, Centrifuged CSF in a traumatic tap. The supernatant is nearly clear. **D**, CSF from a patient with subarachnoid hemorrhage. There is blood at the bottom of the tube and the supernatant is yellow (xanthochromic) as a result of breakdown of blood cells in the CSF before the lumbar puncture. (From Forbes CD, Jackson WD. *Color Atlas and Text of Clinical Medicine,* 3rd ed. London: Mosby; 2003, with permission.)

TABLE 403-3 CHARACTERISTIC CEREBROSPINAL FLUID FORMULAS

	TURBIDITY AND COLOR	OPENING PRESSURE	WBC COUNT	DIFFERENTIAL CELLS	RBC COUNT	PROTEIN	GLUCOSE
Normal	Clear, colorless	70-180 mm H_2O	0-5 cells/μL^3	Mononuclear	0	<60 mg/dL	> ⅔ serum
Bacterial meningitis	Cloudy, straw colored	↑	↑↑	PMNs	0	↑↑	↓
Viral meningitis	Clear or cloudy, colorless	↑	↑	Lymphocytes	0	↑	Normal
Fungal and tuberculous meningitis	Cloudy, straw colored	↑	↑	Lymphocytes	0	↑↑	↓↓
Viral encephalitis	Clear or cloudy, straw colored	Normal to ↑	↑	Lymphocytes	0 (herpes ↑)	Normal to ↑	Normal
Subarachnoid hemorrhage	Cloudy, pink	↑	↑	PMNs and lymphocytes	↑↑	↑	Normal (early); ↓ (late)
Guillain-Barré syndrome	Clear, yellow	Normal to ↑	0-5 cells/μL^3	Mononuclear	0	↑	Normal

PMN = polymorphonuclear leukocyte; RBC = red blood cell; WBC = white blood cell.

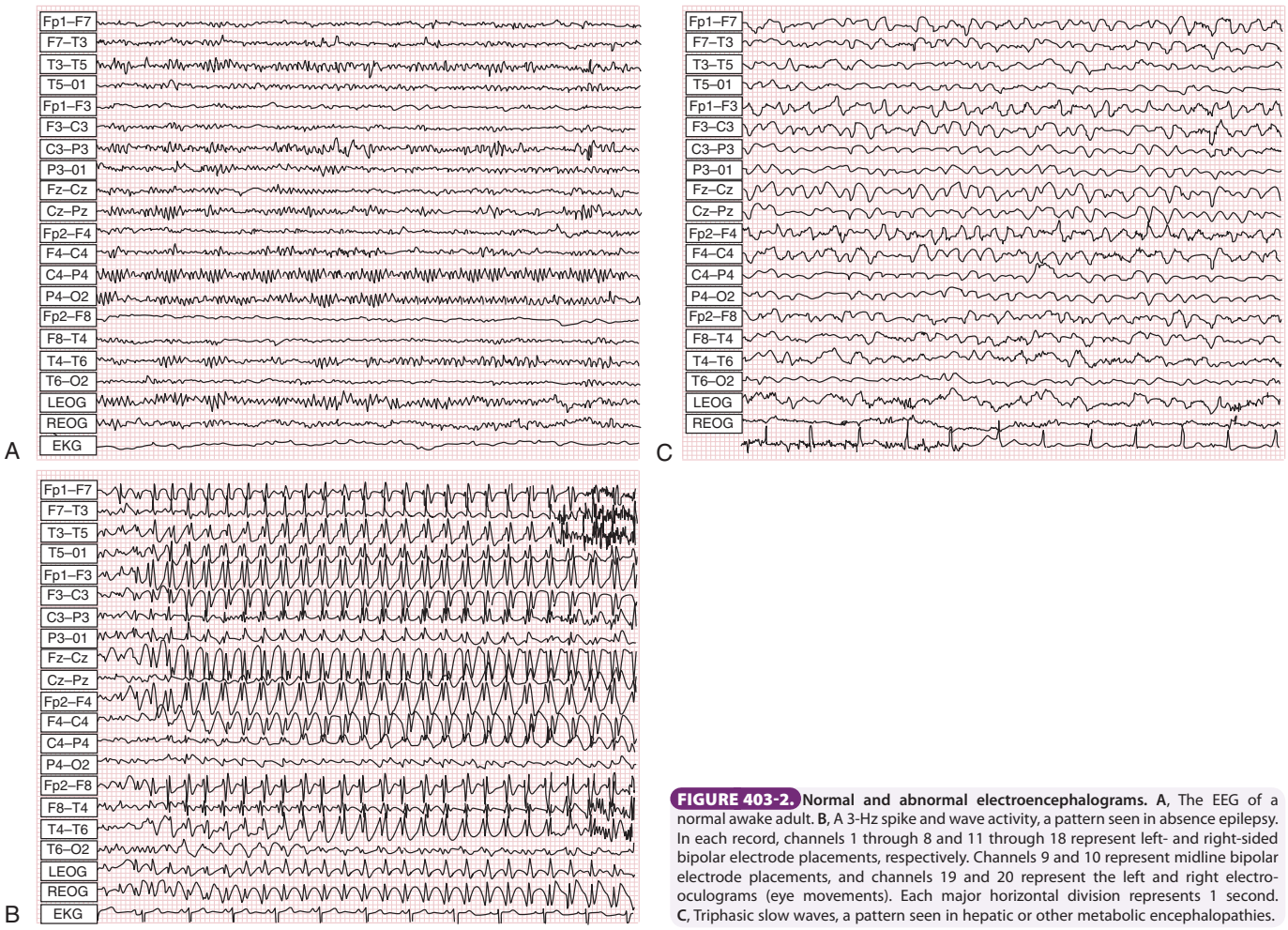


FIGURE 403-2. Normal and abnormal electroencephalograms. A, The EEG of a normal awake adult. **B**, A 3-Hz spike and wave activity, a pattern seen in absence epilepsy. In each record, channels 1 through 8 and 11 through 18 represent left- and right-sided bipolar electrode placements, respectively. Channels 9 and 10 represent midline bipolar electrode placements, and channels 19 and 20 represent the left and right electro-oculograms (eye movements). Each major horizontal division represents 1 second. **C**, Triphasic slow waves, a pattern seen in hepatic or other metabolic encephalopathies.

A lumbar puncture should not be performed in patients who have an obstructive, noncommunicating hydrocephalus or a focal CNS mass lesion causing raised intracranial pressure because reducing CSF pressure acutely in these settings by lumbar puncture may result in cerebral or cerebellar herniation. Lumbar puncture may be safely performed in patients with a *communicating* hydrocephalus, such as with idiopathic intracranial hypertension (pseudotumor cerebri), and it may even be an effective treatment in selected patients with this condition.

Electroencephalography

Electroencephalography is the recording and measurement of scalp electrical potentials to evaluate baseline brain functioning and paroxysmal brain electrical activity suggestive of a seizure disorder.

Electroencephalography is performed by securing 20 electrodes to the scalp at predetermined locations based on an international system that uses standardized percentages of the head circumference, the "10-20 system." Each electrode is labeled with a letter and a number, the letter identifying the skull region (Fp = frontopolar; F = frontal; P = parietal; C = central; T = temporal; O = occipital) and the number identifying the specific location, with odd numbers representing left-sided electrodes and even numbers right-sided electrodes. These electrodes are then connected in various combinations of pairs to generate voltage potential differences, and the potentials are recorded on a chart recorder.

To delineate the spatial distribution of the changing electrical field for an electroencephalogram (EEG), an orderly arrangement of electrode pairs is used, and each specific arrangement is known as a montage. Montages are generally of two types: *referential,* in which each electrode is connected to a single reference electrode, such as the ear; and *bipolar,* in which electrodes are connected sequentially to one another to form a chain. A standard EEG generally records about 30 minutes of brain activity, both in the awake state and in the first two stages of sleep. Various activating procedures are used during the recording of an EEG, including hyperventilation and photic stimulation. These activating procedures may precipitate seizure discharges in some patients with seizure disorders, thereby increasing the sensitivity of the test.

The amplitudes of scalp electrical potentials are quite low, averaging 30 to 100 μV. They represent a summation of excitatory postsynaptic potentials and inhibitory postsynaptic potentials that are largely generated by the pyramidal cells in layer 4 of the cerebral cortex. Action potentials are of too brief a duration to have an effect on the EEG.

The EEG is analyzed with respect to symmetry between each hemisphere; wave frequency and amplitude; and the presence of spikes (20 to 70 msec) and sharp waves (70 to 200 msec), which may indicate a seizure focus. Electroencephalographic frequencies are divided into four categories as follows: delta: <4 Hz; theta: 4-7 Hz; alpha: 8-13 Hz; beta: >13 Hz.

The normal waking EEG (Fig. 403-2A) in a patient with eyes closed contains rhythms of alpha frequency in the occipital leads and beta frequency in the frontal leads. Normal sleep causes a generalized slowing of electroencephalographic frequencies and an increase in amplitude in each stage of sleep such that stage 4 sleep consists of more than 50% large-amplitude delta rhythms. Electroencephalographic abnormalities are of two types: abnormalities in background rhythm and abnormalities of a paroxysmal nature (Table 403-4).

The major usefulness of electroencephalography is for diagnosis and categorization of a seizure disorder (Fig. 403-2B). EEGs are neither highly sensitive nor completely specific for diagnosis of seizures. Because seizures are paroxysmal events, it is not unusual for an EEG to be normal—or only minimally abnormal—in a patient with epilepsy if it is recorded during an interictal phase (the period between seizures). Only about 50% of patients with seizures show epileptiform activity on the first EEG. Repeating the EEG with provocative maneuvers, such as sleep deprivation, hyperventilation, and photic stimulation, may increase this percentage to 90%. Conversely, about

TABLE 403-4 ELECTROENCEPHALOGRAPHIC ABNORMALITIES

ELECTROENCEPHALOGRAPHIC ABNORMALITY	CLINICAL CORRELATE
BACKGROUND RHYTHM ABNORMALITIES	
Generalized slowing	Most metabolic encephalopathies
Triphasic waves	Hepatic, renal, and other metabolic encephalopathies
Focal slowing	Large mass lesions (tumor, large stroke)
Electrocerebral inactivity with lack of response to all stimuli	Brain death
PAROXYSMAL ABNORMALITIES	
3-Hz spike and wave, augmented by hyperventilation	Absence epilepsy
3- to 4-Hz spike and wave in light sleep or with photic stimulation	Primary generalized epilepsy
Central to midtemporal spikes	Benign rolandic epilepsy, other partial epilepsies
Anterior temporal spikes or sharp waves	Simple or complex partial seizures of mesial temporal origin
Hypsarrhythmia (high-voltage chaotic slowing with multifocal spikes)	Infantile spasms (West's syndrome)
Burst suppression	Severe anoxic brain injury, barbiturate coma

1% of adults and 3.5% of children who are neurologically normal and who never had a seizure have epileptiform activity on an EEG.

The EEG may provide clues to the diagnosis of certain neurologic conditions, including viral encephalitis, prion disorders, and some forms of coma. In each of these situations, the EEG can have specific patterns that suggest a specific neurologic diagnosis. In herpes simplex encephalitis, periodic lateralizing epileptiform discharges emanating from the temporal lobes are frequently present. Triphasic slow waves are common in hepatic encephalopathy (Fig. 403-2C) but are a nonspecific finding. Creutzfeldt-Jakob disease is characterized by the presence of bilateral synchronous repetitive sharp waves. The EEG is also helpful in evaluating comatose patients, in confirming brain death when an apnea test cannot be performed because of cardiac instability, and for staging sleep in polysomnography.

In the past, the EEG was often used to localize neurologic lesions such as stroke, brain tumor, and abscess. With the advent of neuroimaging, EEG is almost never used for these purposes.

Nerve Conduction Study

A nerve conduction study (NCS) is the recording and measurement of the compound nerve and muscle action potentials elicited in response to an electrical stimulus.

To perform a motor NCS, a surface (active) recording electrode is placed over the belly of a distal muscle that is innervated by the nerve in question. A reference electrode is placed distally over the tendon. The nerve is then supramaximally stimulated at a predetermined distance proximal to the active electrode, and the resultant compound motor action potential (CMAP) is recorded. The terminal latency, amplitude, and duration of the evoked potential are measured directly, and the conduction velocity is calculated from the latencies of the evoked potentials with stimulation at two different points; the distance between the two points (conduction distance) is divided by the difference between the corresponding latencies (conduction time) to derive a calculated velocity (conduction velocity = distance ÷ time).

To perform a sensory NCS, the active recording electrode is placed over the portion of the skin innervated by the nerve in question, and a sensory nerve action potential is recorded after electrical stimulation of the nerve, similar to that noted for a motor NCS. NCS abnormalities include reduced amplitudes, prolonged terminal latencies, conduction block, and slowed conduction velocities (Table 403-5).

The NCS is helpful in documenting the existence of a neuropathy, quantifying its severity, and noting its distribution (i.e., whether it is distal, proximal, or diffuse). In addition, the NCS can provide information on the modality involved (i.e., motor versus sensory) and can suggest whether the lesion is axonal or demyelinating. The NCS is also helpful in diagnosis of compressive mononeuropathies, such as carpal tunnel syndrome, ulnar palsy, peroneal nerve palsy, and tarsal tunnel syndrome.

TABLE 403-5 NERVE CONDUCTION STUDY ABNORMALITIES

ABNORMALITY	CLINICAL CORRELATE
Reduced CMAP amplitude	Axonal neuropathy
Prolonged terminal latency	Demyelinating neuropathy Distal compressive neuropathy
Conduction block	Severe focal compressive neuropathy Severe demyelinating neuropathy
Slowed conduction velocity	Demyelinating neuropathy

CMAP = compound muscle action potential.

F Wave and H Reflex

The F wave and H reflex are ways of looking at the conduction characteristics for proximal portions of nerves, including the nerve roots. The F wave is a late CMAP evoked intermittently from a muscle by a *supramaximal* electrical stimulus to the nerve, and it is due to antidromic activation (backfiring) of alpha motor neurons. F waves can be elicited from practically all distal motor nerves. The H reflex is a late CMAP that is evoked regularly from a muscle by a *submaximal* stimulus to a nerve, and it is due to stimulation of Ia afferent fibers (a spinal reflex). The H reflex can be routinely obtained from calf muscles only with stimulation of the tibial nerve in the popliteal fossa.

F waves are helpful in diagnosis of Guillain-Barré syndrome, in which demyelination is often confined to the proximal portions of nerves early in the course of the disease. The H reflex is often absent in patients with acute S1 radiculopathy.

Repetitive Stimulation Study

A repetitive stimulation study is a method of measuring electrical conduction properties at the neuromuscular junction. To perform a repetitive stimulation study, a surface recording electrode is placed over a muscle belly, and the nerve innervating that muscle is electrically stimulated with a supramaximal stimulus at a certain frequency. A series of electrical potentials are then recorded whose amplitude is roughly proportional to the number of muscle fibers that are being activated.

A repetitive stimulation study is helpful in diagnosis of neuromuscular junction disorders, such as myasthenia gravis and myasthenic syndrome (Lambert-Eaton syndrome). In myasthenia gravis, the amplitudes of evoked potentials become progressively smaller with repetitive stimulation in clinically involved muscles. Clinically uninvolved muscles often do not demonstrate this decrement. In myasthenic syndrome, an *increment* is seen in the amplitudes of evoked potentials with rapid repetitive electrical stimulation.

Electromyography

Electromyography (EMG) is the recording and study of insertional, spontaneous, and voluntary electrical activity of muscle. It allows physiologic evaluation of the motor unit, including the anterior horn cell, peripheral nerve, and muscle.

EMG is performed by insertion of a needle electrode into the muscle in question and evaluation of the motor unit action potentials both visually (on the oscilloscope screen) and aurally (over the loudspeaker). Muscles are typically studied at rest and during voluntary contraction. During EMG, the electrical activity of muscle is studied in four settings (Table 403-6): *insertional activity* (occurring within the first second of needle insertion), *spontaneous activity* (electrical activity at rest), *voluntary activity* (electrical activity with muscle contraction), and *recruitment pattern* (change in electrical activity with maximal contraction).

EMG is helpful in evaluation of patients with weakness in that it can help determine whether the weakness is due to anterior horn cell disease, nerve root disease, peripheral neuropathy, or an intrinsic disease of muscle itself (myopathy). EMG can differentiate acute denervation from chronic denervation and may thus give an indication about the time course of the lesion causing the neuropathy. In addition, on the basis of which muscles have an abnormal EMG pattern, it is possible to determine whether the neuropathy is due to a lesion of a nerve root (radiculopathy), the brachial or lumbosacral plexus (plexopathy), an individual peripheral nerve (mononeuropathy), or multiple peripheral nerves (polyneuropathy).

EMG is also helpful in differentiation of active (inflammatory) myopathies from chronic myopathies. Active myopathies include dermatomyositis, polymyositis, inclusion body myositis, and some forms of muscular dystrophy, such as Duchenne's dystrophy. Chronic myopathies include the other muscular dystrophies, the congenital myopathies, and some metabolic myopathies. Myotonic dystrophy and myotonia congenita produce characteristic myotonic discharges.

It may take several weeks for a muscle to develop EMG signs of acute denervation after nerve transection. For this reason, EMG performed in the acute setting after nerve injury should be interpreted with caution, and it may need to be repeated at a later date.

Evoked Potentials

Evoked potentials are ways of measuring conduction velocities for sensory pathways in the CNS by means of computerized averaging techniques. Three types of evoked potentials are routinely performed: visual, brain stem auditory, and somatosensory.

Pattern Reversal Visual Evoked Responses

The pattern reversal visual evoked response (PVER) assesses the function of central visual pathways, in particular the optic nerves. To perform this test, EEG electrodes are placed over the occipital regions of the scalp, and the patient is asked to look at the center of a black-and-white checkerboard screen with one eye patched. The color of the checks alternates about twice per second, a process known as pattern reversal. The scalp potentials elicited by approximately 100 such pattern reversals are then recorded and signal averaged by a computer. This signal averaging cancels the random EEG activity and differentially amplifies the evoked potential. A single waveform (P 100) is recorded for each eye, and its latency is measured. Normal latency for the P 100 waveform is approximately 100 msec. A prolonged P 100 latency in one eye, in the absence of ocular disease, implies slowed conduction velocity in the optic nerve and suggests demyelination of that nerve. PVER testing is helpful when multiple sclerosis is suspected clinically and it is necessary to document the presence of a second demyelinating lesion in the CNS that may not be clinically evident (Fig. 403-3).

TABLE 403-6 ELECTROMYOGRAPHIC ABNORMALITIES

ABNORMALITY	CLINICAL CORRELATE
INSERTIONAL ACTIVITY	
Prolonged	Acute denervation Active (usually inflammatory) myopathy
SPONTANEOUS ACTIVITY	
Fibrillations and positive waves	Acute denervation Active (usually inflammatory) myopathy
Fasciculations	Chronic neuropathies Motor neuron disease (rare fasciculations may be normal)
Myotonic discharges	Myotonic disorders Acid maltase deficiency
VOLUNTARY ACTIVITY	
Neuropathic potentials: large-amplitude, long-duration, polyphasic potentials	Chronic neuropathies and anterior horn cell diseases
Myopathic potentials: small-amplitude, short-duration, polyphasic potentials	Chronic myopathies Neuromuscular junction disorders
RECRUITMENT	
Reduced	Chronic neuropathic disorders
Rapid	Chronic myopathies

Brain Stem Auditory Evoked Responses

The brain stem auditory evoked response (BAER) assesses function in the central auditory pathways in the brain stem. EEG electrodes are placed over the vertex and mastoid process, and a series of clicks at a frequency of 5 Hz are delivered to each ear separately for 3 minutes. The scalp potentials elicited by the clicks are then recorded and signal averaged by a computer. This signal averaging cancels the random EEG activity and differentially amplifies the evoked potential. A series of five waves are recorded for each ear, and each wave corresponds to a different point in the central auditory pathway (Table 403-7). The wave latencies for the right and left ears are compared, and a delay in any of the latencies suggests a lesion at that point in the central brain stem auditory pathway. BAER testing is helpful in diagnosis of acoustic schwannoma and other tumors in the cerebellopontine angle.

Somatosensory Evoked Responses

The somatosensory evoked response (SER) assesses conduction in the central somatosensory pathways in the posterior columns of the spinal cord, brain stem, thalamus, and primary sensory cortex in the parietal lobes. To perform SER testing, recording electrodes are placed over Erb's point and the

TABLE 403-7 BRAIN STEM EVOKED RESPONSE WAVE GENERATORS

WAVE	LOCATION
I	Auditory nerve
II	Cochlear nucleus
III	Superior olivary nucleus
IV	Lateral lemniscus
V	Inferior colliculus

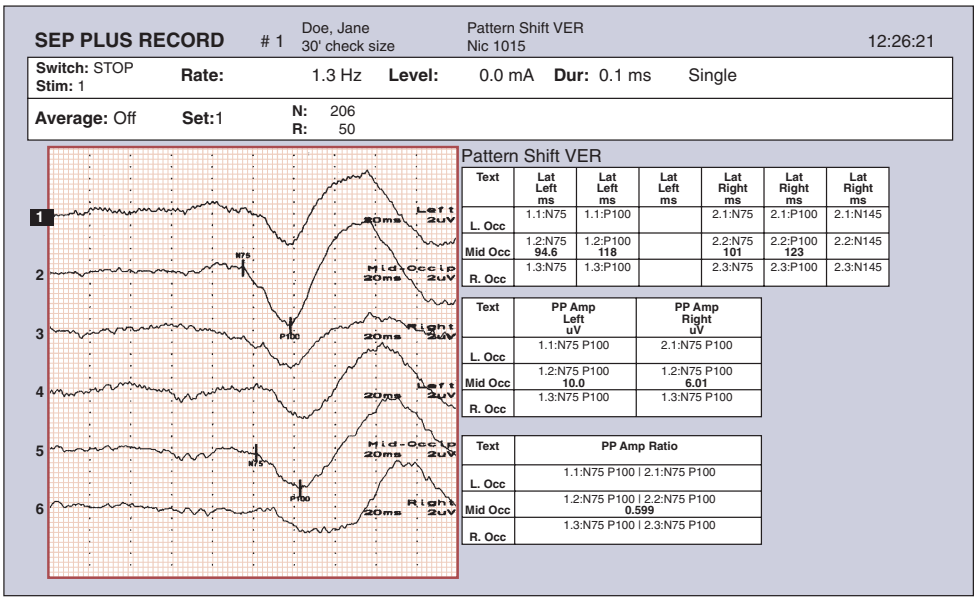


FIGURE 403-3. Abnormal pattern reversal visual evoked response in a patient with multiple sclerosis. The prolonged P 100 wave latency with left eye stimulation suggests a conduction defect in the left optic nerve. The top three channels represent right eye stimulation, and the bottom three channels represent left eye stimulation. Each horizontal division represents 20 msec.

TABLE 403-8 STRENGTHS AND WEAKNESSES OF SELECTED IMAGING MODALITIES

MODALITY	STRENGTHS	WEAKNESSES
Computed tomography (CT)	Fast; best test for acute intraparenchymal or subarachnoid hemorrhage and calcification; easy to monitor patients; excellent for bones	Less sensitive to parenchymal lesions than MRI; potential for significant reaction to contrast material; radiation exposure
Conventional angiography	Best imaging modality for aneurysms, vascular malformations, and vasculitis	Invasive and often lengthy; risk of stroke and other complications
Conventional myelography	Good images of nerve roots and small osteophytic lesions; accurate for bony stenosis; useful in patients with contraindications to MRI	Invasive, with risk of complications from lumbar puncture and instillation of contrast material; does not image intramedullary lesions well
CT myelography	Excellent for imaging nerve roots and detecting root compression from degenerative processes	Invasive, with risk of complications from lumbar puncture and instillation of contrast material
Magnetic resonance imaging (MRI)	Noninvasive; no radiation; multiplanar; extremely sensitive, safe contrast agent	Less sensitive than CT for detection of subarachnoid hemorrhage and calcification; less sensitive for bony skull fractures; contraindicated in patients with implanted metallic devices or foreign bodies; the patient must be able to cooperate and tolerate confined space; time-consuming relative to CT
Magnetic resonance angiography (MRA)	Noninvasive; good for screening for extracranial and intracranial vascular disease; may be performed with or without contrast agent	Need cooperative patient; technically demanding; may overestimate the degree of vascular stenosis (noncontrast MRA); cannot image distal vessels optimally without contrast agent; may miss small lesions (e.g., aneurysms)
Positron emission tomography (PET)	Limited role in helping to distinguish radiation necrosis from tumor; sometimes helpful in the diagnosis of Alzheimer's disease and epilepsy	Requires a cyclotron to generate radioisotopes with a short half-life; lower resolution and less available than MRI or CT
Single-photon emission computed tomography (SPECT)	Occasionally useful in epilepsy; sensitive for diffuse pathologic processes; easier to use than PET	Lower resolution than PET, MRI, or CT
Proton magnetic resonance spectroscopy	Localization of seizure focus; may help diagnose and classify dementias, such as Alzheimer's disease; may distinguish brain tumors from other mass lesions; may distinguish radiation necrosis from recurrent tumor	Specificity not yet determined; not routinely available; lower resolution; time-consuming
Ultrasonography	Fast; easy to use; can be performed at the bedside to assess vessel patency	Does not assess the vertebral arteries; less sensitive and specific than MRA; cannot visualize vessels in the upper neck and cranial base
Transcranial Doppler (TCD)	Fast; easy to use; assesses vascular velocities quantitatively; can assess cerebral vasospasm and occluded vessels	Does not provide images of vessels

Reproduced and modified from Hackney D. Radiologic imaging procedures. In: Goldman L, Ausiello D, eds. *Cecil Medicine,* 23rd ed. Philadelphia: Saunders Elsevier; 2008:2623-2627.

cervical spine (for medial or ulnar nerve stimulation), over the popliteal fossa and lumbar spine (for peroneal or tibial nerve stimulation), and over the scalp. A series of 1000 to 2000 electrical shocks at a frequency of 5 Hz are delivered to the median or ulnar nerve (for an upper extremity SER) or to the peroneal or tibial nerve (for a lower extremity SER). The scalp potentials elicited by the electrical shocks are then recorded and signal averaged by a computer. This signal averaging cancels the random EEG activity and differentially amplifies the evoked potential. A series of waves are recorded for each nerve stimulated, with each wave corresponding to a different point in the somatosensory pathways in the spinal cord, brain stem, and cerebral cortex. The wave latencies for the right and left limbs are compared, and a delay in any of the latencies suggests a lesion at that point in the somatosensory pathways.

SER testing, like PVER, is helpful when multiple sclerosis is suspected clinically and it is necessary to document the presence of a second demyelinating lesion in the CNS that may not be clinically evident. SER testing is also useful for monitoring of spinal cord function intraoperatively in patients undergoing spinal surgery.

Electronystagmography

Electronystagmography accurately records eye movements and nystagmus after certain provocative maneuvers. To perform this test, disc electrodes are placed over the bridge of the nose and lateral to each outer canthus, and the electrical leads from these discs are connected to an oscilloscope. Because the cornea is electropositive and the retina is electronegative, these electrodes accurately record lateral eye movements. The patient is first observed for spontaneous nystagmus with the eyes open and closed and then for nystagmus evoked with lateral gaze, for nystagmus induced by hot and cold air instilled in the outer ears (caloric induced), and for positional nystagmus. The last is performed by rotating the patient in a specialized chair. Spontaneous nystagmus suggests a vestibular pathologic lesion, as does an imbalance in the nystagmus evoked by these maneuvers in the right and left ears.

Imaging

On the basis of the relative advantages and disadvantages of computed tomography (CT), magnetic resonance imaging (MRI), and other neuroimaging modalities, different clinical entities can and should be assessed differently (Table 403-8). In acute ischemic stroke (Chapter 414) without bleeding, CT abnormalities typically appear within 4 to 12 hours and are seen even earlier with larger infarctions and embolic infarctions. CT detects hemorrhagic stroke (Chapter 415) acutely and can estimate its age. CT is also the preferred initial imaging modality for detection of intraparenchymal hemorrhage and subarachnoid hemorrhage, and it often suggests whether an aneurysm is the likely cause. Either CT angiography or magnetic resonance arteriography can display the three-dimensional anatomy of aneurysms with sufficient detail for therapy to be planned, but surgical treatment generally requires pre-procedure catheter arteriography. CT is the first-line method for evaluation of brain trauma and diagnosis of a subdural or epidural hematoma (Chapter 406), usually without requiring intravenous contrast material. However, MRI is better than CT to delineate the anatomy of a subdural hematoma and to estimate the age of the lesion. Many brain tumors are initially recognized on CT scans, but MRI is the preferred modality for detection and characterization of all brain tumors (Chapter 195).

SUGGESTED READINGS

De Luigi AJ, Fitzpatrick KF. Physical examination in radiculopathy. *Phys Med Rehabil Clin N Am.* 2011;22:7-40. *Review.*

Loder E, Cardona L. Evaluation for secondary causes of headache: the role of blood and urine testing. *Headache.* 2011;51:338-345. *Review.*

404 PSYCHIATRIC DISORDERS IN MEDICAL PRACTICE

JEFFREY M. LYNESS

OVERVIEW

Disorders in Psychiatry

Psychiatric disorders, also known as mental illnesses, are extraordinarily common and have a profound impact on well-being and functional status. Collectively, psychiatric disorders account for more aggregate disability than do those involving any other organ system, with depression alone being second only to cardiovascular disorders.

Psychiatric disorders are defined as *disorders of the psyche*, that is, as conditions that affect *thoughts*, *feelings*, or *behaviors*. By definition, such mental disturbances must be sufficient to produce significant *distress* in the patient or *impairment in role or other functioning*. Because the causes and pathogenesis of most psychiatric disorders are incompletely understood, current classification is based on clinical syndromes, which are defined by diagnostic criteria that have high inter-rater reliability because they emphasize discrete reportable or observable symptoms and signs.

TABLE 404-1 IMPORTANT CAUSES OF PSYCHIATRIC SYNDROMES

CENTRAL NERVOUS SYSTEM DISEASES
Trauma
Tumor
Toxins
Seizures
Vascular
Infections
Genetic/congenital malformations
Demyelinating diseases
Neurodegenerative diseases
Hydrocephalus
SYSTEMIC DISEASES
Cardiovascular
Pulmonary
Endocrine
Metabolic
Nutritional
Infections
Cancer
DRUGS (e.g., recreational, prescription, or over-the-counter drugs)
Drug intoxication
Drug withdrawal

Specific Syndromes

Because many *psychiatric disorders* result from the direct influence of neurologic conditions, systemic diseases, or drugs on brain functioning, assessment of any new or worsened psychiatric condition must include evaluation for their potential contributions (Table 404-1). Delirium (Chapter 27) and dementia (Chapter 409), which are *cognitive disorders* that are always the result of one or more neurologic, systemic, or drug causes, are defined by impairment in intellectual functions such as attention, memory, or language. Although cognitive impairment is the hallmark of cognitive disorders, these conditions may also be manifested as alterations in other aspects of mental status, including mood, thought content, thought process, and behavior. If a noncognitive psychiatric syndrome is caused by an identifiable underlying condition, it is known as a *secondary psychiatric disorder* (e.g., depression secondary to hypothyroidism).

The major nonsecondary, noncognitive psychiatric syndromes (Table 404-2) can coexist with multiple syndromes; for example, a patient with severe depression may have depressive, anxiety, and psychotic syndromes simultaneously. Substance use disorders, also known as addictions, are considered in Chapters 32 and 33.

Comorbid Conditions in Psychiatry

It is common for persons who suffer from mental disorders to meet the diagnostic criteria for more than one condition. Although such comorbidity may reflect the limitations of current approaches to diagnosis, psychiatric comorbidity influences the choices or sequence of indicated treatments and may worsen the overall prognosis. Comorbidity with general medical conditions, probably reflecting complex bidirectional causal relationships between physical and mental illnesses, is also common, and such comorbidity often worsens the overall prognosis for both conditions.

Treatments in Psychiatry

Treatments in psychiatry are intended to reduce or eliminate symptoms, thereby improving the patient's distress and dysfunction and averting suicidal behavior. Pharmacotherapy remains an evidence-based mainstay of the treatment of many psychiatric conditions despite the previously underestimated side effects of some drugs. The evidence for a number of forms of psychotherapy, administered in individual, group, or family contexts, supports its use as primary treatment or as co-treatment of many conditions. Other psychosocial interventions, ranging from self-help groups to the use of structured treatment or residential programs, are often important adjuncts to treatment.

TABLE 404-2 IMPORTANT PSYCHIATRIC SYNDROMES AND DISORDERS

SYNDROME	MAIN SYMPTOMS AND SIGNS	MAY OCCUR AS PART OF THESE DISORDERS
Cognitive	Deficits in intellectual functions, e.g., level of consciousness, orientation, attention, memory, language, praxis, visuospatial, executive functions	Cognitive disorders Mental retardation (if onset in childhood)
Mood	Depressive: lowered mood, anhedonia, negativistic thoughts, neurovegetative symptoms *or* Manic: elevated or irritable mood, grandiosity, goal-directed hyperactivity with increased energy, pressured speech, decreased sleep need	Cognitive disorders Mood disorders (primary or secondary) Psychotic disorders (schizoaffective disorder)
Anxiety	All include anxious mood and associated physiologic symptoms (e.g., palpitations, tremors, diaphoresis). May include various types of dysfunctional thoughts (e.g., catastrophic fears, obsessions, flashbacks) and behavior (e.g., compulsions, avoidance behavior)	Cognitive disorders Mood disorders (primary or secondary) Psychotic disorders (primary or secondary) Anxiety disorders (primary or secondary)
Psychotic	Impairments in reality testing: delusions, hallucinations, thought process derailments	Cognitive disorders Mood disorders (primary or secondary) Psychotic disorders
Somatoform	Somatoform symptoms: physical symptoms resulting from unconscious psychogenic causes	Mood disorders (primary or secondary) Anxiety disorders (primary or secondary) Somatoform disorders
Personality pathology	Enduring patterns of dysfunctional emotional regulation, thought patterns, interpersonal behavior, impulse regulation	Cognitive disorders (dementia) Change in personality because of general medical condition Personality disorders

Based on categories and criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Association; 2000.

Nonpharmacologic evidence-based therapies include electroconvulsive therapy or light therapy for particular forms of major depression, and encouraging data are emerging to support deep brain stimulation for severe depressive or obsessive-compulsive disorders.

Mood Disorders

Mood disorders are categorized as either *unipolar*, characterized by depressive episodes only, or *bipolar*, characterized by manic or hypomanic episodes but typically also including depressive episodes.

MAJOR DEPRESSIVE DISORDER

DEFINITION

Major depressive disorder is characterized by one or more episodes of idiopathic major depressive syndrome (Table 404-3).

TABLE 404-3 SYMPTOMS/SIGNS OF AN EPISODE OF MAJOR DEPRESSIVE SYNDROME

DIAGNOSTIC CRITERIA (*EACH MUST BE PRESENT PROMINENTLY, MOST OF THE DAY AND NEARLY EVERY DAY FOR A MINIMUM OF 2 CONSECUTIVE WEEKS*)
Depressed mood (may be irritable mood in children and adolescents) *or* Diminished interest or pleasure *and* Weight loss or change in appetite (decrease or increase) Change in sleep (insomnia or hypersomnia) Psychomotor agitation or retardation Fatigue or anergia Feeling of worthlessness or guilt Diminished concentration or indecisiveness Recurrent thoughts of death or suicidal ideation, a suicide attempt, or a specific suicide plan
MNEMONIC TO AID RECALL OF DIAGNOSTIC CRITERIA
SIG: E CAPS (*i.e., prescribe energy capsules*) for depressed mood **S**leep change **I**nterests **G**uilt **E**nergy **C**oncentration **A**ppetite/weight **P**sychomotor changes **S**uicide
DEPRESSIVE SYMPTOMS/SIGNS GROUPED CONCEPTUALLY, WITH ADDITIONAL COMMON PHENOMENA
Emotional
Depressed mood, sadness, tearfulness Irritability (*seen in all ages, perhaps most commonly in children/adolescents and the elderly*) Anxiety Loss of interests or pleasure (anhedonia)
Ideational
Worthlessness/lowered self-esteem Guilt Hopelessness/nihilism Helplessness Thoughts of death, dying, suicide
Somatic/Neurovegetative
Change in appetite/weight Change in sleep Anergia Decreased libido Trouble concentrating Diurnal variation in symptoms (*mornings—worst pattern is most characteristic*)
Other
Ruminative thinking (*tendency to dwell on one [negativistic] theme*) Somatoform symptoms or somatic worry Psychotic symptoms (*negativistic delusions most characteristic*)—defines the subtype "Major Depression with Psychotic Features"

Based on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Association; 2000.

EPIDEMIOLOGY

In the United States, major depression has a point prevalence of approximately 3 to 5% in males and 8 to 10% in females. Lifetime prevalence is up to 10% in males and 20 to 25% in females. It is difficult to determine the true incidence rates of a new depressive disorder, but new episodes have an annual incidence of approximately 3%. Despite minor variations, similar rates are found in most industrialized nations. Depression accounts for more than twice as much disability in midlife as any other medical condition does, and its overall cumulative burden is greater than that from all but cardiovascular disorders. The economic impact is also enormous, with U.S. estimates of annual costs for depression exceeding $12 billion for treatment, $8 billion for associated morbidity, and $33 billion for lost earnings and work productivity.

PATHOBIOLOGY

Major depression is probably not a single disease entity but rather a heterogeneous group of conditions with multiple pathogenic mechanisms. It is both multifactorial and polygenic: genetic factors account for up to 50% of the risk for depression, but multiple gene loci, most of which are currently unknown, are probably involved in a complex interplay with developmental and environmental influences. Alterations in the brain's noradrenergic and serotonergic systems are present and are most likely related to the efficacy of current antidepressant medications. The hypothalamic-pituitary-adrenal axis is hyperactive in depression, as evidenced by a nonsuppressed response to the dexamethasone suppression test, although this test is too insensitive and nonspecific for clinical use as a diagnostic tool. Neuroimaging studies in subjects with depression show an array of findings, including smaller hippocampal volumes, which are thought to be the result of exposure to elevated cortisol levels, and altered regional cerebral metabolic activity of the frontal-striatal circuitry and anterior cingulate cortex. Cognitive psychology studies have demonstrated dysfunctional patterns of negative thinking, with distorted thoughts about self, the future, and the environment. Poor quality or absence of social relationships and stressful life events, particularly events such as deaths, separations, or functional impairment, are powerfully associated with depression as well.

CLINICAL MANIFESTATIONS

The symptoms of depression (see Table 404-3) may be conceptually grouped as alterations in mood, ideation (i.e., thought content), and somatic/neurovegetative functioning. Importantly, patients with depressive illness may be seen without a depressed mood, albeit by definition they must have loss of interest or pleasure in their usually desired activities. They may also exhibit prominent anxiety, irritability, or somatization. Although mild forms of major depression in the community often remit spontaneously within a few months without medical care, patients may already have had persistent symptoms for months or years before seeking treatment.

DIAGNOSIS

The diagnosis is made clinically by elicitation of findings from the history and mental status examination to determine the presence of major depressive syndrome. The differential diagnosis includes other idiopathic disorders with episodes of major depression, such as bipolar disorder (distinguished by a history of manic episodes) and schizoaffective disorder (distinguished by a history of psychotic episodes in the absence of depression). Major depression may accompany delirium or dementia, and secondary depression also commonly accompanies serious medical illnesses; these comorbid conditions require careful, well-coordinated care.

TREATMENT

The three phases of treatment include (1) *acute*, in which treatment is provided to resolve the major depressive episode; (2) *continuation*, in which the acute treatment is continued for at least 4 to 8 months to prevent relapse; and (3) *maintenance*, for those with two to three or more episodes of recurrent depression, for whom treatment is maintained indefinitely to reduce the frequency and severity of future recurrences. Combinations of psychotherapy and medication are used for more complex or severe clinical conditions.

Acute treatment of depression includes focused psychotherapies (Table 404-4), which are more efficacious than usual care and equivalent to medications when used for patients in primary care settings. Based on the patient's preference, psychotherapy rather than medications may be the initial treatment of mild to moderate major depression with prominent psychosocial stressors. Involvement of family members for education and support and sometimes for formal family therapy may be an important adjunctive or

primary therapeutic approach. These therapies may be administered with decreased frequency during the continuation or maintenance phases of treatment. However, psychotherapies may be difficult to implement and are not likely to help patients with more severe forms of depression, including major depression with psychotic features.

Medications should be used as initial treatment for most patients with more severe forms of major depression. Antidepressant medications (Table 404-5) are also effective for acute, continuation, and maintenance therapy. A recent meta-analysis found that sertraline and escitalopram have the best profiles of efficacy and tolerability whereas mirtazapine and venlafaxine also have strong efficacy in head-to-head comparisons with other antidepressants.■ Because antidepressant medications typically do not begin to improve symptoms for at least 1 to 2 weeks, with maximal benefit accruing up to at least 6 to 8 weeks, it is crucial to see patients regularly (every 1 to 2 weeks initially) to monitor their clinical status, to provide support and education, and to foster adherence. Antidepressant medications appear to increase the relative risk for suicidal behavior in adolescents and young adults, so careful benefit/risk assessments must be made in such patients. The relative risk for suicidal behavior is not increased by drug treatment in individuals older than 25 years and is substantially lowered in older adults. Electroconvulsive therapy is preferred for the most severe forms of major depression, including major depression with psychotic features, and is also used for depression that is refractory to other forms of treatment.

Optimal care for depression in primary care settings may be enhanced by the use of on-site mental health collaborative care models. However, despite considerable evidence supporting such models,■ the lack of reimbursement mechanisms has limited their implementation in most communities and clinical settings.

PROGNOSIS

Optimal, guideline-based treatment of major depression results in full remission in at least 80% of patients, and the expectation is that patients with major depression will return to baseline functioning after resolution of the depressive episodes. However, at least 50 to 70% of patients will suffer recurrent episodes, up to 20% may experience chronic major depression, and many more will be in incomplete remission with persistent lower-level symptoms because of a variety of factors, including limited access to care, nonadherence, or insufficiently assertive treatments.

BIPOLAR DISORDER

DEFINITION AND EPIDEMIOLOGY

Bipolar disorder is characterized by recurrent episodes of idiopathic mania. Most persons with bipolar disorder also have recurrent episodes of major depression.

The point prevalence of bipolar disorder is approximately 1%. Males and females are affected equally. The average age at first onset is late adolescence or early adulthood. Childhood onset is possible, but diagnosis may be difficult because of symptomatic overlap with other conditions of childhood, including attention-deficit/hyperactivity disorder. Onset in midlife to late life is also possible, although most persons in whom mania develops in later life have mania secondary to medical conditions or drugs rather than idiopathic bipolar disorder.

PATHOBIOLOGY

Even though the pathogenesis of bipolar disorder remains unclear, genetic factors play a greater role than in unipolar depressive conditions. Heritability has been traced to several specific loci in rare families, but genetic screening is not clinically useful and the gene associations have, to date, revealed no unifying pathophysiologic themes. Most cases of bipolar disorder are polygenic and multifactorial, with nongenetic factors accounting for approximately 50% of the risk for the disorder. Dysregulation of the frontostriatal systems is probably involved in the manifestations of the illness. Though not specific enough to be diagnostic, structural neuroimaging studies show increased ventricular-brain ratios suggestive of parenchymal atrophy. Phase advance of central circadian rhythms can precipitate episodes of mania, so the decreased sleep of persons with incipient mania may produce a vicious cycle in which phase-advanced circadian cycles lead to a further decreased need for sleep, thereby resulting in further phase advancement. Psychosocial stressors also often play a role in precipitating episodes of both mania and depression.

TABLE 404-4 TREATMENTS OF DEPRESSION

NAME OF PSYCHOTHERAPY	APPROACH
Cognitive psychotherapy	Identify and correct negativistic patterns of thinking
Interpersonal psychotherapy	Identify and work through role transitions or interpersonal losses, conflicts, or deficits
Problem-solving therapy	Identify and prioritize situational problems; plan and implement strategies to deal with top-priority problems
Psychodynamic psychotherapy	Use therapeutic relationship to maximize use of the healthiest defense mechanisms and coping strategies

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The symptoms of mania include a distinct period of abnormally and persistently elevated (euphoric) or irritable mood; goal-directed hyperactivity, often for pleasurable activities with poor judgment that leads to long-lasting adverse financial, psychosocial, or medical consequences, such as sprees of spending, sexual activity, or gambling; decreased need for sleep; pressured speech; and distractibility.

As with major depression, the diagnosis is based on findings from the history and examination revealing a pattern of recurrent manic episodes (Table 404-6), which are usually interspersed with major depressive episodes and cannot be explained by general medical conditions, medications, or other substances. Although persons with bipolar disorder may become psychotic while in manic or depressed states, a history of psychotic symptoms in the absence of mania or depression indicates a diagnosis of schizoaffective disorder rather than bipolar disorder. Manic and depressive episodes may also be seen in the course of delirium (Chapter 27) and dementia (Chapter 409), in which case the psychiatric symptoms are accompanied by the cognitive impairment that is the hallmark of the latter conditions.

TREATMENT Rx

The mainstay of treatment of bipolar disorder is mood stabilizer medications to reduce the frequency and severity of recurrent manic and depressive episodes. Traditional mood stabilizers with substantial evidence base to support their use include lithium (typical dose of 600 to 1500 mg/day or higher given in two or three divided doses as needed to achieve plasma levels of 0.6 to 1.2 mEq/L [up to 1.4 mEq/L in acute mania]), valproic acid (typical dose of 500 to 1500 mg/day or higher as tolerated to achieve plasma levels of 50 to 100 μg/mL), and carbamazepine (typical dose of 400 to 1200 mg/day as tolerated to achieve plasma levels of 4 to 12 μg/mL). The combination of lithium plus valproate is superior to valproate alone for prevention of relapses.■ A number of other anticonvulsants have been tried, but generally with less empirical support for their use, although lamotrigine (starting at 25 mg/day, maximum dose of 200 mg/day, titrated slowly to minimize the risk for Stevens-Johnson syndrome) can be used for prophylaxis against depressive episodes. Even though several second-generation antipsychotic medications have received approval by the Food and Drug Administration for their mood-stabilizing properties, their potential to precipitate metabolic syndrome and, to a lesser extent, tardive dyskinesia should limit their use as *maintenance* medications to patients for whom true mood stabilizers are inefficacious or poorly tolerated. For *acute* episodes of mania, second- or first-generation antipsychotics are more rapidly efficacious than mood stabilizers, with doses similar to their use for acute psychosis (see Table 404-12). For acute treatment of depressive episodes, antidepressants may be required, but they may precipitate mania; therefore, patients should receive therapeutic doses of a mood stabilizer first, and exposure to antidepressant medication should be for the minimum dose and duration required to reach euthymia. Electroconvulsive therapy is useful for refractory mania or depression and for patients with relative contraindications to medications, such as pregnant women. Standard psychotherapeutic approaches for unipolar depression may also be used for bipolar patients during depressive episodes. Ongoing psychotherapy may be important to encourage compliance with maintenance therapies and to help patients manage psychosocial stressors in order to minimize their impact on precipitating acute manic or depressive decompensations.

PROGNOSIS

Although the classically described course of bipolar disorder includes return to baseline functioning between episodes, some patients may experience frequent debilitating episodes (known as "rapid cycling," defined as four or more episodes per year), whereas others may experience a deterioration in overall functioning over time.

TABLE 404-5 COMMONLY USED ANTIDEPRESSANT MEDICATIONS

NAME OF CLASS/ SPECIFIC MEDICATION	IMMEDIATE MECHANISM OF ACTION	INITIAL DOSE	TARGET DOSE RANGE*	SIDE EFFECTS	COMMENTS
SSRIs (selective serotonin re-uptake inhibitors)	Inhibit presynaptic re-uptake of serotonin			Nausea, diarrhea, sexual dysfunction, serotonin syndrome	
Citalopram		20 mg qd	20-60 mg qd		Few drug-drug interactions
Escitalopram		10 mg qd	10-20 mg qd		Enantiomer of citalopram
Fluoxetine		20 mg qd	20-40 mg qd (depression), up to 80 mg qd (OCD)		Long half-life; tends to be activating
Paroxetine		20 mg qd	20-50 mg qd	Anticholinergic effects	Tends to be sedating
Sertraline		25-50 mg qd	50-200 mg qd		Few drug-drug interactions
SNRIs (serotonin and norepinephrine re-uptake inhibitors)	Inhibit presynaptic re-uptake of serotonin and norepinephrine			Nausea, diarrhea, serotonin syndrome, sinus tachycardia, mild elevation in blood pressure, tremor	
Duloxetine		30-60 mg qd	30-60 mg qd on a twice-daily schedule, maximum of 120 mg/day		
Venlafaxine		37.5 mg bid	150-375 mg/day on bid schedule		XR form allows once-daily dosing
Desvenlafaxine		50 mg qd	50 mg qd, maximum of 100 mg ER qd		Metabolite of venlafaxine
TCAs (tricyclic antidepressants)	Inhibit presynaptic re-uptake of serotonin and norepinephrine (in varying proportions depending on the specific TCA)			Anticholinergic effects, sedation, orthostatic hypotension, tremor, cardiac conduction delays, ventricular arrhythmias	
Amitriptyline		25-75 mg qhs	150-300 mg qhs		Strongly anticholinergic and sedating; aim for combined amitriptyline/ nortriptyline blood level of 120-250 ng/mL
Desipramine		25-75 mg qd	150-300 mg qd		Aim for blood level of 115-250 ng/mL
Doxepin		25-75 mg qhs	150-300 mg qhs		Strongly sedating
Imipramine		25-75 mg qd	150-300 mg qd		Strongly anticholinergic; aim for combined imipramine/ desipramine blood level of 180-350 ng/mL
Nortriptyline		25-50 mg qhs	50-150 mg qhs		Aim for blood level of 50-150 ng/mL; least anticholinergic of the TCAs
MAOIs (monoamine oxidase inhibitors)	Inhibit monoamine oxidase, the enzyme that catalyzes oxidative metabolism of monoamine neurotransmitters			Need for tyramine-free diet to avoid sympathomimetic (hypertensive) crisis; sedation, anticholinergic effects, tremor, orthostatic hypotension	
Isocarboxazid		10 mg bid	20-60 mg/day in bid-qid dosing		
Phenelzine		15 mg tid	45-90 mg/day in tid or qid dosing		
Selegiline	(selective MAO-B inhibitor)	5 mg bid	5 mg bid	Tyramine-free diet not required	Take with meals
Tranylcypromine		10 mg tid	30-60 mg/day in tid dosing		
Other					
Bupropion	Unknown, although it is a weak inhibitor of presynaptic re-uptake of norepinephrine and dopamine	75-150 mg/day	300-450 mg/day	Activating; risk for seizures reduced by divided dosing and careful dosage titration	Divided dosing required unless using SR or XR forms
Mirtazapine	Antagonist at α_2 and 5-HT_2 receptors	15 mg qhs	30-45 mg qhs; maximum of 45 mg qhs	Sedation, hyperphagia	Becomes more stimulating at higher doses
Trazodone	Inhibits presynaptic re-uptake of serotonin; antagonist at 5-HT_2 and 5-HT_3 receptors	25-50 mg qhs	300-600 mg qhs for depression, 25-100 mg qhs for insomnia	Sedation, priapism	Few sexual side effects

*Target doses in the elderly may be lower.
ER = extended release; 5-HT_2 = 5-hydroxytryptamine; OCD = obsessive-compulsive disorder; qhs = at bedtime; SR = sustained release; XR = extended release.

OTHER MOOD DISORDERS

Although chronic major depression should be the diagnosis in patients with long-lasting major depressive episodes, others may have chronic (≥2 years) lower-level depressive symptoms, known as *dysthymic disorder*, that can be treated with a combination of antidepressant medication and psychotherapy. A significant minority (perhaps 20 to 40%) of such patients will improve substantially with aggressive treatment. Other patients may have "less than major depression" of shorter duration, increasingly being referred to as "subsyndromal" or "subthreshold" depression; growing evidence suggests that broad psychosocial interventions (e.g., bibliotherapy, social activation) may improve outcomes in such patients.

Less severe bipolar spectrum disorders include *bipolar II disorder*, which is characterized by episodes of hypomania (i.e., low-level manic symptoms

TABLE 404-6 SYMPTOMS/SIGNS OF AN EPISODE OF MANIA

DIAGNOSTIC CRITERIA
A distinct period of abnormally, persistently elevated, expansive, or irritable mood lasting ≥1 week *and*
3 or more of the following symptoms/signs (4 or more if the mood abnormality is only irritability):
Inflated self-esteem/grandiosity
Decreased need for sleep
More talkative or pressure to keep talking
Subjective experience of racing thoughts or flight of ideas observed on examination
Distractibility
Increase in goal-directed activity or psychomotor agitation
Excessive involvement in pleasurable activities with high potential for painful consequences
MANIC SYMPTOMS/SIGNS GROUPED CONCEPTUALLY, WITH ADDITIONAL COMMON PHENOMENA
Emotional
Euphoria
Irritability
Labile affect
Ideational
Grandiosity
Somatic/Neurovegetative
Psychomotor agitation
Decreased need for sleep
Distractibility
Other
Goal-directed hyperactivity
Pressured speech
Impaired judgment
Flight of ideas
Psychotic symptoms (may include delusions, hallucinations, or derailment of thought processes such as loose associations)—defines the subtype "mania with psychotic features"

Based on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Association; 2000.

TABLE 404-7 TYPES OF ANXIETY DISORDERS

ANXIETY DISORDER	MAJOR CLINICAL CHARACTERISTICS
Panic disorder	Recurrent unexpected panic attacks, typically with anticipatory anxiety and avoidance behavior
Obsessive-compulsive disorder (OCD)	Recurrent obsessions (distressing thoughts experienced as ego-alien) and compulsions (mental or physical actions in an attempt to neutralize obsessions or in response to rigid rules)
Acute stress disorder and post-traumatic stress disorder (PTSD)	Responses to a severely traumatic event, including re-experiences of the trauma, avoidance behavior, and hyperarousal
Generalized anxiety disorder	Excessive anxiety and worry, not meeting the criteria for other anxiety disorders, lasting ≥6 months
Phobias	
Agoraphobia	Anxiety about or avoidance of places or situations from which escape might be difficult or embarrassing or in which help might not be available in the event of panic symptoms
Social phobia	Anxiety provoked by exposure to social situations, typically with ensuing avoidance behavior; may be generalized (i.e., in response to many interpersonal situations) or specific in response to a particular social situation (e.g., using a public restroom, public speaking)
Specific phobia	Anxiety provoked by exposure to a specific feared object or (nonsocial) situation, typically with ensuing avoidance behavior

Based on categories and criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Association; 2000.

without substantial functional impairment and without psychosis) and episodes of major depression. Such patients typically seek care during depressive episodes rather than during hypomania, but antidepressant medication may worsen the manic symptoms. It is therefore imperative to ask about a history of manic or hypomanic symptoms in the evaluation of all patients with depression. *Cyclothymic disorder*, which includes episodes of hypomania and low-level depressive episodes, may be difficult to distinguish from the mood instability seen in "cluster B" personality disorders (see later).

ANXIETY DISORDERS

DEFINITION

The anxiety disorders (Table 404-7) are a group of conditions whose hallmark is idiopathic anxiety, typically accompanied by psychological (i.e., thought content) and somatic symptoms. Anxiety is a common accompanying symptom in many other psychiatric disorders, but the primary anxiety disorders lack the cognitive deficits, depressive or manic symptoms, or psychosis seen in these other disorders.

EPIDEMIOLOGY

Panic disorder and obsessive-compulsive disorder (OCD) each have point prevalence rates of approximately 1 to 2%. The prevalence of acute stress disorder and post-traumatic stress disorder (PTSD) varies widely by population. Generalized anxiety disorder has a prevalence of approximately 2 to 3%, whereas the phobias collectively have a prevalence of 10% in the adult population. Clear data on incidence rates are not available. Most primary anxiety disorders have an age at first onset in late adolescence through the mid-30s. Most anxiety symptoms with new onset in later life are due to mood or cognitive disorders or are secondary to medical illnesses or drugs; true late-onset primary anxiety disorders are often triggered by traumatic or other stressful life events.

PATHOBIOLOGY

Most of the anxiety disorders may be understood as inappropriate triggering of the stress response system, which is commonly referred to as the "fight or flight" response. However, it is important to recognize that the responses involve a wide range of cognitive, motor, neuroendocrine, and autonomic systems and thus are not limited to manifestations of sympathetic nervous system activity. The central nucleus of the amygdala is believed to play a crucial role in coordinating the anxiety response. The amygdala receives excitatory glutamatergic input from several cortical areas and from the thalamus, thereby allowing it to respond to a wide variety of stimuli, including sensory input from the external world, as well as stressors that are processed and recognized by cortical association areas. The amygdala in turn projects to the many brain regions that subserve the clinical manifestations of the anxiety response, in part through its direct projections to the important centers of monoaminergic systems: dopaminergic neurons of the ventral tegmental area in the midbrain, noradrenergic neurons in the locus caeruleus, and serotonergic neurons in the raphe nuclei.

From a cognitive psychology perspective, the pathogenesis of many anxiety disorders, particularly panic, may be understood as catastrophic misinterpretations of normal somatic sensations. A vulnerable individual may become aware of a normal or minimally abnormal body sensation, which is interpreted as something concerning, thereby leading to sympathetic and other autonomic arousal, which in turn leads to further somatic sensations (e.g., tachycardia, sweating) in what becomes a vicious cycle of thoughts and somatic symptoms. The pathogenesis of acute stress disorder and PTSD may be understood from psychodynamic perspectives as psychological attempts to cope with or master a traumatic life event that is difficult or impossible to "master" and integrate into one's sense of self and the world.

OCD appears to have a pathogenesis distinct from that of the other anxiety disorders. It probably involves altered functioning of the striatofrontal systems, as well as a prominent role of the serotonergic systems. The obsessions and compulsions of OCD may represent inappropriate triggering of neural "scripts" involving thoughts and behaviors that have been analogized to the scripts involved in animal grooming and other complex behavior. Patterns of heritability and symptomatic comorbidity strongly suggest that the pathogenesis of OCD is more closely related to that of movement disorders, such as tic disorders (Chapter 417), than to the other primary anxiety disorders.

CLINICAL MANIFESTATIONS

Most individuals experience one or more somatic symptoms (Table 404-8) that accompany the psychic anxiety, regardless of whether the anxiety is normal or part of a pathologic condition. Such somatic symptoms may be referable to virtually every body organ system.

TABLE 404-8 COMMON SOMATIC MANIFESTATIONS OF ANXIETY

CARDIORESPIRATORY
Palpitations
Chest pain
Dyspnea or sensation of being smothered
GASTROINTESTINAL
Sensation of choking
Dyspepsia
Nausea
Diarrhea
Abdominal bloating or pain
GENITOURINARY
Urinary frequency or urgency
NEUROLOGIC/AUTONOMIC
Diaphoresis
Warm flushes or chills
Dizziness or presyncope
Paresthesias
Tremor
Headache

TABLE 404-9 COMMON TYPES OF OBSESSIONS AND COMPULSIONS IN OBSESSIVE-COMPULSIVE DISORDER

OBSESSIONS
Aggressive (fears of harming self or others, of blurting out obscenities, or of other unwanted aggressive acts; unwanted violent or horrific images)
Contamination (concerns about dirt, germs, body waste or secretions, environmental contaminants, or animals/insects)
Sexual (concerns about unwanted sexual images or impulses)
Hoarding/saving
Religious (*scrupulosity*) (excessive concerns about sacrilege, blasphemy, right/wrong, morality)
Need for symmetry/exactness
Somatic (excessive concern about illness, body part, or appearance)
COMPULSIONS
Cleaning/washing (excessive or ritualized handwashing, showering, or other grooming)
Checking (checking locks, stove, appliances; checking body in relation to somatic obsessions; checking that did not or will not harm self or others)
Repeating rituals (rereading or rewriting; routine activities such as going through a door or arising from a chair)
Counting
Ordering/arranging
Hoarding/saving

Adapted from Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006-1011.

Many anxiety disorders include acute, discrete periods of symptoms known as *panic attacks*. In a panic attack, the patient experiences a rapid rise in anxiety, fear-related thoughts, and somatic symptoms in the space of a few minutes, known as a crescendo onset. The acute symptoms resolve quickly, typically within an hour or less.

Panic Disorder

Panic disorder consists of *recurrent panic attacks*. Although some panic attacks may be precipitated by situations known to be stressful, at least some attacks must be *unexpected* ("out of the blue"). Patients also exhibit *anticipatory anxiety*, in which they experience ongoing psychic distress by worrying about their next panic attack or the attack's effects (e.g., humiliation if the attack were to happen in public view). In addition, patients manifest *avoidance behavior* by staying away from known triggers or from situations in which having a panic attack might be dangerous (e.g., driving) or particularly distressing (e.g., in public spaces). For many patients, the anticipatory anxiety and avoidance behavior may be more disabling than the panic attacks themselves. Avoidance behavior may overlap with *agoraphobia*, which is defined as a distressing and disabling fear of places or situations from which escape might be difficult or embarrassing or from which help might not be available in the event of a panic attack. Common agoraphobic foci include being outside one's home alone, being on bridges or in tunnels, traveling by vehicle, or being in crowds or lines. Up to 40 to 50% of patients with panic disorder have agoraphobia (termed *panic disorder with agoraphobia*), whereas the others have agoraphobia without panic disorder (termed *agoraphobia without history of panic disorder*).

Obsessive-Compulsive Disorder

Patients with OCD have recurrent *obsessions* or *compulsions* (Table 404-9); the vast majority of patients have both. OCD should not be confused with obsessive-compulsive personality traits or disorder, described later under Personality Disorders. *Obsessions*, not to be confused with obsessing (ruminating) on a topic, are recurrent distressing (ego-dystonic) thoughts that at some point during the course of the disorder are experienced as intrusive and inappropriate (ego-alien). Patients may describe their obsessions in language such as "I don't know where this thought comes from" or "I don't know why I have this thought, I would never actually do such a thing!" However, it is important to recognize that the ego-alien quality of obsessions may not be reported by children with OCD or by those with chronic OCD symptoms; for such patients the thought is merely experienced as distressing. *Compulsions* are recurrent mental or physical actions, typically related to the content of obsessions or to rigid rules that must be obeyed; for example, compulsive handwashing may relate to obsessional thoughts about germs or contamination. Again, most adults, at least early in the course of the disorder, experience the compulsions as intrusive and inappropriate or excessive. Patients with OCD typically attempt to ignore, suppress, or neutralize their obsessions and compulsions, but doing so causes great psychic distress, including anxiety until "giving in" and experiencing the unpleasant thought or performing the action. OCD patients may spend many hours per day engaged in or attempting to resist their obsessions and compulsions.

Acute Stress Disorder and Post-traumatic Stress Disorder

Acute stress disorder and PTSD are specific manifestations of symptoms referable to an extremely traumatic event. The event by definition must involve exposure to actual or threatened death, serious injury, or destruction of the physical integrity of the patient or others such that the patient's immediate reaction includes intense fear, helplessness, or horror. Formerly, definitions of the traumatic event involved descriptions such as "beyond usual human experience." It is important to recognize that acute stress disorder or PTSD does not develop in all individuals exposed to a common traumatic event (e.g., a natural or man-made disaster)—major depression may develop in some; other anxiety disorders may develop in others; mania, psychosis, or other conditions may develop in a few; and diagnosable psychopathology may never develop at all in some or many. In acute stress disorder, the patient develops a sense of numbing or emotional detachment, a reduction in awareness of the surroundings ("in a daze"), and dissociative symptoms such as derealization, depersonalization, or dissociative amnesia, as well as symptoms similar to those seen in PTSD. However, PTSD symptoms, by definition, persist for more than 1 month after the traumatic event and include three types of clinical phenomena: (1) re-experiencing the trauma (e.g., intrusive memories, dreams, or flashbacks or intense distressing psychological or physiologic responses to reminders of the trauma), (2) avoidance (e.g., avoiding specific reminders of the trauma; more generalized social withdrawal, emotional detachment, or blunting; or a sense of a foreshortened future), and (3) hyperarousal (e.g., insomnia, irritability, difficulty concentrating, or exaggerated startle response). Several PTSD symptoms overlap considerably with those of major depression, which is commonly a comorbid condition and should also be diagnosed when the diagnostic criteria are met.

Generalized Anxiety Disorder

This diagnostic term encompasses a more heterogeneous group of conditions, defined by the presence of clinically significant anxiety and associated somatic symptoms for 6 or more months. Generalized anxiety disorder is not diagnosed if the anxiety is part of a diagnosable anxiety, mood, or other psychiatric disorder; that is, it is superseded in the diagnostic hierarchy by other conditions that produce anxiety.

Phobias

The phobias are a group of conditions defined by the consistent ability of a specific environmental stimulus to elicit a pathologic anxiety response. Exposure to such a stimulus nearly always produces this response, so the patient avoids the stimulus whenever possible or endures the stimulus with

considerable distress. In addition to agoraphobia, the other main types of phobias are *social phobia* and *specific phobias* (see Table 404-7).

DIAGNOSIS

Diagnosis of anxiety disorders must rest on consideration of both syndromic and etiologic perspectives. From a syndromic perspective, a careful history and mental status examination are required to determine the pattern of anxiety and associated symptoms and to determine whether the phenomenology fits the pattern for any of the anxiety disorders as described earlier. The history and mental status examination must also assess for the presence of any other psychiatric disorder that might truly be comorbid with the anxiety disorder but might also supersede the anxiety disorder in the diagnostic hierarchy. For example, generalized anxiety may be seen as part of cognitive disorders (delirium or dementia), mood disorders (depressed or manic phases), and psychotic disorders; if the generalized anxiety is present only during the cognitive, mood, or psychotic disorder, a separate diagnosis of generalized anxiety disorder is not warranted. As another example, however, major depression may develop in a patient with long-standing PTSD or OCD symptoms, perhaps partly as a consequence of the social and other disability conferred by the PTSD or OCD; in such cases, both the anxiety disorder and major depression would be diagnosed.

From an etiologic perspective, it is important to determine whether the anxiety disorder is primary (idiopathic) or secondary to a systemic or neurologic condition (see Table 404-1), drug intoxication, or withdrawal state. The evaluation should include laboratory tests, such as a toxic drug screen, as guided by the differential diagnosis that is generated from the clinical evaluation.

TREATMENT

Rx

Considerable empirical evidence from controlled trials demonstrates the efficacy of cognitive-behavioral psychotherapies for most of the anxiety disorders.[5] Such therapies, which use the principles of learning theory to extinguish unhelpful behavior and positively reinforce more functional behavior, help the patient learn to identify and correct the dysfunctional patterns of thinking ("automatic thoughts") that underlie or trigger the cognitive-physiologic cascade of pathologic anxiety responses. Cognitive behavioral therapy may be used as sole therapy, particularly for specific phobias, or in combination with pharmacotherapy. Frequently, cognitive behavioral therapy may be administered as part of family therapy (e.g., to help family members avoid behavior that inadvertently reinforces the patient's obsessions and compulsions) or in group therapy settings.

Although anxiolytic drugs, such as the benzodiazepines (Table 404-10), will usually relieve acute anxiety symptoms, concerns about their long-term efficacy and side effects (e.g., risk for abuse, risk for cognitive impairment or falls) make antidepressant medications the more attractive pharmacologic agents for most anxiety disorders (see Table 404-5). Most classes of antidepressants, with the probable exception of bupropion, are helpful for panic disorder, PTSD, generalized anxiety disorder, and social phobia. For OCD, the only efficacious antidepressants are those with strong activity on the serotonergic system, such as selective serotonin re-uptake inhibitors and also the tricyclic compound clomipramine.

PROGNOSIS

In general, most persons with anxiety disorders, other than transient acute stress disorder or other situation-dependent anxiety states, tend to have a chronic course of waxing and waning symptoms. At one extreme, a small minority of patients (≈5%) with OCD have intermittent episodes alternating with periods of full remission; at the other extreme, up to 15% of OCD patients may have a continuous and progressively worsening course over time. Maintenance therapies should often be used for patients with more chronic anxiety disorders, although evidence to support long-term therapies is not as robust as for mood disorders.

PSYCHOTIC DISORDERS

Psychotic symptoms, defined as a loss of reality testing, include delusions (fixed false beliefs), hallucinations (false sensory perceptions), and major derailments in thought processes (e.g., loose associations). Psychotic symptoms may be seen in the course of cognitive, secondary, and mood disorders. The psychotic disorders are defined by the presence of psychotic symptoms in the absence of prominent mood disturbance or cognitive deficits at the level seen in delirium or dementia. In general, the diagnosis and care of most patients with psychotic disorders should be conducted in mental health specialty settings, but primary care settings are common points of entry (and re-entry) to care.

Schizophrenia

DEFINITION AND EPIDEMIOLOGY

Schizophrenia, which is the prototypical psychotic disorder, includes acute episodes of psychosis ("positive" symptoms), often accompanied by a decline in overall functioning over time because of "negative symptoms," such as affective flattening, abulia, apathy, and social withdrawal. The point prevalence of schizophrenia is approximately 1%, and its chronic, debilitating course takes a considerable toll on patients, families, and society. Peak onset is in late adolescence to young adulthood, slightly younger for males than females. The annual incidence is approximately 15 per 100,000, but with marked variability across study samples and populations; recent data suggest that the condition is slightly more common in males than in females.

PATHOBIOLOGY

The pathogenesis of schizophrenia remains unknown. Twin studies show that the disease is multifactorial. Genetic factors account for about 50% of the risk, and multiple gene loci appear to be involved. Studies of postmortem brains indicate a nongliotic neuropathologic process with subtle disruptions of cortical cytoarchitecture. It is likely that psychosocial factors and neurodevelopment interact with a nonlocalizable brain "lesion" that is either present at birth or acquired early in life. The dopaminergic mesocortical and mesolimbic pathways are important in the production of psychotic symptoms.

DIAGNOSIS

The diagnosis of schizophrenia is based on the presence of delusions, disorganized speech and behavior, and major impairment in social functioning for

TABLE 404-10 DRUGS FOR ANXIETY AND PANIC

DRUG	TRADE NAME	INITIAL DOSE	TARGET DOSE RANGE*	SIDE EFFECTS	COMMENTS
Benzodiazepines				Sedation, ataxia, risk for falls	Potential for abuse/dependence
Lorazepam	Ativan	0.5 mg bid-qid	2-6 mg/day, tid-qid dosing		Reliable IM absorption
Diazepam	Valium	2-5 mg bid-tid	10-40 mg/day, bid-tid dosing		Long half-life of drug and active metabolites
Triazolam	Halcion	0.125 mg qhs	0.125-0.25 mg qhs	Rebound insomnia	Used as hypnotic
Chlordiazepoxide	Librium	5 mg bid-tid	10-40 mg/day, bid-tid dosing		Long half-life of drug and active metabolites
Temazepam	Restoril	7.5 mg qhs	7.5-30 mg qhs		Used as hypnotic
Alprazolam	Xanax	0.25 mg tid-qid	2-8 mg/day, tid-qid dosing	Possibly greater addictive potential	
Clorazepate	Tranxene	7.5-15 mg bid-tid	15-60 mg/day, bid-tid dosing		
Flurazepam	Dalmane	15-30 mg qhs	15-30 mg qhs	Daytime somnolence	Used as hypnotic
Oxazepam	Serax	10-15 mg tid-qid	10-30 mg tid-qid		
Clonazepam	Klonopin	0.5 mg bid-tid	0.5-5 mg bid-tid		Long duration of action
Zaleplon	Sonata	5-10 mq qhs	5-20 mg qhs		"Nonbenzodiazepine" hypnotic
Zolpidem	Ambien	5-10 mg qhs	5-10 mg qhs		"Nonbenzodiazepine" hypnotic
Eszopiclone	Lunesta	1-2 mg qhs	1-3 mg qhs		"Nonbenzodiazepine" hypnotic
β-Blockers					
Propranolol	Inderal	20 mg bid	Individualize, 40-120 mg/day	Bradycardia, hypotension, potential for mental slowing	Only helps with sympathetically mediated somatic symptoms of anxiety

*Target doses in the elderly may be lower.
qhs = at bedtime.

at least 6 months (Table 404-11). In patients with single schizophrenia-like psychotic episodes of briefer duration, with subsequent return to asymptomatic baseline functioning, *brief psychotic disorder* (<1 month) or *schizophreniform disorder* (1 to 6 months) may be diagnosed.

TABLE 404-11 SYMPTOMS AND SIGNS OF MAJOR PSYCHOTIC DISORDERS

SCHIZOPHRENIA
Delusions
Hallucinations
Disorganized speech (i.e., thought process derailments)
Grossly disorganized or catatonic behavior
Negative symptoms: affective flattening, alogia, avolition
Major impairment in social or occupational functioning
Duration of at least 6 months
SCHIZOAFFECTIVE DISORDER
During the course of illness, at least one episode of schizophrenia-like psychotic symptoms *plus* a mood syndrome (either major depression, mania, or mixed episode) *and*
During the course of illness, at least 2 weeks of schizophrenia-like psychotic symptoms *in the absence of* a mood syndrome
DELUSIONAL DISORDER
Delusions that are nonbizarre (i.e., potentially plausible, such as delusions of being followed, poisoned, infected, loved at a distance, deceived by a spouse or lover, or having a disease)
Not meeting full criteria for an acute episode of schizophrenia
Functioning *not* markedly impaired other than as related to the impact of the delusion (or delusions) and its ramifications

Based on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Association; 2000.

TREATMENT

Antipsychotic medications (Table 404-12), often with adjunctive benzodiazepines, are used to treat acute psychotic episodes, commonly in acute inpatient settings so that the patient can be managed safely until the acute symptoms improve. Although maintenance antipsychotic medications help reduce the severity and frequency of acute psychotic episodes, comprehensive psychosocial rehabilitation programs are required to help patients manage interpersonal and other stressors and to improve overall clinical outcomes. In the past decade, second-generation ("atypical") antipsychotic medications have replaced first-generation antipsychotics because of their greater short-term tolerability and lower rates of extrapyramidal side effects, including tardive dyskinesia, although their efficacy is not generally better than that of first-generation drugs.■ However, second-generation drugs contribute to the increase in obesity and metabolic syndrome in patients with chronic schizophrenia (Chapter 442). One trial found that oral long-chain ω-3 polyunsaturated fatty acids reduced the rate of onset of psychosis by more than four fifths during a 1-year follow-up of adolescents and young adults with especially high risk profiles for incipient psychosis, but the usefulness of this approach in broader populations remains to be determined.

PROGNOSIS

The prognosis of individuals with schizophrenia may often be poor, with recurrent episodes of psychotic exacerbations superimposed on progressively deteriorating baseline functioning. However, some patients may have preservation of relatively high baseline functioning, and some experience periods of prolonged remission or improvement in functioning. Prominent negative symptoms, younger age at first onset, and enduring psychosocial stressors and family discord all predict poorer outcomes. Although many patients with schizophrenia survive into later life, overall life expectancy is shortened by at least 10 to 15 years because of poor health behavior and self-care, higher rates of medical disorders, including metabolic syndrome, and a lifetime suicide risk of approximately 10%.

TABLE 404-12 COMMONLY USED ANTIPSYCHOTIC MEDICATIONS

DRUG NAME	INITIAL DOSE FOR PSYCHOSIS IN SCHIZOPHRENIA*	TARGET DOSE FOR PSYCHOSIS IN SCHIZOPHRENIA†	SIDE EFFECTS	CHLORPROMAZINE DOSAGE EQUIVALENCE (FIRST-GENERATION DRUGS ONLY)/ OTHER COMMENTS
First-generation drugs			Low-potency drugs: anticholinergic effects, orthostatic hypotension, prolongation of QT interval, cholestatic jaundice High-potency drugs: extrapyramidal side effects (dystonias, akathisia, parkinsonism, neuroleptic malignant syndrome), hyperprolactinemia with galactorrhea	
Chlorpromazine	100 mg qd	300-1000 mg/day, qd-bid dosing		100 mg
Thioridazine	50-100 mg qd	300-800 mg/day, qd-bid dosing	Pigmentary retinopathy at higher doses	100 mg
Thiothixene	2-5 mg qd	5-60 mg/day, qd-bid dosing		5 mg
Trifluoperazine	2-5 mg qd	5-40 mg/day, qd-bid dosing		5 mg
Perphenazine	4-8 mg qd	8-64 mg/day, qd-tid dosing		8 mg
Haloperidol	0.5-2 mg qd	2-10 mg/day (up to 40 mg/day or higher in refractory cases), qd-bid dosing		2 mg; available in depot IM form
Fluphenazine	1-2.5 mg qd	2.5-10 mg/day (up to 40 mg/day in refractory cases), qd-bid dosing		2 mg; available in depot IM form
Second-generation drugs			Metabolic syndrome, risk for stroke and mortality in older patients with dementia, QT prolongation	
Risperidone	0.5-1 mg qd-bid	2-4 mg/day, qd-bid dosing	Extrapyramidal side effects at higher doses	Available in depot IM form
Olanzapine	5 mg qd	5-10 mg qd (up to 20 mg/day in refractory cases)		
Ziprasidone	20 mg bid	20-80 mg bid		
Quetiapine	25-50 mg bid-tid	300-800 mg/day, bid-tid dosing		Extended-release form for qd dosing
Asenapine	5 mg bid	5-10 mg bid		Sublingual form only
Paliperidone	3-6 mg qd	6-12 mg qd		
Iloperidone	1 mg bid	2-12 mg bid		
Aripiprazole	10-15 mg qd	10-30 mg qd		Partial agonist/antagonist at D_2 receptors
Clozapine	12.5 mg qd-bid	300-900 mg/day, qd-bid (titrate dose slowly by 25-50 mg/day every 3-7 days)	Risk for agranulocytosis, requires ongoing monitoring of complete blood count	Efficacy superior to that of other antipsychotics, but hematologic risks and need for monitoring limit its use

*Doses for other indications, such as agitation in delirium or dementia, may be much lower.
†Target doses in the elderly may be lower.

Schizoaffective Disorder

Schizoaffective disorder is a chronic, recurrent disorder with a prevalence slightly lower than that of schizophrenia. It is characterized by episodes of non–mood-associated psychosis and also by mood episodes (manic or depressed) with psychotic features. As a result, the diagnosis of schizoaffective disorder cannot be based on the patient's clinical findings at any one point in time but rather requires knowledge of the overall course. Treatment is symptomatic and involves the use of antipsychotic medications (see Table 404-12), mood stabilizers (see the section on treatment of bipolar disorders), and antidepressant medications (see Table 404-5) to target specific psychotic and mood symptoms. The outcomes of schizoaffective disorder are heterogeneous but on average intermediate between those of schizophrenia and mood disorders.

Delusional Disorder

Delusional disorders are characterized by potentially plausible ("nonbizarre") delusions, such as those regarding marital infidelity, in the absence of a thought process disorder, prominent hallucinations, or the negative symptoms seen in schizophrenia. Delusional disorder has a point prevalence of approximately 0.03% and a lifetime prevalence of 0.05 to 0.1%. The pathogenesis of delusional disorder, like the other the nonschizophrenic primary psychotic disorders, remains largely unknown. It is often only partially responsive to antipsychotic medications (see Table 404-12), but patients' functioning may be largely unimpaired if they are able, with the aid of antipsychotics and psychotherapy, to avoid speaking publicly about their delusions or acting on them.

SOMATOFORM DISORDERS

Somatoform symptoms (Table 404-13), often broadly referred to as "somatization," resemble the symptoms caused by systemic or neurologic diseases but are thought to arise from unconscious psychogenic causes rather than identifiable physical causes. Somatization may range from normal human experiences (e.g., abdominal cramping in response to an acute stressor), to time-limited episodes, to chronic, disabling conditions.

The prevalence of somatoform disorders varies widely among various populations, in part based on diagnostic ascertainment. Full-fledged somatization disorder may have a lifetime prevalence of 0.2 to 2% in females and less than 0.2% in males. Prevalence estimates for conversion disorder are as low as 0.01% in the general population but may be much higher (1 to 14%) in medical/surgical inpatients and even higher in neurologic treatment settings.

Although the symptoms of somatoform disorders are not due to identifiable physical disease, they are nonetheless "real" and are just as distressing and baffling to patients as would be similar symptoms produced by physical disease. Somatoform symptoms and disorders must be distinguished from other conditions in which psychological factors lead to manifestations resembling physical disorders. *Factitious disorder* (also known as Munchausen's syndrome) is a mental disorder in which patients consciously produce stigmata of disease (e.g., simulated or artificially induced fever or hypoglycemia) for the unconscious gain of assuming the sick role. *Malingering* is the conscious feigning of illness for conscious gain and is therefore not a mental disorder.

TABLE 404-13 TYPES OF SOMATOFORM DISORDERS

TYPE	MAIN CLINICAL MANIFESTATIONS
Disorders characterized by somatoform symptoms (i.e., physical symptoms due to unconscious psychological factors)	
Somatization disorder	Also known as Briquet's syndrome: chronic recurrent disorder with multiple somatoform symptoms across multiple organ systems, including pain, neurologic, sexual, and other symptoms, beginning before the age of 30 years
Conversion disorder	Neurologic somatoform symptoms (other than pain), e.g., paralysis, blindness, dyscoordination, convulsion-like phenomena, memory or other cognitive complaints
Pain disorder	Pain (may or may not be associated with a physical disorder)
Undifferentiated somatoform disorder	Other somatoform symptoms not meeting criteria for the disorders above
Other types of somatoform disorders	
Hypochondriasis	Inappropriate worry about illness and help seeking (in the absence of somatoform symptoms per se)
Body dysmorphic disorder	Preoccupation with a perceived body defect or deformation ("imagined ugliness"); may have more in common with the obsessions of obsessive-compulsive disorder than with the other somatoform disorders

Based on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Association; 2000.

TREATMENT Rx

Management of patients with somatoform disorders is often difficult because physicians must simultaneously maintain an appropriate level of vigilance for undiagnosed physical illness while avoiding unnecessary tools and therapies. Keys to ongoing care include maintaining an ongoing therapeutic alliance, setting regular office visits, conveying empathy for the patient's very real distress without colluding with the patient's belief in an identifiable physical disorder, and assertively treating depression, anxiety, or other comorbid psychopathology. Antidepressant medications may benefit selected patients (e.g., some chronic pain syndromes), even in the absence of comorbid psychiatric disorders.

PERSONALITY DISORDERS

Personality is defined as the total repertoire of enduring patterns of thinking, feeling, and behaving, including affect and impulse regulation, defense and coping mechanisms, and interpersonal relatedness. Personality and personality disorders are the result of complex interactions among genetic, environmental, and developmental factors. The cumulative point prevalence of all personality disorders in the general adult population is approximately 10 to 15%, with rates as high as 50% in patients receiving care in psychiatric treatment settings.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A *personality disorder* is diagnosed when personality trait repertoires lead to enduring (if variable) subjective distress or dysfunction in social role performance (Table 404-14). In diagnosing personality disorders, care must be taken to distinguish personality *traits*, which by definition are enduring, from time-limited *states*. Most persons can regress to more primitive personality styles, not characteristic of their baseline personality traits, under the influence of substantial psychosocial stressors, including those posed by significant medical illnesses. For example, a patient who exhibits dependent features only while acutely ill does not have a dependent personality disorder. Similarly, patients with personality disorders are prone to mood, anxiety, eating, and substance abuse disorders, which should be diagnosed and treated assertively.

TREATMENT Rx

In most circumstances the goal is not to alter fundamental personality structure, but rather to help the patient maximize use of personality strengths (e.g., optimal defense and coping mechanisms) while minimizing the harmful effects of emotional dysregulation, dysfunctional defenses, and destructive behavior. Dialectic behavior therapy is an evidence-based, focused psychotherapy that is based on specific cognitive-behavioral techniques and has been demonstrated to reduce self-injurious behavior and suicidality in patients with borderline personality disorder.

Although pharmacotherapy is not the mainstay of treatment of most personality disorders, drugs can be useful in selected patients. Antipsychotic drugs may be used to target escalating paranoia in paranoid personality disorder or for short-term reduction in emotional and impulse regulation with a wide range of (often cluster B, see Table 404-14) personality disorders in times of crisis. For longer-term treatment of emotional dysregulation in borderline and other cluster B personality disorders, mood stabilizers or antidepressants may be used.

TABLE 404-14 PERSONALITY DISORDERS

TYPE OF PERSONALITY DISORDER	MAIN IDENTIFYING CHARACTERISTICS
CLUSTER A: ODD/ECCENTRIC	
Schizoid personality disorder	Detachment from social relationships, restricted emotional expression
Schizotypal personality disorder	Discomfort with close relationships, cognitive or perceptual distortions, eccentric behavior
Paranoid personality disorder	Pervasive distrust and suspiciousness of others' motives as malevolent
CLUSTER B: DRAMATIC/EMOTIONAL	
Borderline personality disorder	Instability of interpersonal relationships and self-image and poorly regulated emotional states and impulse control
Narcissistic personality disorder	Inflated self-esteem, need for admiration from others, and lack of empathy for others
Antisocial personality disorder	Pervasive disregard for and violation of the rights of others, lack of conscience
Histrionic personality disorder	Pervasive excessive emotionality (theatricality) and attention seeking
CLUSTER C: ANXIOUS/FEARFUL	
Avoidant personality disorder	Social inhibition because of feelings of inadequacy and sensitivity to negative views from others
Dependent personality disorder	Submissive and clinging behavior because of excessive need to be taken care of
Obsessive-compulsive personality disorder	Preoccupation with orderliness, perfectionism, and control

Based on criteria from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Association; 2000.

SUICIDE AND EVALUATION OF SUICIDALITY

Suicide is a leading cause of death worldwide. Suicide rates in the United States average approximately 11 per 100,000 per year, with considerable variability geographically and demographically. Of all age-, gender-, and race-based demographic groups, the highest suicide rates occur in older white men. Suicide is the 3rd leading cause of death in adolescents and young adults and the 11th leading cause of death in the population overall. Suicide attempts, which outnumber completed suicides by a factor of at least 3:1, lead to considerable morbidity and utilization of health care resources. Persons who attempt suicide represent an overlapping but distinct population from those who die by suicide. Nonetheless, a previous history of a suicide attempt is a powerful risk for subsequent death by suicide. Suicide attempts and verbal threats should always be evaluated carefully and never dismissed as "gestures" or "attention-seeking" behavior.

Suicide is a potentially preventable cause of death, but despite considerable research on risks for suicidal behavior, specific predictions about an individual's behavior cannot be made with certainty. Nonetheless, the linchpin of clinical evaluation is a methodic assessment of risks for suicide (Table 404-15), together with direct questioning of the patient regarding thoughts of death, dying, and suicide; specific plans (in ideation or action) for suicide; and the details of any attempts. Patients at significantly increased risk for suicide should immediately be referred for psychiatric evaluation, with emergency referral if the risk is deemed to be imminent or increasing.

WHEN TO REFER A PATIENT FOR PSYCHIATRIC EVALUATION

Clinical decisions to refer a patient for specialty psychiatric evaluation must be made on an individual basis by taking into account both the patient's clinical findings, including any previous history and immediate needs, and the clinician's own experience and expertise in assessing and managing the disorder (Table 404-16).

TABLE 404-15 SOME IMPORTANT RISKS FOR SUICIDE AND SUICIDE ATTEMPTS

Mental disorder, particularly mood, substance use, psychotic, and personality disorders
Other symptoms of acute psychic distress, particularly hopelessness and panic attacks
Previous history of suicide attempt
Family history of suicide or suicide attempt (and, to a lesser degree, of any mental disorder)
Family violence, including physical or sexual abuse
Access to firearms or other lethal methods
Exposure to suicidal behavior of others (family, peers, public figures)
Social isolation
Interpersonal discord or other psychosocial stressors
Demographic factors, including male gender, non-Hispanic white or American Indian/Alaska Native race, older age

TABLE 404-16 GENERAL CONSIDERATIONS IN DECIDING TO REFER A PATIENT FOR PSYCHIATRIC SPECIALTY CARE

Diagnosis or ongoing care of severe/chronic mental disorders, including bipolar disorder, psychotic disorders such as schizophrenia, and psychotic symptoms in other disorders
Management of more severe forms of other mental disorders (as well as those refractory to treatment), including depression, anxiety disorders, and substance use disorders
Need for safety evaluation or management, including suicidality, homicidality or other aggressivity, or inability to care for self
Diagnostic uncertainty
Psychiatric comorbid conditions complicating diagnosis or treatment, including personality and substance use disorders coexisting with other psychiatric disorders
Psychiatric-medical comorbid conditions complicating diagnosis or treatment, including management of psychiatric disorders during pregnancy
Need for expertise in psychopharmacologic treatment
Need for expertise in other somatic therapies, e.g., electroconvulsive therapy
Need for expertise in psychotherapy or other psychosocial interventions

Grade A

1. Bortolotti B, Menchetti M, Bellini F, et al. Psychological interventions for major depression in primary care: a meta-analytic review of randomized controlled trials. *Gen Hosp Psychiatry*. 2008;30:293-302.
2. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373:746-758.
3. Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med*. 2010;363:2611-2620.
4. BALANCE investigators and collaborators. Lithium plus valproate combination therapy versus monotherapy for relapse in bipolar I disorder (BALANCE): a randomized open-label trial. *Lancet*. 2010;375:385-395.
5. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *J Clin Psychiatry*. 2008;69:621-632.
6. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008; 371:1085-1097.

SUGGESTED READINGS

Abramowtiz JS, Taylor S, McKay D. Obsessive-compulsive disorder. *Lancet*. 2009;374:491-499. *Review*.

Frye MA. Clinical practice. Bipolar disorder—a focus on depression. *N Engl J Med*. 2011;364:51-59. *Review*.

Leichsenring F, Leibing E, Kruse J, et al. Borderline personality disorder. *Lancet*. 2011;377:74-84. *Review*.

O'Connor EA, Whitlock EP, Beil TL, et al. Screening for depression in adult patients in primary care settings: a systematic evidence review. *Ann Intern Med*. 2009;151:793-803. *Review*.

U.S. Preventive Services Task Force. Screening for depression in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009;151:784-792. *Review*.

van Os J, Kapur S. Schizophrenia. *Lancet*. 2009;374:635-645. *Review*.

Weissman MM, Neria Y, Gameroff MJ, et al. Positive screens for psychiatric disorders in primary care: a long-term follow-up of patients who were not in treatment. *Psychiatr Serv*. 2010;61:151-159. *Emphasizes the high rate of enduring symptoms and use of emergency psychiatric services for untreated patients with positive screening.*

405

HEADACHES AND OTHER HEAD PAIN

KATHLEEN B. DIGRE

DEFINITION

Headache, which is a very common symptom, can be caused by a serious underlying abnormality but is usually a primary headache disorder, such as migraine headache, tension-type headache, cluster headache, and paroxysmal hemicrania.

EPIDEMIOLOGY

About 90% of all adults experience headache at some time in their lives, and more than 75% of children have reported significant headaches by the age of 15 years. In the United States, the cost associated with migraine is almost $17 billion annually in both direct and indirect costs. Patients at most risk for lost days of employment are those with transformed migraine and daily headache.

In large population-based studies, the relative risk of having migraine, tension-type headaches, or cluster headaches increases up to four times if a first-degree relative has the same kind of headaches. Studies of twins, especially identical twins, also show a similar susceptibility.

PATHOBIOLOGY

Headache pain is initiated by primary trigeminal afferents that innervate the blood vessels, mucosa, muscles, and tissues. Fibers from these sources coalesce in the trigeminal ganglion, especially the first division. The trigeminal afferents terminate in the primary sensory nucleus of cranial nerve V and its spinal nucleus, which has several small subnuclei, the most important of which is the subnucleus caudalis. This subnucleus receives afferents from meningeal vessels, dura-sensitive neurons, and even the upper cervical cord and then projects them to the lateral and medial thalamus by way of the spinothalamic tract and to diencephalic and brain stem regions that are involved in the regulation of autonomic functions. Thalamic nociceptive information ascends to the sensory cortex, as well as to other areas of the brain.

Although secondary headaches may stimulate the pathway by way of processes such as inflammation and compression, primary headache disorders occur spontaneously by means of chemical mediators. The sequence of events commences with peripheral activation caused by neurogenic plasma extravasation activated spontaneously or by cortical spreading depression. The trigeminocervical complex, especially the nucleus caudalis, is then activated, and patients can experience allodynia, a condition in which a nonnoxious stimulus is sensed as painful.

Aura is defined as a focal visual, sensory, or motor neurologic disturbance that may occur with or without headache. Aura is thought to occur when cortical spreading depression causes depolarization of membranes. Both neurons and glia can cause both constriction and dilation of blood vessels.

Migraine headache clearly has a genetic component. Familial hemiplegic migraine can be caused by mutations in the *CACNA1A* gene, which is located on chromosome 19p13.2-p13.1 and encodes for voltage-gated neuronal calcium channels. Many mutations are found in the *CACNA1A* gene, and other phenotypes include episodic ataxia and epilepsy. Another mutation is on *ATP1A2*, also called the familial hemiplegia migraine 2 (*FHM2*) gene, which is located on chromosome 1q21-q23 and encodes for the sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase) transport protein. A third genetic locus is the *SCN1A* gene on chromosome 2q24.3, which is a voltage-gated sodium channel. Although there are linkages to many genetic loci for more common forms of migraine, migraine and other headaches probably have multiple gene interactions with environmental factors.

CLINICAL MANIFESTATIONS

Patients with headache may describe the pain as throbbing, bandlike, or aching, but it is invariably moderate to severe and interferes with activities. The pain is frequently unilateral but can be bilateral. Migraine headache is often associated with nausea, vomiting, photophobia, and phonophobia. Other autonomic manifestations that can accompany migraine, cluster, and other headache variants include ptosis, rhinorrhea, Horner's syndrome, and facial edema. Secondary headaches may appear to be similar to tension-type or migraine headaches, but there may be "red flags" suggesting a secondary rather than a primary headache disorder (Table 405-1).

TABLE 405-1 REASONS FOR FURTHER EVALUATION TO LOOK FOR SECONDARY HEADACHES

Beginning of headaches at an older age without a previous history or a positive family history
Unexplainable and abnormal worsening of previously existing migraines
Dramatic or unusual change in character of the prodrome or the headache previously present
Headaches awakening the patient in the middle of the night (except for a cluster headache)
Headaches much worse when recumbent or with coughing, sneezing, or the Valsalva maneuver
Unusually severe headache of sudden onset ("worst headache of my life")
Focal deficits that do not disappear after the headache is over
Any abnormal neurologic finding on examination
A new headache in a patient with human immunodeficiency virus infection, malignancy, or pregnancy

DIAGNOSIS

Evaluation of an individual's headache is almost entirely based on five elements of the history. The family history helps determine whether a person has a genetic predisposition to headache. The life history of headache determines whether the headache is new or has evolved over the course of a lifetime. The attack history provides the clinical features of the headache or headaches. The medical and psychiatric history determines whether there are comorbid conditions that can cause or worsen the headache. The medication and drug history determines whether the headache could be caused by or worsened by medications or drugs that the person has ingested.

Diagnosis of the type of headache is based on the type of pain, the duration of headache, and accompanying features (Table 405-2). Secondary headaches are usually due to an underlying condition, such as a brain tumor (Chapter 195), increasing intracranial pressure, sinus disease (Chapter 434), or a vascular malformation (Chapter 415); on removing the cause, the headache generally improves. Headaches that occur at a frequency of less than 15 days a month are called episodic, whereas headaches that occur more than 15 days a month are considered chronic.

The diagnostic evaluation for headache depends on the clinical findings. If there is a typical history without any reason for further evaluation and if the findings on neurologic examination are completely normal, no further evaluation is needed. The features of the history that are most likely to predict migraine headache without a secondary disorder include a pulsating quality, duration of 4 to 72 hours, unilateral headache, nausea, and disabling headache. However, if there are atypical features of the history or any abnormality on neurologic examination, further evaluation is indicated. Patients with cluster headache types and headaches of undetermined cause need imaging to exclude secondary causes.

In patients with acute headache, computed tomography (CT) is best for assessing acute hemorrhage as the cause of the headache, whereas magnetic resonance imaging (MRI) is best for assessing most persistent headaches to look for mass lesions, evidence of intracranial hypertension or hypotension, hemosiderin (old hemorrhage), and congenital abnormalities (e.g., Chiari malformation). In individuals older than 60 years with an unexplained new or unusual headache, the erythrocyte sedimentation rate (ESR) needs to be determined to evaluate for giant cell arteritis (Chapter 78). Cerebrospinal fluid (CSF) analysis, including opening pressure, protein, glucose, cells, culture, and cytology, is indicated in patients with suspected intracranial hypertension or meningitis.

TREATMENT

Rx

Treatment of acute headache depends on the type and severity of the headache. For mild headaches, simple analgesics such as acetaminophen■ (500 to 1000 mg), aspirin (250 to 1000 mg),■ and nonsteroidal anti-inflammatory drugs■ (NSAIDs) (e.g., ibuprofen, 400 to 800 mg; naproxen sodium, 220 to 500 mg) will suffice. If the migraine headaches are moderate to severe, patients benefit from migraine-specific therapies (Table 405-3) such as triptans (sumatriptan, zolmitriptan, rizatriptan, almotriptan, naratriptan, frovatriptan, and eletriptan), ergotamine (dihydroergotamine, ergotamine tartrate), or isometheptene,■ and the combination of naproxen plus sumatriptan is better than either alone.■

TABLE 405-2 DIFFERENTIAL DIAGNOSIS OF HEADACHE

HEADACHE TYPE	GENETICS	EPIDEMIOLOGY	CHARACTERISTIC FEATURES	LENGTH	ACCOMPANYING SYMPTOMS
Migraine headache	Complex genetics but usually a family history	More frequent in women	Unilateral, bilateral; throbbing; moderate to severe; worsens with activity	Hours to days	Photophobia, phonophobia, nausea and/or vomiting
Tension-type headache	Usually a family history	Equal frequency in men and women	Tight band–like pain; bilateral; pain may be mild to moderate; improves with activity	Hours to days	No nausea or vomiting; small amount of light or sound sensitivity, but not both
Cluster headache	May have a family history	More frequent in men	Unilateral, severe pain in the face	Minutes to hour	Ipsilateral ptosis, miosis, rhinorrhea, eyelid edema, tearing
Paroxysmal hemicrania	Usually no family history	More frequent in women	Unilateral pain in the face	Minutes	Ipsilateral ptosis, miosis, rhinorrhea, eyelid edema, tearing; responds to indomethacin
Hemicrania continua	No family history	More frequent in women	Unilateral, continuous headache with episodic stabbing pains	Continuous	Ipsilateral autonomic features: ptosis, miosis, rhinorrhea, eyelid edema, tearing

TABLE 405-3 ACUTE MIGRAINE-SPECIFIC TRIPTAN MEDICATIONS FOR THE TREATMENT OF MIGRAINE

	SUMATRIPTAN	ZOLMITRIPTAN	NARATRIPTAN	RIZATRIPTAN	ALMOTRIPTAN	FROVATRIPTAN	ELETRIPTAN
Trade Name	Imitrex	Zomig	Amerge	Maxalt	Axert	Frova	Relpax
Forms	SQ, nasal (NS), oral	Oral: tablet/ZMT, NS	Oral	Oral: tablet/MLT	Oral	Oral	Oral
Dose	Oral: 50-100 mg (200 mg/24 hr max.) SQ: 4-6 mg (12 mg/24 hr max.) NS: 5-20 mg (40 mg/24 hr max.)	2.5-5 mg (10 mg/24 hr max.) 5 mg (10 mg/24 hr max.)	1-2.5 mg (5 mg/24 hr max.)	5-10 mg (30 mg/24 hr max.)	6.25-12.5 mg (25 mg/24 hr max.)	2.5 mg (7.5 mg/24 hr max.)	20-40 mg (80 mg/24 hr max.)
Half-life	2-3 hr	3-4 hr	6-8 hr	2-3 hr	3-4 hr	26 hr	4-6 hr
Crosses blood-brain barrier	–	+	+	+	+	+	+
Use with monoamine oxidase inhibitor (MAOI)	–	–	+	–	+	+	–
Good for recurrences	–	–	+	–	–	+	–
Rapid response	SQ, 10-15 min NS, 15-20 min Oral, 30 min	30 min	1-4 hr	30 min	60 min	1-4 hr	20-30 min
Menstrual migraine	+	+	+	+	+	+	+
Other	Now in combination with naproxen (Treximet)			Decrease dose by ½ with propranolol			Do not use with CYP3A4 drugs (ketoconazole and some macrolide antibiotics)

NS = nasal spray; SQ = subcutaneous.

PREVENTION

Preventive medications are recommended when headaches are frequent or severe enough to interfere with quality of life. The choice of medications should be based on the type of headache (migraine, tension type), their side effect profiles, and the patient's comorbid conditions (Table 405-4).■

PROGNOSIS

The natural history of headache depends on many factors, including the type of headache, the comorbid conditions that accompany the headache, and the success of treatment. Risk factors for chronic headache include female gender, migraine-type headaches, frequent headaches, obesity, low education and socioeconomic level, overuse of medication, stressful events, and sleep apnea.

MIGRAINE HEADACHE

DEFINITION

Migraine is an inherited headache disorder that is typically unilateral but sometimes bilateral, moderate to severe, worsened by routine physical activity, associated with nausea and vomiting, and accompanied by photophobia and phonophobia. The headache occurs anytime and persists from 4 to 72 hours. It may occur with an aura (a focal neurologic symptom that may be visual, sensory, or motor) or without an aura. Visual auras may have positive (photopsias) and negative (scotomas) features.

EPIDEMIOLOGY

The prevalence of migraine is 15 to 20% in women and 4 to 7% in men. In children the prevalence may be as high as 17% and is equal in boys and girls. At puberty, the prevalence rises in girls and remains higher throughout their lifespan. The highest prevalence occurs between the ages of 25 and 55. Migraine with aura affects 5% of the adult population, and 90% of auras are visual. Migraine is more prevalent in white persons and in those with a lower socioeconomic status or income.

Comorbid conditions that may be associated with migraine headache include epilepsy, stroke, depression, anxiety, myocardial infarction, patent foramen ovale, Raynaud's syndrome, irritable bowel syndrome, and pain disorders such as fibromyalgia. Menstruation and ovulation may increase the frequency of headache.

PATHOBIOLOGY

The aura of a migraine headache is thought to be due in part to cortical spreading depression, which is associated with a brief reduction in flow followed by hyperemia. These changes do not seem to correlate with the phase of the headache. Pain occurs when trigeminal afferents of the dura are stimulated.

TABLE 405-4 PREVENTIVE MEDICATIONS FOR HEADACHE

DRUG	RATIONAL USE	DOSAGE	SIDE EFFECTS	CONTRAINDICATIONS/ CAUTION	LEVEL OF EVIDENCE
β-Blockers: e.g., propranolol, nadolol, timolol	Migraine, anyone with elevated blood pressure	20-80 mg; may increase	Lethargy, depression	Asthma, low blood pressure	A
Calcium-channel antagonists: verapamil, amlodipine	Cluster headache, elevated blood pressure	Verapamil, 120 to 480 mg/day	Low blood pressure		B
Nonsteroidal anti-inflammatory drugs: naproxen sodium, ibuprofen	Migraine, tension-type, and menstrual migraine	Naproxen, 200-600 mg/day; ibuprofen, 600-800 mg bid-tid	Gastrointestinal	Ulcers, sensitivity, allergy	A
Indomethacin	Paroxysmal hemicrania, hemicrania continua	25 mg tid	Gastrointestinal	Ulcers	A
Tricyclic antidepressants: amitriptyline, nortriptyline, imipramine	Migraine, tension-type headache, anyone with poor sleep	10-25 mg qhs	Dry mouth, orthostatic hypotension	Sensitivity	A—amitriptyline
Anticonvulsants: topiramate valproate	Migraine, cluster headache	Topiramate, 25-50 mg bid; valproate, 250-500 mg bid	Topiramate: weight loss, kidney stones, intra-ocular hypertension Valproate: weight gain	Pregnancy	A

CLINICAL MANIFESTATIONS

Migraine headache often begins with a prodrome, which may persist for hours to days, when patients note difficulty concentrating or fatigue without headache. An aura may or may not occur but is generally present before the headache begins. The headache may be unilateral or bilateral, throbbing, moderate to severe, and worsened with activity. Accompanying clinical features include nausea, vomiting, and sensitivity to light and sound. Other clinical features include neck pain, occasionally dizziness, osmophobia, and difficulty thinking.

The migraine aura is generally visual but can be sensory or can include aphasia or vertigo. Migraine aura without headache begins with a neurologic disturbance, such as a visual phenomenon, but without a subsequent headache.

DIAGNOSIS

The diagnosis of migraine is based on the history. The differential diagnosis includes tension-type headache, but most moderate to severe headaches are migraine. In patients with a history suggestive of a secondary headache, further evaluation with MRI should be considered (see Table 405-2). However, if the headache is typical of migraine and the findings on neurologic examination are normal, no further studies are needed.

TREATMENT

Rx

Treatment of migraine is divided into treatment of the acute headache and prevention of subsequent migraine attacks. Acute treatment is most effectively accomplished with migraine-specific stepped care: a nonspecific analgesic agent, combination analgesic therapy, opioids, and aggressive migraine-specific therapy (see Table 405-3). For example, *mild attacks* can generally be treated successfully with over-the-counter analgesics such as acetaminophen (suggested dose, 650 to 1000 mg■) or NSAIDs (aspirin, 900 to 1000 mg■; ibuprofen, 1000 to 1200 mg; naproxen, 500 to 825 mg; or ketoprofen, 75 mg). During pregnancy, mild to moderate attacks can be treated with acetaminophen. Moderate headaches may respond to the combination of acetaminophen, isometheptene mucate (a mild vasoconstrictor, 65 mg), and dichloralphenazone (a mild sedative, 100 mg). Antinausea agents include prochlorperazine (10 to 25 mg) and metoclopramide (2.5 to 10 mg).

Stratification of care, including tailoring the treatment according to the type of headache, results in fewer days of disability and use of medications.■ Which migraine-specific drug will work for any individual patient depends on the patient. It is important to avoid overuse of analgesic and other medications because overuse can cause chronic daily headache in susceptible individuals. Prompt treatment improves the outcome of headache when compared with late treatment. Contraindications to use of the triptans (Table 405-3) include uncontrolled hypertension, clinical evidence of ischemic heart disease, and Prinzmetal's angina.

Opioids such as *N*-acetyl-*p*-aminophenol (APAP) with codeine, or butorphanol, benefit some patients, but meperidine is not effective. Oral opiates should not be used for chronic recurrent, primary headaches, although sometimes opiates (e.g., acetaminophen, 325 mg, with codeine, 30 mg) are the only option during pregnancy or in patients with severe vascular disease. When opiates are used, caution is required, and the associated risks of rebound headache and dependency must be recognized by both the patient and physician. Barbiturates (e.g. APAP, caffeine, and butalbital or aspirin) have not been efficacious in controlled trials but may be helpful in individual patients in whom other migraine-specific drugs cannot be used.

For *moderate to severe attacks*, options include dihydroergotamine (1 to 2 mg intranasally); oral, intranasal, or subcutaneous administration of sumatriptan (25 to 100 mg orally, 20 mg intranasally, or 4 to 6 mg subcutaneously); or sumatriptan-like drugs (e.g., naratriptan, 2.5 mg; zolmitriptan, 5 mg; rizatriptan, 10 mg; eletriptan, 40 mg; frovatriptan, 2.5 mg; or almotriptan, 12.5 mg).■ Ergotamine (2 mg sublingually or 1 to 2 mg orally), when given early in the migraine attack, can be effective if the associated nausea and peripheral vasoconstriction are tolerable. Telcagepant (300 mg), a calcitonin gene–related peptide antagonist, may be as effective as zolmitriptan (5 mg), with fewer side effects.■

For *very severe attacks*, dihydroergotamine (1 mg subcutaneously or 0.5 to 1 mg intravenously) is usually effective but generally requires an antiemetic (e.g., promethazine, 25 mg) before intravenous use. Intramuscular injections of ketorolac (60 mg) or prochlorperazine (10 to 25 mg) may be helpful. For patients who are nonresponsive or have contraindications to vasoactive abortive agents, 10 mg of intravenous prochlorperazine (10 mg delivered over a 5-minute period) is another alternative.■

PREVENTION

Preventive treatment (see Table 405-4) is often recommended when the headaches interfere with activities on 3 or more days per month, the headaches are severe or prolonged, or migraine is complicated by events such as cerebral infarction. Prophylactic options include β-adrenergic blockers, calcium-channel antagonists, NSAIDs, tricyclic antidepressants, and anticonvulsants. Other alternatives include the serotonergic drug cyproheptadine (4 to 20 mg) or the monoamine oxidase inhibitor phenelzine (30 to 60 mg). Acupuncture and biofeedback have been used successfully.■■ OnabotulinumtoxinA injection is also effective for prophylaxis.■■

PROGNOSIS

The prognosis for patients with migraine is variable. In many patients, headaches decrease in severity with age, but migraine aura without headache becomes more frequent with older age. Modification of inciting factors such as avoiding dietary triggers (tyramine, phenylethylamine, ethanol), ameliorating or preventing insomnia, and averting environmental triggers (light, sound, odor) may improve outcome. Migraines may become chronic, defined as more than 15 days per month, especially when associated with obesity and low socioeconomic status.

TENSION-TYPE HEADACHE

DEFINITION

Tension-type headache is defined as a holocranial headache without nausea or vomiting. Patients may have either photophobia or phonophobia but not both, and the headache does not worsen with activity.

EPIDEMIOLOGY

The 1-year prevalence is 14 to 93 per 100,000 individuals for episodic tension-type headache and 8.1 per 100,000 for chronic tension-type headache. Tension-type headaches are more common in women than in men, regardless of age, race, and educational level. Tension-type headaches are more common in Western countries and less frequent in Asian countries, and they are more common in white persons than in African Americans.

PATHOBIOLOGY

The pathophysiology of tension-type headache is less well understood than that of the other types of headache. Myofascial tenderness is increased, especially in chronic tension-type headache. Genetic factors are uncertain. Migraine and tension-type headache often coexist. Although tension-type headaches are not due to emotion or muscle contraction, triggers of a tension-type headache are similar to those associated with migraine: stress, fatigue, and lack of sleep. Comorbid conditions in patients with tension-type headache include depression and anxiety in more than 50% of individuals.

CLINICAL MANIFESTATIONS

Tension-type headaches are usually mild to moderate in severity, and most individuals do not seek care. Tension-type headache can be episodic, occurring less than 15 days per month, or chronic, occurring more than 15 days per month. In many patients headaches remain episodic, but about 25% progress to chronic headache. Of the patients with chronic tension-type headache, about a quarter to a third continue as chronic, half can improve to episodic, and in about a quarter medication overuse headache can develop. Episodic tension-type headaches can last minutes, hours, or days.

DIAGNOSIS

Headaches that can be misdiagnosed as tension-type headache include migraine, hemicrania continua, new daily persistent headache, and headaches caused by brain tumors, elevated or low intracranial pressure, or giant cell arteritis. A careful history is the best way to distinguish other types of headaches.

TREATMENT

Rx

Episodic tension-type headaches are generally treated successfully with acetaminophen (650 to 1000 mg) or NSAIDs (aspirin, 900 to 1000 mg; naproxen, 250 to 500 mg; ibuprofen, 200 to 800 mg; or ketoprofen, 12.5 to 75 mg). However, analgesic use for more than 3 days per week can worsen headaches.

PREVENTION

Chronic tension-type headaches may benefit from prophylactic treatment with amitriptyline (starting with 10 mg at bedtime and increased slowly up to 100 mg until the patient improves or intolerable side effects develop), nortriptyline (25 to 100 mg each evening), doxepin (25 to 75 mg/day), maprotiline (10 to 25/mg/day), or fluoxetine (10 to 20 mg/day). Muscle relaxants, physical therapy, and acupuncture are also useful.

PROGNOSIS

Tension-type headache has a variable prognosis. Adolescents with tension-type headache and two or more psychiatric factors (e.g., depression and anxiety) have a worse prognosis.

CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

DEFINITION

Trigeminal autonomic cephalalgias, including cluster headaches, are unilateral headaches associated with ipsilateral autonomic features. Other trigeminal autonomic cephalalgias include paroxysmal hemicrania, which is characterized by bouts of headache that persist for 5 to 30 minutes, is generally unilateral, and usually occurs in women; they typically respond to indomethacin. Hemicrania continua, another indomethacin-responsive headache that is seen in both men and women, is characterized by continuous unilateral pain and mild associated autonomic features; it is frequently observed in conjunction with chronic daily headache but not with trigeminal autonomic cephalalgia. Short unilateral neuralgiform headache with conjunctival injection and tearing is a rare trigeminal autonomic cephalalgia that occurs in men, and the individual headache attack persists for only a very short time.

EPIDEMIOLOGY

Cluster headache occurs in 56 to 401 per 100,000 persons and is more frequent in men (3:1 to 7:1). Attacks usually begin between 20 and 30 years of age. Paroxysmal hemicrania occurs in 56 to 381 per 100,000 persons; it affects women more often (2:1) and can begin at any age but usually commences at 34 to 41 years. Short unilateral neuralgiform headache with conjunctival injection and tearing is rare, with a slight male preponderance (2:1).

PATHOBIOLOGY

There appears to be a genetic predisposition for cluster headache. Imaging studies such as positron emission tomography and functional MRI show inferior posterior hypothalamic activation at the onset of cluster headache and other trigeminal autonomic cephalalgias. In addition, the trigeminovascular complex and the cranial autonomic system are activated. The pathophysiology of hemicrania continua is unknown, and there is debate whether it is associated with hypothalamic involvement or whether it resembles migraine.

CLINICAL MANIFESTATIONS

Cluster headaches are almost always unilateral, rarely bilateral, and have characteristic ipsilateral autonomic features, commonly including lacrimation and conjunctival injection and sometimes including nasal congestion, rhinorrhea, ptosis, miosis, flushing, and eyelid edema (Table 405-5). The location of the pain is usually behind or above the eye or in the temple, but other areas of pain can include the forehead, cheek, teeth, or jaw. The pain reaches its maximum intensity in about 9 minutes and tends to end abruptly. Attacks occur one to eight times a day and are usually described as "boring" or "stabbing" excruciating pain that persists for 15 minutes to 2 hours. Migraine symptoms may coexist, including unilateral photophobia, phonophobia, and rarely, an aura. Unlike migraine patients, who usually try to rest, patients with cluster headaches pace and are unable to sit or lie down. Cluster headaches, when precipitated by alcohol, histamine, or nitroglycerin, have a daily periodicity and may also have a seasonal periodicity. For example, episodic cluster headache may occur annually or every 2 years, often in the same season each time. Chronic cluster headache may occur without a remission.

Paroxysmal hemicrania is pain of short duration, usually 2 to 30 minutes, and occurs unilaterally around the eye, temple, or maxillary region, sometimes precipitated by head movements. Autonomic features similar to cluster headache can occur. The usual attack rate is up to 40 episodes each day. Bouts of pain may be episodic, separated by a remission, but most patients have daily chronic paroxysmal hemicrania without a remission.

Short unilateral neuralgiform headache with conjunctival injection and tearing attacks are unilateral and consistently on the same side. Although the pain is excruciating, the attack is brief, usually seconds; most patients are free of pain between attacks, although a dull ache can be present. Associated autonomic features include ipsilateral conjunctival injection and tearing.

DIAGNOSIS

The diagnostic criteria for *cluster headache* include severe unilateral orbital, supraorbital, or temporal pain persisting for 15 to 180 minutes with at least one of the following: ipsilateral conjunctival injection or lacrimation, nasal congestion or rhinorrhea, eyelid edema, forehead and facial sweating, miosis with or without ptosis, and restlessness or agitation. Attacks occur between once and as often as eight times each day. There is no other cause of the disorder.

Paroxysmal hemicrania is defined by unilateral pain persisting for 2 to 30 minutes, about 5 times each day, with one or more autonomic features such as conjunctival injection, nasal congestion, eyelid edema, forehead and facial sweating, and miosis or ptosis (or both). Complete prevention may be achieved with indomethacin.

Hemicrania continua is a unilateral headache that occurs daily and continuously without pain-free periods; its intensity is moderate with exacerbations of severe pain. During the exacerbations, at least one autonomic feature is present and is ipsilateral to the pain: conjunctival redness, lacrimation, nasal congestion, ptosis, or miosis.

Short unilateral neuralgiform headache with conjunctival injection and tearing is diagnosed by unilateral orbital, supraorbital, temporal stabbing pain persisting for 5 to 240 seconds at a frequency of 3 to 200 per day. It is associated with conjunctival injection and tearing.

TABLE 405-5 DISTINGUISHING CHARACTERISTICS OF THE TRIGEMINAL AUTONOMIC CEPHALALGIAS

CHARACTERISTIC	CLUSTER	PAROXYSMAL HEMICRANIA	HEMICRANIA CONTINUA	SHORT UNILATERAL NEURALGIFORM HEADACHE WITH CONJUNCTIVAL INJECTION AND TEARING
Sex—F:M	1:3-7	2:1	2:1	1:2
Unilateral	+	+	+	+
Attack frequency	1-8/day	1-40/day		3-200/day
Attack duration	15-80 min	2-30 min	Continuous with episodic exacerbations	5-240 sec
Autonomic features	+	+	+ with exacerbations	+
Indomethacin effect	–	+++	+++	–
Acute treatment at onset	Oxygen, sumatriptan SQ, DHE nasal spray; sumatriptan or zolmitriptan nasal spray (A level evidence)	None	None	None
Preventive medications	Verapamil, lithium, corticosteroids, anticonvulsants (A level)	Indomethacin (A level)	Indomethacin (A level)	Lamotrigine, topiramate, gabapentin (B level)

DHE = dihydroergotamine.

An imaging procedure such as MRI is indicated for all patients with cluster headaches or the other trigeminal autonomic cephalalgias because they can be caused by a primary lesion such as an infection (Chapters 420 through 422), vascular malformation (Chapter 415), or neoplasm, especially a pituitary tumor (Chapter 195). Other possibilities in the differential diagnosis include migraine, hypnic headache (rare, short-lasting headaches exclusively during sleep in the elderly), and trigeminal neuralgia.

TREATMENT

Rx

Because the course of the headache is brief, oral medications take too long to work to be effective. The use of 100% oxygen at 7 to 10 L/min for 15 to 30 minutes benefits some patients.[1A] Sumatriptan or zolmitriptan nasal spray or sumatriptan subcutaneously (4 to 6 mg) can be helpful. Dihydroergotamine can be helpful when given nasally, intramuscularly, or even intravenously. Refractory cases may respond to occipital nerve stimulation. Short unilateral neuralgiform headache with conjunctival injection and tearing attacks is so short that there are no medications to treat it acutely.

PREVENTION

Preventive medications should be started at the beginning of a cluster bout. Verapamil, 240 to 480 mg, is the drug of choice. Lithium (300 mg twice daily) is another alternative. Corticosteroids (e.g., prednisone, 40 mg/day, or dexamethasone, 4 mg twice daily for 2 weeks) act rapidly to prevent cluster headache and can be used acutely while other preventive medications are started. Valproic acid (500 to 1500 mg/day in divided doses), topiramate (50 to 100 mg/day), melatonin (4 mg at bedtime), and gabapentin (300 mg three times daily) are sometimes beneficial. Surgical approaches, including occipital nerve stimulators, hypothalamic stimulation, and destructive procedures, are sometimes necessary for this disabling headache.

Paroxysmal hemicrania and hemicrania continua respond to daily indomethacin (25 to 50 mg three times daily). If the patient cannot tolerate indomethacin, calcium-channel blockers (e.g., verapamil, 240 to 480 mg/day) may be helpful. Preventive treatment of short unilateral neuralgiform headache with conjunctival injection and tearing includes lamotrigine (100 to 400 mg/day), topiramate (50 to 100 mg), gabapentin (300 to 900 mg), or intravenous lidocaine (starting at 2 mg/min with cardiac monitoring).

PROGNOSIS

Cluster headache is often a lifelong problem, but remissions may persist for longer periods as the patient ages. The other trigeminal autonomic cephalalgias are probably lifelong; nevertheless, symptomatic treatment combined with preventive medications is helpful.

CHRONIC DAILY HEADACHE

DEFINITION

Though not a specific disorder, chronic daily headache, defined as a headache that is present on more than 15 days per month, is challenging for both patients and physicians. These headaches may be chronic migraine, chronic tension-type headache, new daily persistent headache, or chronic cluster headache, with or without overuse of medications.

EPIDEMIOLOGY

About 4 to 5% of the population suffers from chronic daily headache, most commonly chronic tension type. Trigger factors such as a previous infection, mild head injury, or stressful life event can be present in 40 to 60% of patients with new daily persistent headache. Risk factors for chronic daily headache include medication overuse, history of migraine headache, depression, female gender, obesity, snoring, stressful life events, and low educational level.

PATHOBIOLOGY

The pathophysiology of chronic daily headache is probably related to migraine, with both central and peripheral abnormalities. Once migraine has been prolonged and headache occurs on a daily basis, allodynia, a sense that a usually nonpainful stimulus is becoming painful, often develops. Central sensitization associated with painful structures around the head increases.

CLINICAL MANIFESTATIONS

New daily persistent headache is characterized by daily occurrence and an unrelenting course. It is generally bilateral, nonpulsating, mild to moderate, and associated with no more than one of the following: photophobia, phonophobia, or nausea. Severe nausea or vomiting is rare. New daily persistent headache can be disabling.

Chronic daily headache is often associated with profound psychiatric comorbidity, especially depression and anxiety, and psychiatric comorbidity predicts intractability.

Use of an opiate for more than 8 days per month, especially in men, use of barbiturates for more than 5 days per month, especially in women, or use of triptans for more than 10 to 14 days per month can often lead to chronic migraine headache or at least worsening of headaches.

DIAGNOSIS

Diagnosis of chronic daily headache is based on the history. It is important to identify the underlying type of primary chronic daily headache: chronic migraine, chronic tension-type headache, new daily persistent headache, or hemicrania continua. Of note is that headaches of less than 4 hours' duration can also be chronic and daily: cluster headache; paroxysmal hemicrania; hypnic headaches, occurring every night, usually in the elderly; and episodic stabbing headache. It is most important to exclude secondary headaches, including post-traumatic headache, headaches associated with vascular disorders (e.g., giant cell arteritis, arteriovenous malformations, carotid and vertebral artery dissections), and headaches associated with nonvascular disorders (e.g., intracranial hypertension, intracranial hypotension, infections). MRI and laboratory studies (e.g., ESR in an elderly individual) are commonly recommended. Lumbar puncture to assess intracranial pressure may also be indicated in selected patients.

TREATMENT

Rx

The most common cause of chronic daily headache is overuse of medications, so patients must be weaned off the overused symptomatic medication. Treatment of underlying depression, anxiety, and pain may also be helpful. Occasionally, hospital admission is necessary to break the headache cycle. Acute migraine–specific treatments (see earlier), especially intravenous dihydroergotamine (0.5 to 2 mg), are helpful in terminating migrainous attacks.

PREVENTION

Medications that are helpful in preventing chronic daily headache include tricyclic antidepressants, selective serotonin re-uptake inhibitors if patients are depressed, anticonvulsants, β-blockers, and calcium-channel blockers (see Tables 405-3 and 405-4). For hemicrania continua, indomethacin (25 to 50 mg three times daily) is the preferred treatment.

PROGNOSIS

The prognosis depends on the underlying headache diagnosis. If medication overuse is the cause but the patient is successfully detoxified, about 75% of patients improve when treated with preventive medications. Treatment may fail if the diagnosis is incorrect or because of continued overuse of medications, overuse of caffeine, lack of sleep, dietary or other life triggers, hormonal factors, or psychiatric factors.

SINUS HEADACHE

Rhinosinusitis (Chapter 434) is characterized by inflammation or infection of the nasal mucosa and sinuses. The sinuses themselves are relatively insensate, but ducts, turbinates, and ostia are the painful structures.

Headaches attributed to rhinosinusitis are frontal headaches with pain in the face, ears, or teeth. The onset of pain is simultaneous with the rhinosinusitis, and the headache and face pain resolve within 7 days after successful treatment. The diagnosis requires imaging (see Fig. 434-4) and clinical evidence that support the diagnosis of acute or chronic rhinosinusitis, and most headaches that are initially thought to result from sinus disease are found to be migraine or tension-type headache.

Treatment of acute sinusitis (Chapter 434) should resolve the headache. If it does not, an underlying primary headache disorder is likely.

SECONDARY CAUSES OF HEADACHES

Temporal (Giant Cell) Arteritis

Temporal arteritis (Chapter 279) is an inflammatory process seen mainly in elderly individuals. Headache is one of the most common features. Its incidence is approximately 12 per 100,000 and increases with age to 51 per 100,000 in individuals over 80 years of age. It affects women more often than men (3:1) and is more common in white individuals, especially those of Scandinavian and British descent. It is associated with polymyalgia rheumatica.

The headache has no specific feature, but the pain is usually continuous, generalized, and occasionally throbbing. The temples are generally painful, and patients complain of pain when performing certain activities of daily living, such as chewing food or combing their hair. Transient monocular blindness and diplopia can occur.

Elevation of the ESR and C-reactive protein occurs almost invariably. The diagnosis is made by finding giant cells in a temporal artery biopsy specimen. Immediate treatment with corticosteroids, sometimes before the biopsy result is available, is necessary in doses between 40 and 80 mg daily, with the dose then titrated downward while monitoring the ESR. Used early enough, corticosteroids generally prevent the complications of temporal arteritis, including blindness. The disorder can be long lasting.

Intracranial Hypertension

Intracranial hypertension can be primary and idiopathic in obese women of childbearing age. Secondary intracranial hypertension can be seen with cerebral venous thrombosis (Chapters 414 and 421), masses in the brain (Chapter 195), hydrocephalus, or other intracranial processes.

Idiopathic increased intracranial pressure occurs in 20 per 100,000 individuals (15 to 55 years of age) who are obese. Women are affected more frequently than men. Onset is usually in young adulthood. The cause of the increased pressure is either poor CSF absorption, as is thought to be the problem in idiopathic intracranial hypertension, venous hypertension, as is seen in venous thrombosis, or a mass that causes an increase in pressure.

CLINICAL MANIFESTATIONS

Idiopathic intracranial hypertension is characterized by headache in more than 90% of individuals, about 90% of whom are obese. Other symptoms include pulsatile tinnitus, transient visual obscurations, and double vision.

On examination, papilledema (see Fig. 431-27) may be found. The remainder of the general and neurologic examination is usually normal in patients with idiopathic intracranial hypertension, but abnormalities on examination may point to a secondary cause, such as underlying venous sinus thrombosis (Chapter 414), ischemic stroke, central nervous system infection (Chapter 420), or brain tumor (Chapter 195). Although some individuals have idiopathic intracranial hypertension for years, the condition can be self-limited. In about a third of patients, permanent visual sequelae related to the effect of papilledema develop.

DIAGNOSIS

The diagnosis of intracranial pressure is made by the presence of clinical features, as well as by signs such as papilledema (see Fig. 431-27). MRI is necessary to exclude secondary causes of increased intracranial pressure. MR or CT venography is often needed to exclude venous sinus thrombosis (Chapter 414). Lumbar puncture must be performed unless patients have a contraindication such as an intracranial mass lesion, and CSF pressure should be measured. The diagnosis can be made if the pressure is elevated (CSF > 200 mm H_2O), but the fluid itself is normal. Visual fields must be examined formally because visual acuity is not affected until late in the course of the disorder.

TREATMENT AND PROGNOSIS Rx

Although no controlled trials of treatment of intracranial hypertension have been conducted, acetazolamide in doses of 500 to 1000 mg/day appears to be useful for the treatment of idiopathic intracranial hypertension. Any underlying secondary cause should also be treated. Weight loss may be beneficial in obese subjects. The prognosis of patients with idiopathic intracranial hypertension is good with treatment, but up to a third of inadequately treated patients can experience permanent loss of visual fields or visual acuity.

Intracranial Hypotension

Intracranial hypotension causes a headache that is characteristically better when the patient is supine and worse when the patient is upright. It can be primary (spontaneous) or secondary to another underlying cause, most commonly a previous lumbar puncture.

Intracranial hypotension was once considered rare, but modern imaging techniques suggest an incidence of about 5 per 100,000 per year.

PATHOBIOLOGY

The cause of primary intracranial hypotension is thought to be a small leak or tear in the dura, usually in the lumbar region around cystic structures called Tarlov's cysts. The cause of intracranial hypotension may not be not the tear itself, but low epidural venous pressure that assists in development of the lower pressure and hence the leak.

CLINICAL MANIFESTATIONS

Intracranial hypotension is characterized clinically by a positional headache. The location of the pain is variable, and the most constant characteristic is the orthostatic change in the pain. Double vision can develop if hindbrain herniation occurs.

DIAGNOSIS

The diagnosis of intracranial hypotension is made by MRI showing pachymeningeal enhancement and thickening, along with herniation of the hindbrain. Lumbar puncture may also show low (<50 mm H_2O) CSF pressure. The differential diagnosis includes chronic daily headache, migraine, or a secondary headache. The diagnosis is confirmed if a CSF leak is demonstrated by isotope studies or CT myelography.

TREATMENT AND PROGNOSIS Rx

Treatment of CSF leaks includes bedrest, caffeine, and fluids. For post–dural puncture headache, an epidural blood patch improves the symptoms.[1,2] Surgical repair is rarely required. With treatment, the symptoms and MRI findings should resolve completely.

Trigeminal Neuralgia

Trigeminal neuralgia is a distinct, excruciatingly painful condition provoked by sensory stimuli in the distribution of the trigeminal nerve. Trigeminal neuralgia occurs in 4 per 100,000 individuals, most commonly in persons

between 50 and 70 years of age and in women slightly more than in men (1.5:1).

In younger individuals, multiple sclerosis (Chapter 419) can be associated with the condition. In older individuals, an ectatic artery in the vertebrobasilar system can cause the syndrome. The trigeminal nerve root entry zone is thought to be the site of pathology. Either demyelination or compression of this region increases the firing of trigeminal afferents. When a specific cause can be defined, the term "symptomatic trigeminal neuralgia" is often used.

CLINICAL MANIFESTATIONS

Trigeminal neuralgia pain is characteristically sharp, shooting, and electric shock–like in the distribution of the trigeminal nerve: cheek (V2), chin or lower teeth (V3), and around the eye (V1). A combination of V2 and V3 is the most common. The paroxysms are brief—seconds to up to 2 minutes. Some patients have a dull and continuous interictal pain, whereas most have only staccato-like volleys of pain. Pain is usually triggered by stimuli such as touching the face, brushing the teeth, air moving across the face, or masticating food. Once a volley of pain is triggered, there is usually a refractory period in which pain will not occur.

DIAGNOSIS

Diagnostic criteria include paroxysmal attacks of pain persisting for a second to 2 minutes and affecting one or more divisions of the trigeminal nerve. To make the diagnosis, the pain must be intensely sharp, stabbing, or precipitated by a trigger. Each attack is stereotypical, and there are usually no other neurologic defects. Idiopathic trigeminal neuralgia by definition has no causative lesion, whereas symptomatic trigeminal neuralgia has a cause, such as vascular compression of the trigeminal nerve root exit zone. The differential diagnosis includes trigeminal autonomic cephalgia, which has autonomic accompaniments that are not associated with trigeminal neuralgia. Atypical facial pain and Tolosa-Hunt syndrome, an inflammatory syndrome of the anterior cavernous sinus, are also included in the differential.

TREATMENT

Rx

Trigeminal neuralgia is treated with medications or surgery. Carbamazepine (400 to 1200 mg) is considered the first-line agent for the neuralgia.[14] Phenytoin (200 to 300 mg), baclofen (40 to 80 mg), clonazepam (2 to 6 mg), valproic acid (500 to 1500 mg), lamotrigine (100 to 400 mg), gabapentin (900 to 1800 mg), oxcarbazepine (300 to 1800 mg), and topiramate (50 to 200 mg) are also used. Surgical treatments include microvascular decompression, which may alleviate the symptoms and preserve sensory function. Other treatments include partial destruction of the trigeminal nerve with heat (radio frequency lesions) or with glycerol (chemical destruction).

PROGNOSIS

Patients with trigeminal neuralgia can have spontaneous or medication-induced remissions. Microvascular decompression is often curative.

Glossopharyngeal Neuralgia

Less common than trigeminal neuralgia, glossopharyngeal neuralgia is unilateral pain in the distribution of the glossopharyngeal and vagal nerves in the ear, jaw, throat, and tongue. The cause is thought to be compression of the glossopharyngeal nerve by blood vessels, tumor, aneurysm, or infection. The pains are paroxysmal and persist for less than seconds to 2 minutes, but patients can experience 30 to 40 attacks in a day. Like trigeminal neuralgia, the pain is triggered by chewing, swallowing, or talking. Pharmacologic therapy is similar to that for trigeminal neuralgia. Rarely, surgical therapy and microvascular decompression are required.

Grade A

1. Prior MJ, Codispoti JR, Fu M. A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache. *Headache*. 2010;5:819-833.
2. Kirthi V, Derry S, Moore RA, et al. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2010;4:CD008041.
3. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. *Eur J Neurol*. 2009;16:968-981.
4. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA*. 2007;297:1443-1454.
5. Silberstein SD: Preventive migraine treatment. *Neurol Clin*. 2009;27:429-443.
6. Lipton RB, Stewart WF, Stone AM, et al. Disability in Strategies of Care Study Group. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: a randomized trial. *JAMA*. 2000;284:2599-2605.
7. Bigal ME, Krymchantowsky AV, Ho T. Migraine in the triptan era: progresses achieved, lessons learned and future developments. *Arq Neuropsiquiatr*. 2009;67(2B):559-569.
8. Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene–related peptide receptor, compared with zolmitriptan for acute migraine: a randomized, controlled, parallel-treatment trial. *Lancet*. 2008;372:2115-2123.
9. Kostic MA, Gutierrez FJ, Rieg TS, et al. A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department. *Ann Emerg Med*. 2010;56:1-6.
10. Linde K, Allais G, Brinkhaus B, et al. Acupuncture for migraine prophylaxis. *Cochrane Database Syst Rev*. 2009;1:CD001218.
11. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*. 2010;50:921-936.
12. Fumal A, Schoenen J. Tension-type headache: current research and clinical management. *Lancet Neurol*. 2008;7:70-83.
13. Linde K, Allais G, Brinkhaus B, et al. Acupuncture for tension-type headache. *Cochrane Database Syst Rev*. 2009;1:CD007587.
14. Bennett MH, French C, Schnabel A, et al. Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. *Cochrane Database Syst Rev*. 2008;3:CD005219.
15. Boonmak P, Boonmak S. Epidural blood patching for preventing and treating post–dural puncture headache. *Cochrane Database Syst Rev*. 2010;1:CD001791.
16. Gronseth G, Cruccu G, Alksne J, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. *Neurology*. 2008;71:1183-1190.

SUGGESTED READINGS

Garza I, Schwedt TJ. Diagnosis and management of chronic daily headache. *Semin Neurol*. 2010;30:154-166. *Review*.

Halker RB, Hastriter EV, Dodick DW. Chronic daily headache: an evidence-based and systematic approach to a challenging problem. *Neurology*. 2011;76:S37-S43. *Review*.

Ju YE, Schwedt TJ. Abrupt-onset severe headaches. *Semin Neurol*. 2010;30:192-200. *Emphasizes serious causes, including subarachnoid hemorrhage, intracranial aneurysm, cervical artery dissection, and cerebral venous sinus thrombosis*.

Leone M, Bussone G. Pathophysiology of trigeminal autonomic cephalalgias. *Lancet Neurol*. 2009;8:755-764. *Review*.

Mathew PG, Garza I. Headache. *Semin Neurol*. 2011;31:5-17. *Review*.

406

TRAUMATIC BRAIN INJURY AND SPINAL CORD INJURY

GEOFFREY S. F. LING

EPIDEMIOLOGY

Traumatic brain injury and traumatic spinal cord injury are all too common preventable diseases. Traumatic brain injury is the leading cause of traumatic death and disability (Chapter 112). Approximately 1.4 million cases per year result directly in about 52,000 deaths in the United States annually—almost a third of all injury-related deaths. The majority of traumatic brain injuries are due to falls (Chapters 24), motor vehicle accidents, and assaults. An additional approximately 11,000 cases of severe spinal cord injury occur each year in the United States, primarily the result of motor vehicle accidents, falls, sports-related injuries, and work-related accidents (Chapter 112). The majority of patients with traumatic brain and spinal cord injuries are young adult men.

During the past 20 years, the marked improvement in overall mortality associated with traumatic brain and spinal cord injuries can largely be ascribed to improved care in intensive care units, early aggressive neurosurgical intervention, and prevention of long-term conditions such as deep vein thrombosis and decubitus ulcers. The almost 5.5 million survivors of traumatic brain and spinal cord injuries in the United States often require extended rehabilitation. Because the majority of these patients are young and otherwise in good physical health at the time of injury, many need chronic care for decades. Even minor injury can lead to major disability; approximately 75% of patients who are classified as having mild to moderate traumatic brain injury continue

to have residual symptoms months later, and many of these patients are unable to return to gainful employment.

PATHOBIOLOGY

Traumatic injury to the central nervous system has two phases. The first, neuronal injury, is a direct result of the initiating traumatic event. The second or late phase, which is caused by multiple neuropathologic processes, can continue for days to weeks after the initial insult.

Primary Injury Phase

The primary injury phase is immediate, and its damage, which can cause death almost instantaneously, is often complete by the time that medical care can be instituted. In closed compartment injury to the head or spine, the direct impact of neuronal tissue against the bony vault and shearing of neurovascular structures result in wounding. Because the neuronal structures reside in a fluid-filled compartment, these structures often lag behind the bony structure as it moves during sudden stopping of the body in motion. Thus, the structures will strike both anteriorly and posteriorly against the inner bony table, and a coup-contrecoup lesion will result. If a rotational component is present, the structures will torque, twist, and shear, thereby causing diffuse axonal injury. Motor vehicle accidents are particularly injurious because of the sudden deceleration. In penetrating lesions, the moving projectile will tear neural, vascular, and support structures as it traverses through the brain or spinal cord. If the projectile is moving at high velocity, such as a bullet, the vacuum created by its wake will give rise to tissue cavitation. The temporary cavity, which will ultimately collapse, may be many-fold larger than that of the projectile itself; the transient expansion of surrounding tissue will be sufficient to cause substantial irreversible damage.

Secondary Injury Phase

The delayed secondary phase of injury, which begins quickly after the primary phase and can continue for a prolonged period, involves both neurons and glia. Most neurologic injury is thought to be related to this secondary injury, when "neuron suicide" is caused by processes such as hypoxia, ischemia, and inflammation and the effects of free radicals, excitatory amino acids, and certain ions (e.g., calcium).

The injured brain is more susceptible to hypoxic-ischemic states. The most commonly affected areas are the hippocampus and "watershed" areas. It has been hypothesized that delayed neurologic compromise can be attributed to delayed ischemia.

Diffuse microvascular damage is due to early loss of cerebral vascular autoregulation and loss of integrity of the blood-brain barrier, with resulting endothelial changes such as the formation of intraluminal microvilli. Although the clinical significance of this injury is uncertain, it may play a role in the development of cerebral edema.

Diffuse axonal injury, which consists of shearing of axons in cerebral white matter, causes neurologic deficits such as nonfocal encephalopathy. The consequences of this type of injury can be delayed for up to 12 hours after the initial trauma.

CLINICAL MANIFESTATIONS

Traumatic Brain Injury

The signs and symptoms of traumatic brain injury vary with its severity. Patients suffering from mild traumatic brain injury often experience headache, difficulty concentrating, anxiety, and disrupted sleep; findings on clinical examination are normal, but detailed neuropsychological testing may reveal mild cognitive abnormalities. With moderate traumatic brain injury, patients may have an abnormal sensorium, motor and sensory involvement, and impaired language; the results of neurologic examination will be abnormal. In very severe traumatic brain injury, patients are comatose; at best, they may exhibit some eye opening and decorticate or decerebrate posturing to stimulation.

Focal injuries cause neurologic deficits related to the site of impact. The orbitofrontal and anterior temporal lobes are most commonly affected. Extreme vigilance is needed to recognize the development of delayed hematomas and edema, which can be manifested days later.

Traumatic brain injury may be accompanied by a transient increase in systemic arterial pressure. Apnea or cerebral dysfunction may develop. Depending on the degree of injury, spontaneous resolution may be delayed, and laceration of the microvasculature will exacerbate this injury.

Traumatic Spinal Cord Injury

Spinal Cord Syndromes

There are three main spinal cord syndromes: Brown-Séquard, central cord, and anterior cord syndrome. In Brown-Séquard syndrome, the deficits are referable to a lesion of a lateral half of the cord; findings consist of loss of ipsilateral motor, touch, proprioception, and vibration sensation as well as contralateral pain and temperature sensation. Central cord or "man in a barrel" syndrome is manifested as bilateral loss of motor function involving the upper extremities but sparing the lower extremities. Proximal weakness is greater than distal weakness. Pain and temperature sensation is generally reduced, whereas proprioception and vibration are usually spared. Anterior cord syndrome is manifested by deficits referable to bilateral anterior and lateral spinal cord columns or funiculi. There is loss of touch, pain, and temperature sensation and motor function below the level of the lesion, but the posterior column functions of proprioception and vibratory sensation remain intact.

Spinal Shock

After acute traumatic spinal cord injury, patients may suffer from spinal shock, or temporary loss of spinal reflexes below the level of injury. Clinically, there is loss of deep tendon reflexes, the bulbocavernosus reflex, and the anal wink. In high cervical injuries, the lower reflexes (bulbocavernosus and anal wink) may be preserved. Some patients demonstrate the Schiff-Sherrington phenomenon, in which reflexes are affected above the level of injury. Loss of autonomic reflexes can lead to neurogenic shock, ileus, and urinary retention.

DIAGNOSIS

Traumatic Brain Injury

The Glasgow Coma Scale score (Table 406-1) should be calculated promptly, and a detailed neurologic examination should be performed to determine the extent of injury and the severity of impairment. Important clinical signs of occult injury may be revealed on a general physical examination. For example, a scalp laceration should be palpated for evidence of an underlying skull fracture. Periorbital ecchymosis ("raccoon eyes") and postauricular ecchymosis ("Battle's sign") are concerning for a basal skull fracture. A clear or blood-tinged watery discharge from the nose or ear may be a cerebrospinal fluid leak.

Intracranial bleeding caused by traumatic brain injury includes subdural hematoma, epidural hematoma, intraparenchymal hemorrhage, contusion, and traumatic subarachnoid hemorrhage (Chapter 415). The most common is subdural hematoma, which is the basis of approximately 50% of admissions for head injury. Epidural hematoma accounts for about 3%. An associated skull fracture, especially at the temporoparietal junction, increases the incidence of epidural hematoma, usually by disrupting the middle meningeal artery.

Imaging

A computed tomography (CT) scan without contrast should be obtained as soon as possible after the initial clinical assessment. The need for neuroimaging is best determined by use of the Glasgow Coma Scale score and a validated clinical prediction instrument such as the Canadian CT Head Rule (Table 406-2). In any patient thought to have suffered a head injury, the

TABLE 406-1 GLASGOW COMA SCALE SCORE

BEST EYE RESPONSE	BEST VERBAL RESPONSE	BEST MOTOR RESPONSE
1 = No eye opening	1 = No verbal response	1 = No motor response
2 = Eye opening to pain	2 = Incomprehensible sounds	2 = Extension to pain
3 = Eye opening to verbal command	3 = Inappropriate words	3 = Flexion to pain
4 = Eyes open spontaneously	4 = Confused 5 = Oriented	4 = Withdrawal from pain 5 = Localizing pain 6 = Obeys commands

To calculate the score, sum the numbers from each of the three columns.

TABLE 406-2 DECISION RULES TO DETERMINE INDICATIONS FOR CT SCAN IN PATIENTS WITH MINOR HEAD INJURY

			*Reported Validity (%)**	
STUDY	**POPULATION OF PATIENTS**	**INDICATIONS FOR CT SCAN**	**SENSITIVITY**	**SPECIFICITY**
Canadian CT Head Rule[†]	GCS score of 13-15, loss of consciousness, no neurologic deficit, age ≥16 yr	High-risk patients: GCS score <15 at 2 hr after injury, suspected skull fracture, any sign of basal skull fracture, vomiting (≥2 times), age ≥65 yr[‡] Medium-risk patients: retrograde amnesia >30 min, dangerous mechanism (pedestrian vs. motor vehicle, ejection from motor vehicle, fall from height >1 m or 5 stairs)[§]	100	24.5
New Orleans Criteria[¶]	GCS score of 15, loss of consciousness, no neurologic deficit, no seizure, no anticoagulation, age >3 yr	Headache, vomiting, seizure, intoxication, short-term memory deficit, age ≥ 60 yr, or injury above the clavicles	98.4	49.6

*Validity for identification of patients with traumatic CT findings.
[†]Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor head injury. *Lancet.* 2001;357:1391-1396.
[‡]High-risk patients in whom a CT scan is mandatory.
[§]Medium-risk patients in whom a CT scan is recommended but close clinical observation is an alternative.
[¶]Haydel MJ, Preston CA, Mills TJ, et al. Indications for computed tomography in patients with minor head injury. *N Engl J Med.* 2000;343:100-105.
CT = computed tomography; GCS = Glasgow Coma Scale.

TABLE 406-3 AMERICAN ACADEMY OF NEUROLOGY: DIAGNOSIS AND MANAGEMENT OF CONCUSSION

GRADE 1 (MILD)*	**GRADE 2 (MODERATE)[†]**	**GRADE 3 (SEVERE)[‡]**
Remove from duty/work/play	Remove from duty for the rest of the day	Take to the emergency department
Examine immediately and at 5-minute intervals	Examine frequently for signs of CNS deterioration Physician's neurologic examination as soon as possible (within 24 hours)	Neurologic evaluation, including appropriate neuroimaging
May return to duty/work if clear within 15 minutes	Return to duty after 1 full asymptomatic week (after being cleared by the physician)	Consider hospital admission

GRADE OF CONCUSSION	**RETURN TO PLAY/WORK**
Grade 1 (first)	15 minutes
Grade 1 (second)	1 week
Grade 2 (first)	1 week
Grade 2 (second)	2 weeks
Grade 3 (first) (brief loss of consciousness)	1 week
Grade 3 (first) (long loss of consciousness)	2 weeks
Grade 3 (second)	1 month
Grade 3 (third)	Consult a neurologist

*Mild: transient confusion, no loss of consciousness, symptoms associated with concussion (such as amnesia) or mental status changes lasting less than 15 minutes.
[†]Moderate: transient confusion, no loss of consciousness, symptoms lasting longer than 15 minutes.
[‡]Severe: any loss of consciousness.

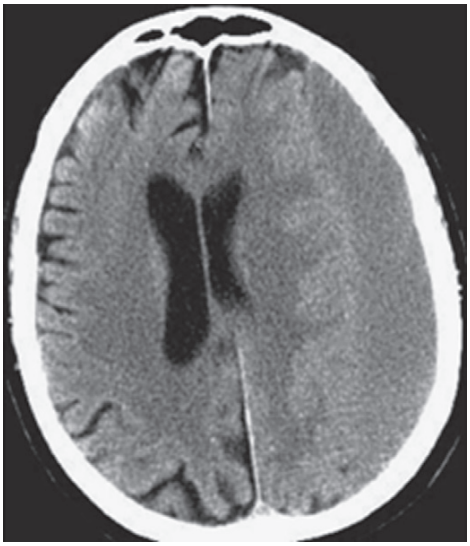


FIGURE 406-1. Subdural hematoma.

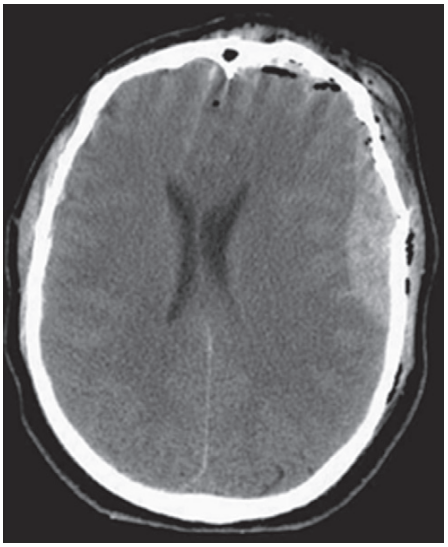


FIGURE 406-2. Epidural hematoma.

severity of the concussion should be assessed (Table 406-3). A subdural hematoma (Fig. 406-1) is blood that accumulates above the brain but below the dura; on CT imaging, it appears as a crescentic or concave opacity overlying the brain. An epidural hematoma (Fig. 406-2) is blood that accumulates below the skull but above the dura; it appears as a convex or lenticular opacity on CT imaging. Skull fractures are best diagnosed with the use of CT bone windows.

Traumatic Spinal Cord Injury

A detailed neurologic examination is needed to identify the level of the injury and the severity of any deficits as well as to document the degree of neurologic dysfunction at the earliest time possible. The level of the injury is the lowest spinal cord segment with intact motor and sensory function. Normal neurologic findings in patients with a clear sensorium obviate the need for

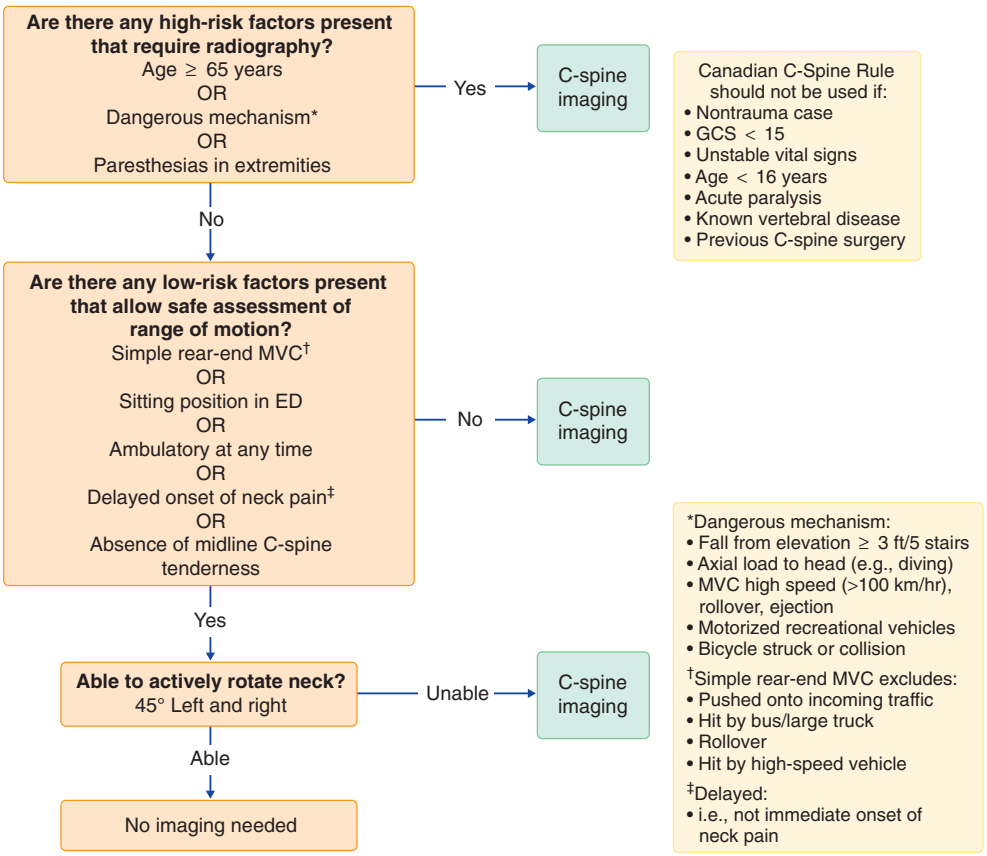


FIGURE 406-3. Canadian C-Spine Rule. For alert (Glasgow Come Scale ≥ 15) and stable trauma patients in whom cervical spine injury is a concern. ED = emergency department; GCS = Glasgow Coma Scale (see Table 406-1); MVC = motor vehicle collision. (Modified from Stiell IG, Clement CM, McKnight RD, et al. Comparative validation of the Canadian C-Spine Rule and the NEXUS low-risk criteria in alert and stable patients. *N Engl J Med.* 2003;349:2510-2518; and Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-Spine Rule for radiography in alert and stable trauma patients. *JAMA.* 2001; 286:1841-1848).

imaging studies. However, any complaints of pain over the spine, numbness, tingling, or weakness should raise suspicion of spinal cord injury. In particular, a complaint of "burning hands" suggests traumatic spinal cord injury.

The time of injury should be recorded as accurately as possible. The prognosis for neurologic improvement is better if the lesion is incomplete as opposed to complete. During the acute period, serial examinations must be performed frequently.

If spinal cord injury is suspected, the patient should be appropriately immobilized, such as with a rigid collar and back board. In patients who are able to cooperate with a neurologic examination, are not intoxicated, and do not have painful distracting injuries (such as a femoral fracture, which would interfere with the leg motor and sensory examination), normal neurologic findings effectively rule out cervical spine disease.

Imaging

In patients in whom a cervical injury cannot be excluded, the radiologic evaluation should begin with plain radiographs of the bony spine, with further neuroimaging of any abnormalities that are found. In patients who are alert and stable, the Canadian C-Spine Rule (Fig. 406-3) can be used to reduce unnecessary imaging without any adverse effect on patients' outcomes.■ Bony vertebrae should be examined with CT and the spinal cord with magnetic resonance imaging. Intervertebral and paravertebral soft tissues are best studied with magnetic resonance imaging. A chest radiograph is usually indicated to provide images of the lower cervical and thoracic vertebrae; the presence of a pleural effusion in the setting of a possible thoracic spine injury suggests a hemothorax.

Ligamentous Injury Versus Spinal Cord Injury

If plain radiographs of the cervical spine are normal but the patient still complains of neck pain, a ligamentous injury should be considered. Ligamentous injury can be evaluated by flexion-extension radiographs of the cervical spine. If pain prevents an adequate study, patients should be kept in a rigid cervical collar for 3 to 5 days until the pain and muscle spasm resolve. If studies at that time are normal, the patient will no longer require the collar. Conversely, abnormal results warrant surgical evaluation to determine whether further immobilization or surgical correction is necessary.

TREATMENT Rx

The immediate goals of therapy are to arrest ongoing injury, to preserve and if possible to restore neurologic function, and to avoid secondary medical complications. To achieve these goals, an organized team approach is essential. Despite major research efforts, current clinical treatment is largely confined to supportive measures: maintaining perfusion pressure, minimizing intracompartment hypertension (e.g., increased intracranial pressure [ICP]), and indirectly treating edema.

Traumatic Brain Injury

Initial Management

It is crucial that prehospital providers optimize perfusion and oxygenation because the duration and severity of hypoxia and hypotension in this critical early period have dramatic consequences on clinical outcome. Treatment begins with immediate attention to airway and cardiopulmonary function, early identification of the potential for traumatic brain injury, and minimization of secondary insults such as hypoxia and ischemia.

Patients with mild or moderate traumatic brain injury often have returned to normal or are rapidly recovering by the time that they reach an emergency department. The critical element is the duration of amnesia or loss of consciousness (see Table 406-3). Longer periods of abnormal sensorium are associated with higher grades of concussion, and higher grades of concussion necessitate longer periods of convalescence.

Severe Traumatic Brain Injury

Patients with Glasgow Coma Scale scores of 8 or lower are considered to have severe traumatic brain injury. With this level of impaired consciousness, even with an intact gag reflex, patients are unable to protect the airway adequately. Intubation should be performed with either an endotracheal or a nasotracheal tube, depending on clinical circumstances. The patient should be in a rigid neck collar with the head elevated 30 degrees. The neck collar is used not only to protect the cervical spine until appropriate imaging can be performed but also to keep the head midline to avoid compromising venous drainage.

If intracranial hypertension is suspected, a 30-mL intravenous dose of 23% hypertonic saline through a central venous catheter■ may be better than mannitol (intravenously at a dose of 0.5 to 1.0 g/kg) to reduce it. Continuous infusion of 3% hypertonic saline through a central venous catheter may be started at a rate of 75 to 100 mL/hr with the goal of a serum sodium level of 150 to 155 mM/L to maintain ICP below 20 mm Hg. Intravenous

steroids are of no benefit acutely and increase mortality at 2 weeks after the injury.[1] Hyperventilation may also be tried but has the potential to exacerbate ischemia; if it is used, the goal should be hyperventilation to a P_{CO_2} of 34 to 36 mm Hg. Induced hypothermia reduces ICP in patients with traumatic brain injury. However, its use is not currently recommended,[2] and a large study found no benefit and potential harm in children.[3]

In addition to ICP control, cerebral perfusion must be maintained. The goal is to maintain cerebral perfusion pressure, which is the difference between mean arterial pressure and ICP, higher than 60 mm Hg. Volume resuscitation is the first therapeutic intervention, with the aim of achieving euvolemia or only slight hypervolemia to a central venous pressure (CVP) goal of 4 to 6 mm Hg. For fluid resuscitation, saline is preferred to albumin.[4] Furthermore, for treatment of elevated ICP, an osmolar gradient between the systemic vasculature and the brain is needed. Thus, intravenous hyperosmolar solutions may be used, including normal saline and hypertonic saline (e.g., 3% sodium solutions). The initial goal is 310 mOsm or a serum sodium level of 150 to 155 mM/L. If a cerebral perfusion pressure above 60 mm Hg cannot be achieved with intravenous fluids alone, vasoactive pharmacologic agents such as norepinephrine (beginning at 2 µg/min by continuous intravenous infusion) and phenylephrine (100 µg/min) may be required. Invasive hemodynamic monitoring with an arterial pressure line and CVP catheter may be needed.

Types of Injury

Certain lesions require prompt surgical intervention, whereas others do not. Penetrating wounds, intracerebral hemorrhage with a mass effect (including subdural and epidural blood), and bone injury (such as a displaced fracture and vertebral subluxation) require emergency surgical evaluation for intervention. However, focal, hypoxic-anoxic, diffuse axonal, and diffuse microvascular injuries do not warrant surgical intervention; treatment remains primarily with the critical care clinician. Skull fractures and intracranial hemorrhages require neurosurgical evaluation. In general, if a fracture is displaced more than the thickness of the skull, it needs to be elevated.

If a surgical lesion is not identified, the patient should be admitted to an intensive care unit. If the patient is still at a Glasgow Coma Scale score of 8 or lower, an ICP-monitoring device should be used. An intraventricular catheter provides the most reliable data. It is also a treatment option because it allows drainage of cerebrospinal fluid. However, a subdural bolt and fiberoptic catheter are less invasive alternatives.

Pharmacologic Coma and Surgical Decompression

If ICP remains poorly controlled after the aforementioned efforts, pharmacologic coma or surgical decompression is considered. The postulated effect of pharmacologic coma on ICP is through reduction of cerebral metabolism. If the decision to use pharmacologic coma is made, pentobarbital can be administered at a loading dose of 5 mg/kg intravenously, followed by an infusion of 1 to 3 mg/kg/hr. Another option is propofol (loading dose of 2 mg/kg intravenously, followed by an infusion of up to 100 µg/kg/hr). Continuous electroencephalographic monitoring is helpful because the target response is burst suppression. Barbiturates and propofol are myocardial depressants, so aggressive cardiovascular management is often necessary to achieve the desired cerebral perfusion pressure. Recalcitrant elevated ICP despite these interventions is an ominous sign; serious consideration should be given to frontal or temporal lobe decompression and hemicraniectomy.

Complications

If the patient is agitated, an evaluation should be made to determine whether the patient is in pain or poorly tolerating mechanical ventilation. If pain is a concern, a narcotic analgesic such as fentanyl (50 to 100 µg intravenously) or morphine (1 to 2 mg intravenously) should be administered. Because these agents are easily reversed by naloxone, periodic reassessment of neurologic status can be performed. If agitation alone is the issue, haloperidol (0.5 to 2 mg intravenously), a nonsedating agent that still maintains the ability for a neurologic examination to be performed, should be considered.

The P_{O_2} level should be maintained at approximately 100 mm Hg. Phenytoin (loading dose of 1000 mg intravenously followed by a maintenance dose of 300 mg/day intravenously) reduces seizures during the first week after traumatic brain injury, but its later usefulness is less clear. Fever greatly increases cerebral metabolism; antipyretic interventions such as acetaminophen and cooling blankets should be used as needed. Gastric stress ulcers may be prevented with H_2-antagonists such as ranitidine (50 mg intravenously four times daily) or proton pump inhibitors such as omeprazole (20 mg/day orally). Low-dose heparin (5000 units subcutaneously twice daily) or a low-molecular-weight heparin such as enoxaparin (40 mg/day subcutaneously) and pneumatic stockings should be instituted to avoid deep vein thrombosis. A nasogastric or orogastric tube should be placed for nutrition. Feeding should be initiated as soon as practical, usually on the second day after injury. Because cerebral edema is a concern, hyperosmotic feeding should be instituted. If ileus is present, total parenteral nutrition (TPN; Chapter 224) should be given.

After the first 6 to 12 hours, effort should be made to reduce hyperventilation. Otherwise, the metabolic compensation to chronic hyperventilation negates the ameliorative effects of the respiratory alkalosis.

Regular neurologic examinations and monitoring of ICP and cerebral perfusion pressure are useful to guide ongoing therapy. In general, the peak period of cerebral edema is 48 to 96 hours after traumatic brain injury. Thereafter, cerebral edema spontaneously resolves, often in association with clinical improvement.

Recovery

Recovering patients may experience "postconcussive syndrome," which is primarily manifested as headache. Other symptoms may include difficulty concentrating, changes in appetite, sleep abnormalities, and irritability. In general, postconcussive syndrome lasts a few weeks after injury, but it can persist beyond a year or more. Therapies are based on the patient's symptoms. For headache, nonsteroidal anti-inflammatory agents (such as ibuprofen at an oral dose of 400 to 600 mg), migraine drugs (such as sumatriptan at an oral dose of 25 to 50 mg), and biofeedback may be considered. For cognitive dysfunction, neuropsychological testing may be helpful in determining appropriate intervention.

Traumatic Spinal Cord Injury

Initial Management

Emergency management of traumatic injury to the spinal cord begins with the basics of airway, breathing, and circulation. A secure airway is essential. For patients suffering from high cervical lesions, spontaneous ventilation will be lost. Cervical lesions below C5 may also be associated with impaired ventilatory capability. If there is any concern that the airway or ventilatory effort is compromised, emergency intubation is required. In a patient in whom the cervical spine has not been imaged, the preferred method is nasotracheal intubation under fiberoptic guidance. Other approaches are nasotracheal (blind) or orotracheal intubation, provided that in-line traction is applied.

Other immediate concerns are bleeding and circulation. Hypotension (systolic blood pressure < 90 mm Hg) may be due to either neurogenic shock or hypovolemia and should be avoided. For neurogenic shock, vasopressive pharmacologic agents such as phenylephrine (beginning as a continuous intravenous infusion at 100 µg/min with titration to clinical effect) may be needed. If tachycardia is present, hypovolemia is more likely, so fluid resuscitation would be more appropriate.

Targeted Therapy

If closed compartment spinal cord injury is identified, immediate pharmacologic therapy with methylprednisolone may be instituted,[5] but treatment must be started within 8 hours of injury. The initial dose is an intravenous bolus of 30 mg/kg administered during 15 minutes, followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hr for 23 hours; longer durations of therapy are significantly more toxic. The utility of methylprednisolone in penetrating traumatic spinal cord injury has not been demonstrated, and it should not be used.

At this time, the decision for surgical intervention should be based on the stability of the anterior, middle, and posterior vertebral columns. The anterior column consists of the anterior half of the vertebral body and the vertebral disc. The middle column is the posterior half of the body and the disc. The posterior column is composed of the arch, facets, and ligaments. In general, if two of the three columns are damaged, surgical stabilization is needed. If immediate surgery is not indicated, the patient should be admitted to the intensive care unit for further management.

Acute and Subacute Management

Patients with severe spinal cord injuries require close cardiovascular and ventilatory care, supportive care for bladder and bowel function, approaches to avoid pressure ulcers (Chapter 24), and general measures similar to those used for patients with traumatic brain injury.

Neurogenic Shock and Dysautonomia

After traumatic spinal cord injury, patients are at risk for neurogenic shock and dysautonomia. Lesions of the cervical and thoracic spine disrupt the descending sympathetic pathways to the intermediolateral cell column of the thoracolumbar spinal cord, thereby leading to peripheral vasodilation and hypotension. If the lesion is at T3 or above, sympathetic tone to the heart is compromised. In this setting, hypotension is accompanied by bradycardia, thus producing the neurogenic shock triad of bradycardia, hypotension, and peripheral vasodilation.

Initial therapy for dysautonomia should be fluid administration to restore an adequate circulating volume with a target CVP of 4 to 6 mm Hg. A hematocrit of 30 is optimal for perfusion of the central nervous system, so blood can be used if the patient is anemic. If blood is not required, either colloid (e.g., albumin solutions) or crystalloid (e.g., normal saline) may be used. If there is a suspicion of cardiac or pulmonary disease, a pulmonary artery catheter may be needed briefly to assess fluid status and the relationship between pulmonary pressure and CVP.

Once adequate circulating volume has been achieved, hypotension should be managed with vasopressive agents such as phenylephrine (see earlier), norepinephrine (see earlier), or dopamine (beginning at 1 µg/kg/min by continuous intravenous infusion; Chapter 106), with the goal of a mean arterial pressure of 85 to 90 mm Hg that should be maintained for 7 days

after injury. Symptomatic bradycardia can be treated with atropine (1 mg intravenously).

Ventilatory Compromise

An injury at C5 or higher results in diaphragmatic denervation and requires complete ventilatory assistance. Proper management requires endotracheal or nasotracheal intubation and mechanical ventilation, with an appropriate tidal volume (6 to 10 mL/kg), an F_{IO_2} to achieve a P_{O_2} between 80 and 100 mm Hg, and a rate to give a P_{CO_2} of 40 mm Hg. Positive end-expiratory pressure should also be given to minimize atelectasis (Chapter 105). If the patient does not show signs of ventilatory recovery within 2 weeks of intubation, a tracheostomy should be considered.

Lesions below C5 may also be associated with inadequate spontaneous ventilation. Midcervical lesions may be associated with intact but compromised diaphragm function. If this is suspected, a "sniff" test under fluoroscopy can be performed to determine whether both hemidiaphragms are functioning properly. If they are not, intubation or tracheostomy with volume-controlled ventilation may be needed. If function is intact, pressure support ventilation may be sufficient (Chapter 105) to achieve an appropriate tidal volume.

Cervical lesions at C6 and below spare the phrenic nerves but may disrupt innervation of the intercostal muscles. The primary finding is decreased cough and an inability to increase ventilation when needed, thereby leading to atelectasis and pneumonia; assisted elimination of tracheal secretions is essential.

Thromboembolic Disease

Thromboembolic disease (Chapters 81 and 98) is a leading cause of morbidity and mortality after traumatic spinal cord injury. Prolonged immobility of the lower extremities leads to deep vein thrombosis in up to 70% of spinal cord–injured patients. Patients should receive prophylaxis with heparin alone or in combination with intermittent compression devices (e.g., pneumatic stockings) or graduated compression stockings. Anticoagulation therapy with warfarin to a therapeutic goal of an international normalized ratio of 2 to 3 should begin during rehabilitation. An inferior vena cava filter may be placed if anticoagulation and mechanical therapies are contraindicated.

Visceral Function

The abdominal wall musculature is innervated by T7 to T12. The stomach, small bowel, liver, pancreas, and proximal two thirds of the colon receive innervation from T5 to L2. Spinal cord injury at these levels or above may impair visceral function. For ileus, a nasogastric tube should be placed to decompress the stomach. Parenteral nutrition should be started as soon as possible. Enteral feeding should be delayed until gastrointestinal motility returns, usually within 2 to 3 weeks. In comparison with conservative bowel management, transanal irrigation improves constipation, fecal incontinence, and symptom-related quality of life in patients with spinal cord injuries.

Stress-induced peptic ulcer disease occurs in nearly a third of patients without prophylaxis. An H_2-receptor antagonist such as ranitidine (50 mg intravenously four times daily) or a proton pump inhibitor such as omeprazole (20 mg/day orally) reduces the incidence of ulcers.

Bladder tone may be lost because of spinal shock. A Foley catheter should be placed for a minimum of 5 to 7 days to drain the bladder and to evaluate volume and renal status. After spinal shock has resolved, autonomic dysreflexia may occur as a result of bladder distention. Clinical signs such as sweating, skin flushing, and hypertension may be present. Clinical examination with palpation and percussion will reveal a distended bladder, which can be treated by bladder training or intermittent catheterization.

Nutrition

Until enteral feeding can begin, parenteral nutrition should be used. Ideally, TPN should be started. However, if TPN is not possible, peripheral parenteral nutrition should be used until TPN (Chapter 224) can begin. Energy expenditures of 19 kcal/kg/day for high cervical injuries to 35.8 kcal/kg/day for injuries at T10 and below have been reported. A calorie level of 80% of the Harris-Benedict prediction should be used for quadriplegic patients. The full Harris-Benedict predicted amount should be used in patients with thoracic spine injuries and below.

Other Therapy

Patients with traumatic spinal cord injury have a propensity for the development of decubitus ulcers and pressure sores (Chapter 24). Mechanical kinetic beds, regular log rolling (every 2 hours), and padded orthotics are useful in minimizing this complication. Orthotics, physical therapy, and occupational therapy (for cervical cord injury) are also important to minimize contractures and to begin the rehabilitation process.

PROGNOSIS

Traumatic Brain Injury

The most useful prognostic indicator after traumatic brain injury is the neurologic examination at initial evaluation. For patients with severe traumatic brain injury, the initial Glasgow Coma Scale score is the most reliable prognostic indicator. The lower the initial Glasgow Coma Scale score, the less likely a patient will have meaningful neurologic or functional recovery. After traumatic brain injury, 40% of patients with a score of 8 have a good recovery versus only 7% when the score is 3. Furthermore, only 27% of patients with a score of 3 survive versus 88% of patients with a score of 8. Patients in whom the Glasgow Coma Scale score remains the same or worsens during a period of 6 hours do worse clinically than those whose score improves. Further prognostic stratification at 24 hours can be based on pupillary responses, motor responses, and age (see Chapter 411).

A subsequent head injury before full recovery from even a mild traumatic brain injury may occasionally result in "second impact syndrome," which can worsen the clinical outcome. When seen (mostly in children and adolescents), coma develops rapidly after the second injury, often within minutes. There is decreased autoregulation, diffuse cerebral edema, and intracranial hypertension. Second impact syndrome is associated with high mortality.

TABLE 406-4 AMERICAN SPINAL INJURY ASSOCIATION IMPAIRMENT SCALE

GRADE	INJURY TYPE	DEFINITION	LIKELIHOOD OF RECOVERY*
A	Complete	No motor or sensory function below the lesion	15.5% (cervical) and 7% (thoracic)
B	Incomplete	Sensory but no motor function	47%
C	Incomplete	Some motor strength (<3)	84%
D	Incomplete	Motor strength > 3	84%
E	None	Sensory and motor function normal	100%

*Data from Coleman WP, Geisler FH. Injury severity as primary predictor of outcome in acute spinal cord injury: retrospective results from a large multicenter clinical trial. *Spine J.* 2004;4:373-378.

Traumatic Spinal Cord Injury

For traumatic spinal cord injury, the completeness of the injury is the most useful predictor (Table 406-4). A grade "A" or complete motor and sensory deficit below the lesion has a poor prognosis. If such a lesion persists for 24 hours, there is little likelihood of meaningful recovery. On the other hand, even severe partial injuries have a higher probability of recovery.

Grade A

1. Stiell IG, Clement CM, Grimshaw J, et al. Implementation of the Canadian C-Spine Rule: prospective 12 centre cluster randomised trial. *BMJ*. 2009;339:b4146.
2. Wakai A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2007;1:CD001049.
3. CRASH Trial Collaborators. Final results of MRC CRASH, a randomized placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at six months. *Lancet.* 2005;365:1957-1959.
4. Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database Syst Rev.* 2009;2:CD001048.
5. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med*. 2008;358:2447-2456.
6. SAFE Study Investigators. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357:874-884.
7. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA*. 1997;277:1597-1604.
8. Christensen P, Bazzocchi G, Coggrave M, et al. A randomized, controlled trial of transanal irrigation versus conservative bowel management in spinal cord–injured patients. *Gastroenterology*. 2006; 131:738-747.

SUGGESTED READINGS

Gupta R, Bathen ME, Smith JS, et al. Advances in the management of spinal cord injury. *J Am Acad Orthop Surg*. 2010;18:210-222. *Review*.

Husson EC, Ribbers GM, Willemse-van Son AH, et al. Prognosis of six-month functioning after moderate to severe traumatic brain injury: a systematic review of prospective cohort studies. *J Rehabil Med*. 2010;42:425-436. *Glasgow Coma Scale score, midline shift, and subdural hematoma predicted outcome.*

van Middendorp JJ, Hosman AJ, Donders AR, et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study. *Lancet*. 2011;377:1004-1010. *Age, motor scores of the quadriceps femoris (L3) and gastrocsoleus (S1) muscles, and light touch sensation of dermatomes L3 and S1 distinguished independent walkers with excellent predictive accuracy.*

407

MECHANICAL AND OTHER LESIONS OF THE SPINE, NERVE ROOTS, AND SPINAL CORD

RICHARD L. BARBANO

DEFINITION

Disorders of the spine, nerve roots, and spinal cord together are frequent reasons for a patient to visit a physician. Many of these disorders either initially or eventually involve more than one element of the vertebra–spinal cord–nerve root unit, so there is much overlap in the pathobiology and clinical manifestations of these diseases.

The spine consists of 30 vertebrae: 7 cervical (C), 12 thoracic (T), 5 lumbar (L), 5 sacral (S), and the coccyx (Fig. 407-1). The ring shape of the bony vertebrae forms a protective circle around the spinal cord while leaving ample room to allow the cord to move within this canal during flexion and extension of the spine. The vertebral bodies help bear the compressive weight of the body and provide the surface area to support the intervertebral discs, which act to cushion the axial force along the spine. The overlapping facet joints and multiple sets of longitudinal ligaments give the spine stability during its many ranges of motion. The posteriorly placed foramina allow the exit of spinal nerves.

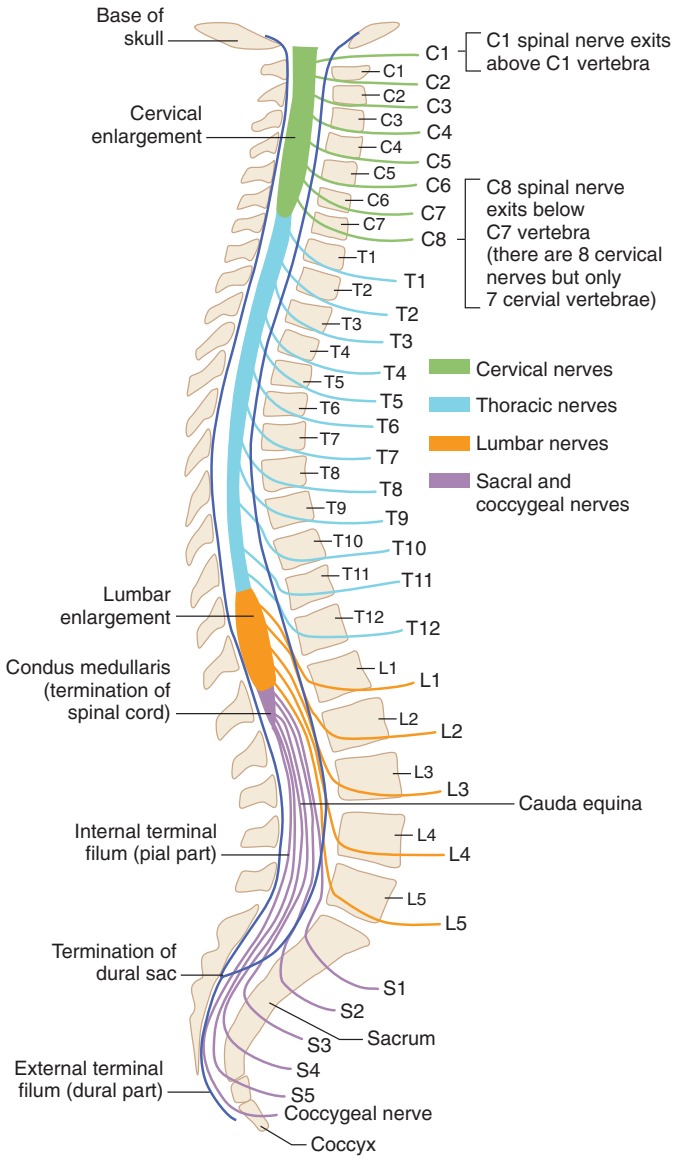


FIGURE 407-1. Anatomy of the spinal cord.

The spinal cord consists of 31 spinal segments, with one more cervical cord segment (8) than vertebrae; each gives rise to a bilateral pair of spinal nerves. Spinal nerves C1 to C7 exit the canal above their corresponding vertebral body, the C8 nerve exits below the C7 vertebra, and subsequent inferior nerves also exit below the numbered vertebrae. The spinal segments of the cord itself, however, lie progressively superior to the vertebrae, so that the end of the spinal cord, the conus medullaris, in adults is approximately adjacent to the L1 vertebra. The more caudal spinal nerves travel as the cauda equina in the subarachnoid space within the spinal canal before exiting their respective foramina. The spinal cord does not have a uniform diameter; the cervical and lumbar segments are wider compared with the thoracic and lower sacral areas because the increased motor and sensory neurons supplying the arms and legs enlarge the cord.

Spinal nerves are formed by the joining of the anterior and posterior spinal roots, which directly exit and enter the spinal cord. The anterior root derives from axons of the anterior horn cells and lateral columns, and it serves motor and autonomic efferent pathways; the posterior root mostly derives from the axons from the dorsal root ganglion and carries afferent sensory signals (Fig. 407-2). The sensory root is twice the thickness of the motor root and lies in a more anterior and inferior location as it crosses the foramen.

CLINICAL MANIFESTATIONS

Disorders of the spinal nerve root produce signs and symptoms referable to the corresponding dermatome or myotome. By far the most frequent complaint is localized neck or back pain, but compromise of the nerve roots or spinal cord will cause symptoms such as abnormal or painful sensations (paresthesias or dysesthesias), loss of sensation, weakness, and autonomic dysfunction (most commonly bladder or bowel incontinence).

When it affects a myotome (the group of muscles served by motor neurons of a spinal cord segment; Fig. 407-3), the motor deficit associated with a spinal root disorder is of the *lower motor neuron* type. Typical findings are weakness, hypotonia, depressed or absent reflexes, and, if the syndrome has persisted for at least several weeks, atrophy with or without fasciculations. Sensation at the root level is diminished or absent for all modalities, but sensation below the affected root level is intact.

Conversely, disorders of the spinal cord produce a "level" below which sensation is abnormal and motor deficits are of the *upper motor neuron* type, with weakness without atrophy (unless complicated by disuse), hypertonia, and increased reflexes. At the level of a spinal cord lesion, the motor deficits can be of the lower motor neuron type as the anterior horn cell bodies or exiting fibers are affected; below this level, an upper motor neuron syndrome will predominate. With strokes (Chapter 414) and other central nervous system disorders (Chapter 195), the full upper motor neuron syndrome may not be present in the acute phase of cord injury and can take time to appear.

DIAGNOSIS

The clinical history can help localize the patient's symptoms, especially complaints of pain and sensory alterations that may exist in the absence of objective sensory loss on probing with light touch, pinprick, and vibration stimuli. The neurologic examination should include evaluation of the sensory, motor (Table 407-1), and reflex (Table 407-2) functions. Careful side-to-side comparisons can help assess subtle deficits. For example, elderly patients often have decreased or absent ankle jerks, so contralateral comparison is necessary. However, all muscles receive innervation from more than one root/spinal cord level, and all roots send fibers to multiple muscles. The clinical implication of this anatomic pattern is that individual muscles are rarely profoundly weak, and patients rarely report isolated muscle weakness in single root involvement syndromes. Likewise, overlap of the sensory dermatomes (see Fig. 407-3) explains why sharp demarcations in the sensory examination rarely occur.

DISORDERS OF THE SPINE

Neck and Back Pain

DEFINITION

Most neck and back pain is *mechanical,* that is, theoretically emanating from the spine's structural elements, which are the vertebrae, discs, ligaments,

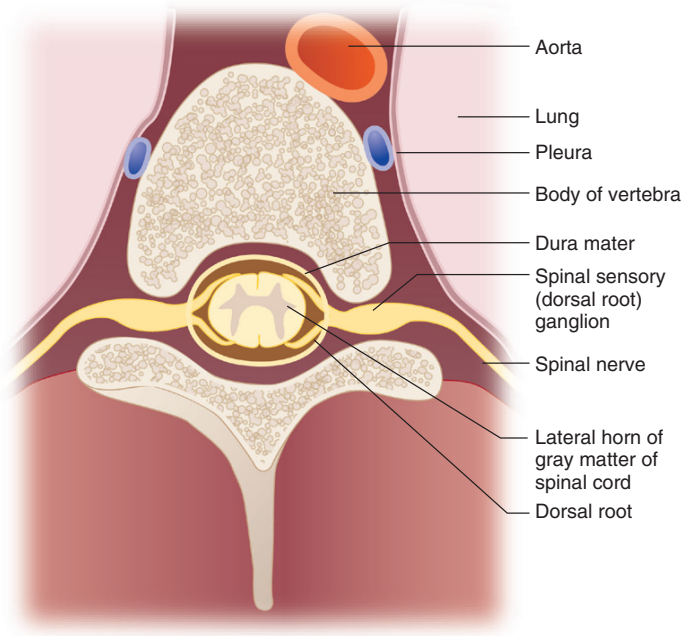


FIGURE 407-2. Anatomy of the spinal cord: section through a thoracic vertebra.

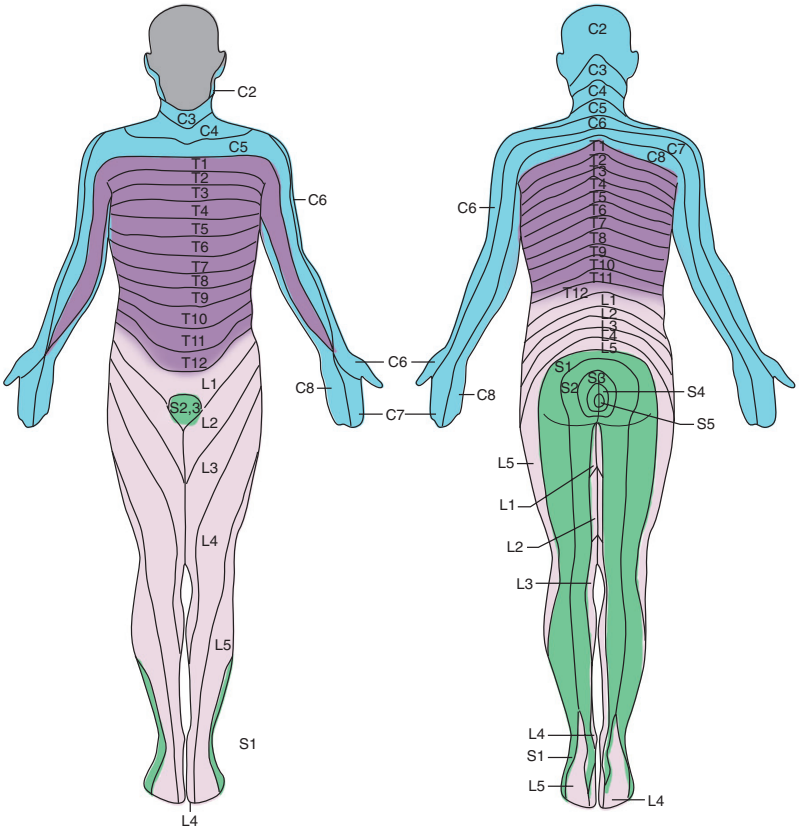
tendons, and muscles. The location of pain is either *axial,* which means it is located along the spine itself, or *referred;* the term *perceived pain* is sometimes used when the pain from a spinal lesion is felt elsewhere by the patient, whereas *referred pain* is often used to describe pain caused by nonspinal structures that is experienced by the patient in the spinal area. If the pain follows a dermatomal (nerve root) distribution, it is referred to as *radicular pain,* which is likely to involve the nerve root.

EPIDEMIOLOGY

Neck and back pain is a frequent reason for visits to a primary care physician. Low back pain is more common than neck pain, but both are common. The thoracic spine, possibly because of rib attachments and limited range of motion, is an uncommon location for back pain.

In the general population, the incidence of self-reported neck pain is 213 per 1000; the 12-month prevalence of any pain is typically between 30 and 50%, and pain severe enough to limit activity is between 1.7 and 11.5%. The prevalence is higher among women. Risk factors for neck pain include inherited factors, poor psychological health, and tobacco use; the presence of disc degeneration is not a significant factor.

More than 70% of people will experience low back pain significant enough to inhibit their participation in daily activities at some time in their life. The highest prevalence is in the 45- to 64-year age group. There is less of a gender difference than with neck pain, although tobacco use is an associated risk factor. Physical work–related factors, such as heavy lifting, prolonged sitting, and repetitive twisting, increase risk; prospective studies show that psychosocial issues, such as work monotony and job dissatisfaction, also are major predisposing factors.



Levels of principal dermatomes

C5	Clavicles
C5,6,7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6,7,8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1,2,3,4	Anterior and inner surfaces of lower limbs
L4,5 S1	Foot
L4	Medial side of great toe
S1,2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2,3,4	Perineum

FIGURE 407-3. Schematic demarcation of levels of principal dermatomes shown as distinct segments. There is actually considerable overlap between any two adjacent dermatomes.

TABLE 407-1 ESSENTIAL MUSCLE TESTING

ROOT	MUSCLES	ACTION/TESTING
ARM		
C5	Deltoid Infraspinatus	Abducts arm Externally rotates arm with elbow flexed
C6	Brachioradialis	Flexes elbow (along with biceps [C5-6])
C7	Triceps Extensor digitorum	Extends elbow Extends fingers
C8	Flexor digitorum Flexor pollicis longus	Flexes fingers (both superficialis and profundus) Flexes distal phalanx of thumb
T1	Interossei	Spread fingers
LEG		
L1-2	Iliacus	Flexes hip
L2-3	Adductor magnus	Adducts thigh (as part of adductor group)
L3-4	Quadriceps	Extends knee
L4	Tibialis anterior	Dorsiflexes foot
L5	Extensor hallucis longus Extensor digitorum longus	Great toe extension Toe extension
S1	Hamstrings Flexor hallucis longus	Flex knee Flexes great toe (along with S2)

TABLE 407-2 ESSENTIAL REFLEX EXAMINATION

REFLEX	EFFECT	ROOT/IMPLICATION
Jaw jerk	Jaw closes with tap on slightly opened jaw	Cranial nerve V; implies lesion above cervical cord
Biceps	Tap tendon: elbow flexion	C5-6; musculocutaneous nerve
Brachioradialis	Tap tendon over distal radius with elbow flexed and mid pronation: elbow flexion	C5-6; radial nerve
Triceps	Tap tendon: elbow extension	C6 < C7
Finger flexion	Tap partially flexed fingertips: finger flexion	C6-T1; when hyperactive, may imply lesion above midcervical spinal cord
Patella	Tap patella: quadriceps contraction (knee extension)	L2-4
Achilles	Tap Achilles tendon: foot plantar flexion	S1-2
Babinski	Scratch sole: great toe flexion	Great toe extension implies lesion of cord (or brain) above L4
Anal wink	Scratch perineum: external anal sphincter contraction	Absence of contraction implies S2-4 lesion

PATHOBIOLOGY

Although the popular impression is that the disc is the source of most spine pain, it is estimated that disc disease such as protrusion accounts for only 5% of all low back problems. Degenerative changes are a much more common cause of both acute and chronic spine pain. There is a genetic predisposition to intervertebral disc degeneration, with heritability estimates in the range of 34 to 61%.

Degenerative changes can result in *spondylosis,* a condition that includes degenerative disc disease with bulging and occasionally herniation. The condition is often accompanied by the formation of osteophytes, ligamentous hypertrophy, and sometimes facet fracture and vertebral subluxation. Spondylosis, which is a consequence of age-related disc disease, is exemplified by the fact that almost everybody has at least anterior osteophytes by the age of 40 years, and it is not necessarily painful. Spondylosis probably starts with age-related disc desiccation and loss of elasticity of the annulus fibrosus. Tension of the longitudinal ligaments results in the formation of hypertrophic osteophytes. Compromise of microvascular supply may also contribute. Eventually, the facet joints can ride over one another, thereby leading to instability, the formation of more osteophytes, and inflammation of the synovial joints. If there is fracture of the pars interarticularis, the term *spondylolysis* is used. Further instability between the intervertebral segments leads to *spondylolisthesis,* in which one vertebral body shifts sagittally in relation to its adjacent vertebra. Spondylolisthesis is graded by the amount of shift as measured with flexion and extension lateral spine films.

Whiplash, an acute flexion-extension injury of the cervical spine, is common after motor vehicle accidents and other situations of rapid deceleration. Although specific acute and chronic manifestations are controversial, the acute syndrome is generally accepted to be a result of mechanical irritation of pain-sensitive structures in the cervical spine with or without nerve root injury. More severe trauma can cause fracture and vertebral instability, both of which require rapid surgical evaluation.

CLINICAL MANIFESTATIONS

Acute neck pain and low back pain are commonly limited to the axial region, although radicular signs and symptoms can occur in the presence of nerve root irritation. The most common radicular pain occurs in the distribution of a dermatome. Other radicular signs and symptoms can include dysesthesias or sensory loss in the affected dermatome, decreased strength in muscles of the affected myotome, and decreased reflex. Cranial nerve findings, diffuse weakness throughout a limb or in more than one limb, hemisensory symptoms, autonomic symptoms, and increased reflexes are not manifestations of spine disease and should prompt more extensive evaluation for other conditions that affect the brain or brain stem. Bowel and bladder symptoms should prompt urgent evaluation of a cauda equina or myelopathy syndrome (see later).

Acute spine problems can also cause referred or perceived pain at sites other than their anatomic source. For example, mechanical low back pain may include aching in the buttocks or thigh, most often posteriorly and occasionally the hip region but rarely below the knee. More commonly, however, the term *referred pain* denotes the situation in which other structures, usually internal organs, refer pain to the spine or back. Areas of referred pain usually share the same embryologic origin and, during development, the same sensory pathways. Differentiation of referred pain from localized back pain depends on the history and examination. Mechanical pain is often exacerbated by movement, such as twisting, bending, extension, or flexion, whereas referred pain tends to be independent of such activities.

Chronic spine disorders lead to chronic back pain directly and as a secondary complication. For example, chronic degenerative arthropathy can lead to degenerative lumbar scoliosis with secondary involvement of neural structures. Back pain and radiculopathy are the most prominent symptoms, present in upward of 80% of patients, but symptoms of neurogenic claudication also develop in about 50% of patients.

DIAGNOSIS

History and Clinical Examination

The history and examination are essential for the initial evaluation and triage of patients with neck and back pain. Patients with so-called red flags (Table 407-3) merit special attention, as does any patient who awakens from sleep because of pain or has pain that is constant and unchanged by position, is unremitting and progressive, or is accompanied by any systemic signs or symptoms.

As part of the history in the setting of acute neck trauma, well-established screening protocols such as the Canadian C-Spine Rule and the NEXUS Low-Risk Criteria (Fig. 407-4) are validated ways to detect cervical spine fracture and to direct appropriate radiographic evaluation. In such a setting, a computed tomographic (CT) scan of the cervical spine would be the imaging test of choice.

On clinical examination, inspection should assess evidence of trauma, muscle wasting, fasciculations, erythema, rashes, and scars. Palpation is directed to areas of point tenderness during evaluation for more diffusely tender regions, muscle spasm, and masses. If light percussion of the spinous process evokes significant pain, a focal process, such as fracture, malignant neoplasm (Chapter 195), or infection (Chapter 421), should be considered because such a finding is unusual in typical mechanical spine pain. Finally, the active and passive range of motion for flexion, extension, rotation, and tilt should be noted. Many provocative tests have been described for the evaluation of neck and back pain, but few have undergone formal evaluation of their diagnostic accuracy. For neck pain, contralateral rotation of the neck with extension of the arm and fingers (Video 407-1) suggests cervical root involvement, particularly in combination with other provocative tests, such as the Spurling maneuver, in which the patient's head is rotated 45 degrees to the contralateral side with the neck in slight extension to minimize the

TABLE 407-3 "RED FLAGS" IN THE EVALUATION OF SPINE PAIN

Recent significant trauma or minor trauma at age >50 years
Unexplained weight loss
Unexplained fever
Immunosuppression
History of cancer
History of prior local surgery
Systemic disorder, bone or arthritic disorder
Intravenous drug use
Prolonged use of corticosteroids or osteoporosis
Age >70 years
Focal neurologic deficit with progressive symptoms
Duration >6 weeks
Thoracic spine pain

Modified from Davis PC, Wippold FJ, Brunberg JA, et al. ACR Appropriateness Criteria on low back pain. *J Am Coll Radiol.* 2009;6:401-407.

The NEXUS Low Risk Criteria (NLC) Algorithm for screening of neck injuries

- No posterior midline cervical spine tenderness—Midline posterior bony cervical-spine tenderness is present if the patient reports pain on palpation of the posterior midline neck from the nuchal ridge to the prominence of the first thoracic vertebrae, or if the patient evinces pain with direct palpation of any cervical spinous process.
- No evidence of intoxication—Patients should be considered intoxicated if they have either of the following: a recent history provided by the patient, or an observer of intoxication or intoxicating ingestion, or evidence of intoxication on physical examination such as an odor of alcohol, slurred speech, ataxia, dysmetria, or other cerebellar findings, or any behavior consistent with intoxication. Patients may also be considered to be intoxicated if tests of bodily secretions are positive for alcohol or drugs that affect level of alertness.
- A normal level of alertness—An altered level of alertness can include the following: a Glasgow Coma Scale score of 14 or less; disorientation to person, place, time, or events; an inability to remember three objects at five minutes; a delayed or inappropriate response to external stimuli; or other findings.
- No focal neurological deficit—A focal neurological deficit is any focal neurological finding on motor or sensory examination.
- No painful distracting injuries—No precise definition of painful distracting injury is possible. This category includes any condition thought by the clinician to be producing pain sufficient to distract the patient from a second (neck) injury. Such injuries may include, but are not limited to, any long-bone fracture; a visceral injury requiring surgical consultation; a large laceration, degloving injury, or crush injury; large burns; or any other injury causing acute functional impairment. Physicians may also classify any injury as distracting if it is thought to have the potential to impair the patient's ability to appreciate other injuries.

FIGURE 407-4. The NEXUS Low-Risk Criteria (NLC) algorithm for screening of neck injuries. (Reproduced from Hoffman JR, Mower WR, Wolfson AB, et al. Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. National Emergency X-Radiography Utilization Study Group. *N Engl J Med.* 2000;343:94-99.)

foraminal opening. Downward pressure on the top of the head by the examiner will reproduce arm dysesthesias (Video 407-2). Provocative tests also can diminish symptoms. For example, in the cervical distraction test, the examiner's hands are placed under the jaw and occiput; gentle upward pulling of the head will temporarily reduce or alleviate the symptoms (Video 407-3).

For low back pain, the straight leg raise (Video 407-4) has sensitivity of 0.85 to 0.91 but a specificity of only 0.26 to 0.52 for the diagnosis of sciatica due to a herniated disc. The crossed straight leg raise test (Video 407-5) has a lower sensitivity of 0.23 to 0.34 but a much higher specificity of 0.86 to 0.90. The seated straight leg raise (Video 407-6) can be used for confirmation of root irritation as the spine-leg angle is increased to 90 degrees. A negative result of the seated straight leg raise in the setting of a positive result of the straight leg raise suggests the possibility of a nonorganic component, although a mechanical alteration of the root exit zone in this position should also be considered.

Ancillary Testing

For neck pain (Fig. 407-5), plain radiography and CT scanning, which are the mainstays of cervical spine imaging, allow adequate view of the bony structures. Magnetic resonance imaging (MRI) has largely replaced myelography, which is still used occasionally to provide information about the spinal cord and nerve roots. However, magnetic resonance abnormalities are common and can have a high false-positive rate; for example, 12 to 17% of patients younger than 30 years and 86 to 89% of patients 60 years of age have disc degeneration as evidenced by loss of signal intensity, disc protrusion, narrowing of the disc space, or foraminal stenosis. Cervical discography also has a high false-positive rate and cannot be recommended as a diagnostic test in the assessment of neck pain.

Uncomplicated acute low back pain, with or without radiculopathy, is generally self-limited, and imaging studies are unnecessary unless any of the red flags (see Table 407-3) are present. For trauma, osteoporosis, or patients older than 70 years, plain radiography *may* suffice if the results are normal and no other abnormalities are present. Otherwise, with few exceptions, MRI is the test of choice given its superiority in evaluating soft tissue structures and its lack of radiation exposure. Care must be taken, however, to ensure correlation with the clinical syndrome because 28% of asymptomatic volunteers with a mean age of 42 years have herniated discs, 52% have bulging discs, and 14% have annular tears. The percentage of imaging abnormalities increases even more in asymptomatic volunteers older than 60 years; 57% have significantly abnormal scans, with 36% showing herniated discs and close to 98% showing disc degeneration. Abnormalities of the Modic end plate, anterolisthesis, and disc extrusion are more strongly associated with low back pain than is disc degeneration without end plate changes. Situations in which alternative imaging should be considered include spondylosis and stress fracture, for which bone scintigraphy with single-photon emission computed tomography is more sensitive than MRI. CT can also be useful when MRI is contraindicated or to evaluate scoliosis, bone graft integrity, surgical fusion, and instrumentation. For back and neck pain that persists for 6 weeks, electrodiagnostic testing can demonstrate compromise of spinal root function but is not usually helpful in axial spine pain without neurologic symptoms.

Differential Diagnosis

Mechanical or idiopathic pain explains up to 97% of cases of neck pain (Table 407-4) and low back pain (Table 407-5); the remaining 3% is nonmechanical in origin and includes referred pain and other conditions. Acute mechanical neck pain is most often caused by a neck strain, a herniated nucleus pulposus, or whiplash; for pain of insidious onset, osteoarthritis and myelopathy are the leading causes. For back pain, muscle strain and a herniated nucleus pulposus are acute causes; insidious causes include osteoarthritis, spinal stenosis, spondylolisthesis, and scoliosis. Queries regarding the red flags will identify serious and nonmechanical causes of neck and back pain (Table 407-6).

Abdominal and pelvic structures can refer pain *to* the low back (referred pain). Abdominal aortic aneurysms (Chapter 78) can present with a mid to low back ache that may radiate to the hips or anterior thighs. Cholecystitis (Chapter 158) can cause pain in the midthoracic area; pancreatic disease (Chapter 146) can cause pain in the L1 region; and diverticulitis (Chapter 144) in the left lower quadrant can cause diffuse low back pain. Genitourinary disorders (Chapter 128) can cause colicky referred pain to the flanks and costovertebral angle. Bladder disorders (Chapter 125) may occasionally refer pain to the sacral area, as can prostate problems (Chapter 131). Pelvic disorders in women that can cause referred low back pain include endometriosis (Chapter 244), ectopic pregnancy, and pelvic inflammatory disease (Chapters 307 and 326). Most of these disorders have additional signs and symptoms to aid in the diagnosis.

Myocardial ischemia (Chapter 71) can be associated with anterior neck pain, although less commonly than with left arm or jaw pain. Arterial dissections (Chapter 78) are more commonly associated with neck pain; for example, up to 20% of patients with carotid dissections complain of anterolateral pain, and about 80% of patients with vertebral dissections have posterior or occipital pain. Patients with arterial dissections frequently but not necessarily have signs and symptoms of stroke (Chapter 414). Disorders of the esophagus (Chapter 140) and mass lesions of the throat (Chapters 196 and 437) can also present as neck pain.

Acute spine pain can precede the rash in herpes zoster (Chapter 383) or can be seen in the vaso-occlusive crisis of sickle cell anemia (Chapter 166).

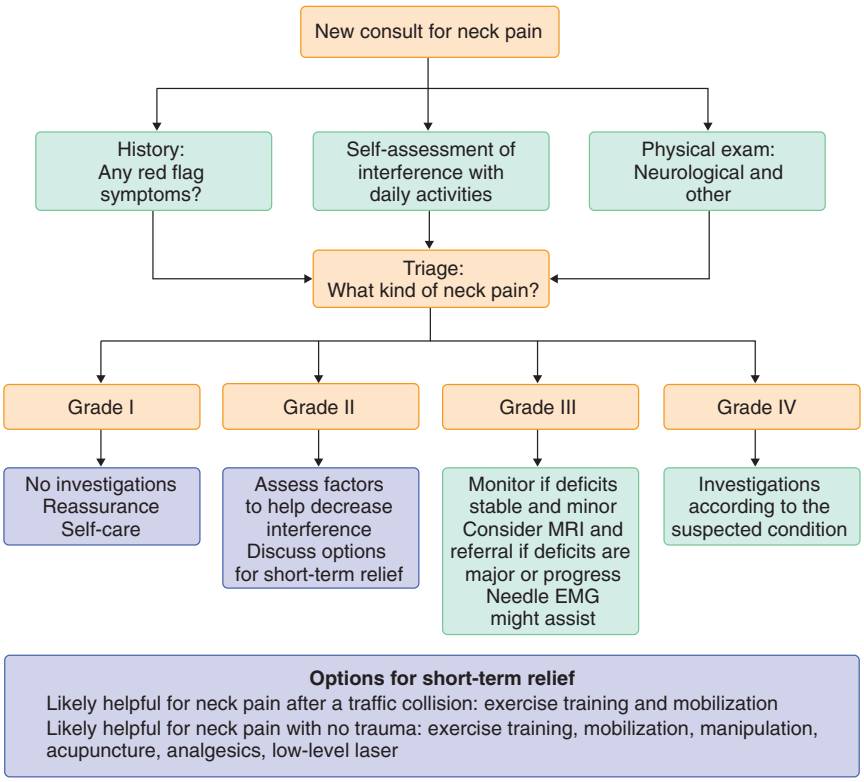


FIGURE 407-5. Approach to new-onset neck pain. (Modified from Guzman J, Haldeman S, Carroll LJ, et al. Clinical practice implications of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. From concepts and findings to recommendations. *Spine.* 2008;33:S199-S213.)

TABLE 407-4 MECHANICAL NECK PAIN

	NECK STRAIN	HERNIATED NUCLEUS PULPOSUS	OSTEOARTHRITIS	MYELOPATHY	WHIPLASH
Age (yr)	20-40	30-50	>50	>60	30-40
Pain location	Neck	Arm	Neck	Arm/leg	Neck
Onset	Acute	Acute	Insidious	Insidious	Acute
Flexion	+	+	–	–	+
Extension	–	+/–	+	+	+
Plain radiography	–	–	+	+	–

+ = present; – = absent.
From Borenstein DG, Wiesel SW, Boden SD. *Neck Pain: Medical Diagnosis and Comprehensive Management.* Philadelphia: WB Saunders; 1996.

TABLE 407-5 MECHANICAL LOW BACK PAIN

	MUSCLE STRAIN	HERNIATED NUCLEUS PULPOSUS	OSTEOARTHRITIS	SPINAL STENOSIS	SPONDYLOLISTHESIS	SCOLIOSIS
Age (yr)	20-40	30-50	>50	>60	20	30
Pain pattern location	Back (unilateral)	Back (unilateral)	Back (unilateral)	Leg (bilateral)	Back	Back
Onset	Acute	Acute (prior episodes)	Insidious	Insidious	Insidious	Insidious
Standing	↑	↓	↑	↑	↑	↑
Sitting	↓	↑	↓	↓	↓	↓
Bending	↑	↑	↓	↓	↑	↑
Straight leg	–	+	–	+ (stress)	–	–
Plain radiography	–	–	+	+	+	+

From Borenstein DG, Wiesel SW, Boden SD. *Low Back Pain: Medical Diagnosis and Comprehensive Management,* 2nd ed. Philadelphia: WB Saunders; 1995.

Infections of the disc (Chapter 421) cause sharp back pain worsened by movement. Arachnoiditis (Chapter 420), an inflammatory process of the arachnoid space, can cause diffuse, chronic back pain, often after the introduction of foreign substances or manipulation of the intrathecal space. Finally, 20 to 50% of patients with depression (Chapter 404) will complain of back pain that often is diffuse and described in emotionally laden terms. Complaints of low back pain are also common in malingering patients.

TREATMENT

Rx

Treatment options vary according to the severity of pain, presence of radicular signs or symptoms, and any underlying disease. *Acute nontraumatic neck pain* is common and usually benign. Beneficial treatments include nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen 600 mg three times daily for 2 weeks), exercise, and physical therapy. The low risk of myocardial

TABLE 407-6 DIFFERENTIAL DIAGNOSIS OF ORGANIC CAUSES OF LOW BACK PAIN*

MECHANICAL LOW BACK OR LEG PAIN (97%)†	NONMECHANICAL SPINAL CONDITIONS (~1%)‡	VISCERAL DISEASE (2%)
Lumbar strain, sprain (70%)§	Neoplasia (0.7%)	Disease of pelvic organs
Degenerative processes of discs and facets, usually age related (10%)	Multiple myeloma	Prostatitis
Herniated disc (4%)	Metastatic carcinoma	Endometriosis
Spinal stenosis (3%)	Lymphoma and leukemia	Chronic pelvic inflammatory disease
Osteoporotic compression fracture (4%)	Spinal cord tumors	Renal disease
Spondylolisthesis (2%)	Retroperitoneal tumors	Nephrolithiasis
Traumatic fracture (<1%)	Primary vertebral tumors	Pyelonephritis
Congenital disease (<1%)	Infection (0.1%)	Perinephric abscess
Severe kyphosis	Osteomyelitis	Aortic aneurysm
Severe scoliosis	Septic discitis	Gastrointestinal disease
Transitional vertebrae	Paraspinous abscess	Pancreatitis
Spondylolysis‖	Epidural or subdural abscess	Cholecystitis
Internal disc disruption or discogenic low back pain¶	Shingles	Penetrating ulcer
Presumed instability**	Inflammatory arthritis (often associated with HLA-B27) (0.3%)	Cardiac or pericardial disease
Other structural anomalies	Ankylosing spondylitis	Pulmonary or pleural disease
	Rheumatoid arthritis	
	Psoriatic spondylitis	
	Reiter's syndrome	
	Inflammatory bowel disease	
	Arachnoiditis	
	Scheuermann's disease (osteochondrosis)	
	Paget's disease of bone	

*Values in parentheses indicate the estimated percentages of patients with these conditions among all adult patients with low back pain in primary care, excluding nonorganic causes such as conversion reaction, psychosis, litigation-related disorders, malingering, and substance abuse. Diagnoses in italics are often associated with neurogenic leg pain. Percentages may vary substantially according to demographic characteristics or referral patterns in a practice. For example, spinal stenosis and osteoporosis will be more common in geriatric patients, spinal infections in injection drug users, and so forth.
†The term *mechanical* is used to designate an anatomic or functional abnormality without an underlying malignant, neoplastic, or inflammatory disease. Approximately 2% of cases of mechanical low back pain or leg pain are accounted for by spondylolysis, internal disc disruption, or discogenic low back pain and presumed instability.
‡Scheuermann's disease and Paget's disease of bone probably account for less than 0.1% of nonmechanical spinal conditions.
§Strain and sprain are nonspecific terms with no pathoanatomic confirmation. Idiopathic low back pain may be a preferable term.
‖Spondylolysis is as common in asymptomatic persons as in those with low back pain, and its role in causing low back pain remains ambiguous.
¶Internal disc disruption is diagnosed by provocative discography (injection of contrast material into a degenerated disc, with assessment of pain at the time of injection). However, discography often causes pain in symptomatic adults, and the condition of many patients with positive discograms improves spontaneously. The clinical importance and appropriate management of this condition remain unclear. Discogenic low back pain is used more or less synonymously with internal disc disruption.
**Presumed instability is loosely defined as more than 10 degrees of angulation or 4 mm of vertical displacement on lateral flexion and extension radiographs. However, the diagnostic criteria, natural history, and surgical indications remain controversial.
From Deyo RA, Weinstein JN. Low back pain. *N Engl J Med.* 2001;344:363-370.

infarction or upper gastrointestinal bleed from NSAIDs must be weighed against pain relief and the relative benignity of the condition. Chiropractic manipulation is of benefit but has the rare complication of posterior circulation stroke from arterial dissection, especially in patients younger than 45 years. Low-level laser therapy and acupuncture are also of short-term benefit. Cervical collars and traction are not of established benefit. Even in the absence of radicular pain, surgical intervention for neck pain is indicated in cases of vertebral instability, such as caused by fracture or dislocation. Surgery, including fusion, may be needed for stabilization after surgery for lesions such as tumors, infections, or hemorrhages. For neck pain that is accompanied by signs or symptoms of radiculopathy, surgery should be considered but is not usually the initial therapy (see later). If a cervical spine lesion is causing spinal cord compression, emergent evaluation for possible surgery is indicated (see later).

Because *acute low back pain* is generally benign, invasive therapy should be avoided in the first 3 months. Conservative treatment includes NSAIDs (e.g., ibuprofen 600 mg three times daily as needed) and controlled physical activity; strict bed rest for longer than 2 days is no better than restricted physical activity. Other options include local heat and massage. Spinal manipulation, exercise therapy, yoga, acupuncture, and cognitive-behavioral therapy are moderately effective.

For *persistent, nonradicular low back pain*, exercise and cognitive-behavioral therapy are recommended. Prolotherapy, in which a mild irritant is injected into a tendon or ligament to increase blood flow and to promote healing, and facet joint injections can be helpful, but intradiscal steroid injections and percutaneous intradiscal radiofrequency thermocoagulation are not effective. When persistent nonradicular low back pain is accompanied by associated degenerative spine changes, surgical fusion is of benefit but not superior to interdisciplinary rehabilitation.

Surgery is indicated for spine instability, progressive neurologic deficits, or severe radicular pain that persists for more than 3 months despite conservative therapy, especially in patients with spinal stenosis and herniated discs. When degenerative changes lead to lumbar scoliosis with or without neurologic signs, decompressive surgery with or without fusion appears effective for at least 5 years for the majority of patients. In more focal disorders, surgery to remove disc material pressure from pain-sensitive structures can be considered; techniques include open, laser, and microdiskectomy approaches, with little evidence to favor one option over the other.

PROGNOSIS

Between 50 and 85% of patients who have neck pain that persists for more than 1 day report recurrence of symptoms in 1- and 5-year follow-up. Patients younger than 45 years have less recurrence, and patients aged 45 to 59 years have the highest risk. Prior neck injury or pain, coexistent low back pain, and self-perceived poor general health are risk factors for recurrence.

Mechanical spine pain, even with radicular symptoms, resolves without specific intervention within 30 days in many patients and within 3 months in 90% of patients. Recurrence is frequent, however, especially in patients with spondylosis, because the underlying process persists and further degeneration of the spinal elements can be expected.

Long-term disability is more common with obesity, low education level, tobacco use, high levels of pain at the onset, tendency to somatization, job dissatisfaction, lack of availability of light-duty employment, and need to perform significant lifting at work. The strongest factors affecting outcome are psychological, especially worrying, fear avoidance, anger, and frustration.

Spinal Stenosis

DEFINITION

Spinal stenosis, which is a narrowing of the spinal canal, results in compression of neural structures in the cervical and lumbar regions, where the

diameter of the spinal cord is largest. Signs and symptoms of spinal stenosis are referable to these levels. In the lumbar region, L4-5 is the most common level of stenosis, followed by L3-4 and L5-S1.

EPIDEMIOLOGY

The annual incidence of spinal stenosis in the United States is about 1 to 2 per l00,000 for the cervical region and 5 per 100,000 for the lumbar region. Spinal stenosis often coexists in the cervical and lumbar regions, and the incidence is higher in patients with more complex degenerative anatomy.

PATHOBIOLOGY

Primary spinal stenosis is due to a congenital narrowing of the spinal canal. Causes of secondary stenosis include chronic degenerative conditions, such as spondylosis and thickening of the ligamenta flava and longitudinale posterius neoplasia, osteomyelitis, and rheumatoid arthritis. In patients receiving corticosteroids long term, epidural lipomatosis is a cause predominantly at the thoracic level.

In spinal stenosis, myelopathy results from compression of the veins that drain the canal, thereby leading to capillary stasis and edema, which result in further compromise of the spinal cord. If the anterior spinal artery is also occluded intermittently or chronically, ischemic gliosis develops. The cord itself can be compressing, and dynamic injury can occur during flexion and extension, especially in chronic degenerative conditions associated with thickening and buckling of the ligamentum flavum. Superimposed trauma, such as severe flexion-extension from whiplash injury or falls, can cause the central cord syndrome (see later, Disorders of the Spinal Cord).

CLINICAL MANIFESTATIONS

Cervical stenosis, which usually results from spondylosis (cervical spondylotic myelopathy) and degenerative spine changes superimposed on congenital stenosis, can be manifested in a number of ways. At the C5-8 level, both the cord and roots are involved, and patients develop lower motor neuron findings in the arms and upper motor neuron signs in the legs; the result is the slow onset of painless atrophy of the weakened hand muscles, accompanied by gait abnormalities. Above the C5 level, the arms may become numb and clumsy, but there is little atrophy. Gait problems are frequently described as leg stiffness, heaviness, or incoordination, and patients may complain of falls or fear of falling, difficulty walking on uneven surfaces, and needing to watch where they are walking. In general, neck pain is not as prominent a complaint as is low back pain in lumbar spinal stenosis, but radicular pain occurs in about one third of patients. On examination, a Lhermitte sign, which is a shocklike tingling traveling down the spine with neck flexion or less commonly with extension, may be elicited. Sensation to pinprick examination will often be decreased in the hands, but this finding may be patchy and not well demarcated. Increased muscle tone will predominate in the legs, and reflexes will likely be increased; the Babinski sign is often present. The stance and gait may be wide based, with slow, short steps. A Romberg sign may be present.

Lumbar spinal stenosis can present with intermittent or persistent signs and symptoms referable to both cord and roots; axial neck or back pain is almost always present. The pain can also radiate in a pseudoradicular pattern from the lumbar region into the gluteal region, groin, and one or both upper legs, but pain rarely radiates distal to the knee unless spinal root involvement occurs. Lumbar neurogenic claudication is perhaps the most specific; symptoms are precipitated by compressive effects on the spinal cord and exiting roots and are characterized by increasing leg paresthesias and weakness as the patient remains standing and gravity pulls the lumbar cord enlargement into the narrowed spinal segment. As opposed to vascular claudication (Chapter 79), symptoms occur even at rest and can be relieved only by bending at the waist or sitting; the patient will characteristically report improved ability to walk if bent at the waist. Other features that suggest neurogenic claudication rather than vascular claudication include back pain, paresthesias, numbness, weakness, and prolonged presence of symptoms after changing of position (seconds to 1 to 2 minutes in vascular claudication but 2 to 20 minutes in neurogenic claudication).

DIAGNOSIS

MRI can localize and quantify the severity of the stenosis. The normal diameter of the lumbar canal is approximately 22 to 25 mm, relative lumbar stenosis is 10 to 12 mm diameter, and a diameter of less than 10 mm is considered absolute stenosis. MRI also can identify any comorbid spinal disease, such as degenerative changes and spondylolisthesis. However, CT myelography, which provides the details needed for surgical treatment, is another alternative. Electromyography (EMG) is not generally useful in the diagnosis of spinal stenosis except in assessment of comorbid conditions, such as localized radiculopathy, which might be important for surgical planning, as well as for detection of other potentially significant disorders, such as polyneuropathy.

The differential diagnosis of lumbar spinal stenosis includes vascular claudication from peripheral vascular disease (Chapter 79) and abdominal aortic aneurysm (Chapter 78). The symptoms of vascular claudication are activity dependent, unlike the positional dependency of the spinal stenosis. Other conditions that can mimic lumbar stenosis include radiculopathy or disc prolapse, polyneuropathy, tethered cord, and spina bifida. Because cervical stenosis can cause both arm and leg symptoms, the differential diagnosis also includes multiple sclerosis (Chapter 419), syringomyelia (Chapter 426), Arnold-Chiari malformation (Chapter 426), cerebrovascular disease (Chapters 414 and 415), normal-pressure hydrocephalus (Chapter 195), and motor neuron disorders (Chapter 418).

TREATMENT

Rx

Spinal stenosis is not necessarily an indication for surgery. Conservative therapy with NSAIDs (e.g., ibuprofen or acetaminophen 600 mg three times daily or acetaminophen 650 mg every 6 hours as needed), muscle relaxants, physical therapy, and a hard cervical collar can help many patients. However, surgery should be considered in patients with severe symptoms and signs of progressive myelopathy. Decompressive laminectomy, with or without fusion, is superior to nonsurgical therapy for improvement of pain and function for at least a year in patients with lumbar spinal stenosis.■

PROGNOSIS

Because spinal stenosis is usually degenerative, it is a slowly progressive condition. After symptoms develop and the condition is affecting quality of life, decompressive surgery should be considered. Because the underlying condition itself is progressive, however, surgery is not a permanent cure, and symptoms often recur.

DISORDERS OF THE NERVE ROOTS

DEFINITION

Disorders of the nerve root, termed radiculopathy, lead to symptoms referable to a dermatome or myotome. Either the ventral (anterior, motor) or posterior (dorsal, sensory) root can be involved independently or after they join to form the spinal nerve. Symptoms will follow the anatomic location. Because the root must traverse the vertebral foramen, it is prone to disorders of the spine at these locations. *Sciatica,* which is a commonly used but poorly defined term, often connotes low back pain with radiation into the ipsilateral leg, thereby implying pain radiating along the sciatic nerve, which anatomically contains fibers originating in the L4-S2 roots. The *cauda equina syndrome* results from disease involving the roots of the lower lumbar and sacral spinal cord levels as they traverse inside the spinal canal on their way to exit below their respective vertebral bodies.

PATHOBIOLOGY

Irritation of the spinal sensory nerve root or dorsal root ganglion causes symptoms referable to that dermatome. Spontaneous dysesthesias are hypothesized to result from ectopic discharges from the injured nerve; sensitization of the injured nerve leads to tactile evoked dysesthesias in the same distribution. Mechanical compression of the nerve contributes to the syndrome. In addition, inflammatory cytokines leak from the nucleus pulposus into the epidural space, where they result in endoneurial edema and pain. The pro-inflammatory cytokine tumor necrosis factor-α is a likely main contributor. Rupture of the nucleus pulposus releases phospholipase A_2, which also plays an important role in the inflammatory process. The inflammatory process itself can cause pain even in the absence of frank root compression.

The nerve root exits through the intervertebral foramen, where it is subject to compression and injury. The proximal portion of the nerve root has a small region of decreased vascular supply, where it is especially prone to edema, which can exacerbate the effect of the original injury. Treatment of this edema is one of the potential therapeutic effects of corticosteroid injections. The S1 root is the most susceptible to injury at the foramen because it is the largest

diameter spinal nerve and exits through the narrowest lumbar foramen. In addition, because it is traveling inferiorly from the S1 spinal cord level to pass out of the foramen under the S1 vertebral body, it passes through the superior, most narrow part of the foramen. The superior location of the sensory root on these nerves may account for the early predominance of sensory symptoms versus motor symptoms.

CLINICAL MANIFESTATIONS

The symptoms of radiculopathy depend on the affected root. Root involvement is likely if pain radiates beyond the shoulder or the knee. In the thoracic region, root involvement often produces symptoms that "wrap around" the trunk. Radicular pain is often worsened by activities that increase intraspinal pressure, such as coughing, sneezing, straining, and other Valsalva maneuvers. The characteristics of the pain vary, but when they are exacerbated by such provocation, they are often described as sharp, shooting, electrical, and tingling. When reporting the symptoms, patients may point to or rub the distal dermatome where they are experiencing the discomfort (perceived pain). Patients also may report specific positions that increase or decrease pain; for example, sitting will often worsen the pain of acute lumbar disc herniation, and neck extension can produce radiating pain in cervical disc herniation or other processes that narrow the foramen.

It is uncommon for patients to spontaneously note anesthesia, but they often note dysesthesias in radiculopathy, even in the absence of spine pain. The localization of these dysesthesias often follows the dermatome but also may be described diffusely by the patient. Likewise, complaints of weakness may be difficult to isolate to a particular muscle; however, exceptions exist, such as when the patient complains of a weak grip or a foot drop.

On examination, side-by-side strength testing of specific muscles (see Table 401-1) can help identify slight weakness. Slight weakness may also be identified by evaluating for pronator drift in the arms or asking patients to walk on their toes, walk on their heels, and do shallow knee bends on each leg independently. Sensory examination should test all potential root distributions; pinprick is often sufficient, and it is helpful to ask the patient to report any abnormalities, not just frank hypesthesia. Hyperreflexia in the arms is not expected in a spinal nerve disorder and, if unexplained, should be further investigated for an injury to the spinal cord or brain (Chapter 406). Patients who are older than 65 years or who have a peripheral neuropathy (Chapter 428) might have reduced or even absent ankle jerks.

The cauda equina syndrome is manifested as unilateral or bilateral leg weakness, saddle anesthesia, urinary dysfunction with hesitancy or retention, and, less commonly, bowel dysfunction. Depending on the cause, it is frequently accompanied by low back pain. The syndrome can be accompanied by severe sciatica, which can be unilateral or bilateral but also involve perineal pain. The weakness of the legs, which may be asymmetrical, is of the lower motor neuron type. The major causes of the cauda equina syndrome include lumbar disc herniation, neoplasm, and lumbar spinal stenosis.

DIAGNOSIS

The history and physical examination are similar to the evaluation of neck and back pain (see earlier), with special emphasis on finding evidence of nerve root involvement.

The patient should be queried about bowel and bladder dysfunction. Frank incontinence needs to be investigated for either the cauda equina syndrome or a myelopathy. If the patient has any loss of perineal sensation, such as might be noted during or after voiding or bowel movement, the examination should test perianal sensation, anal sphincter tone, and anal wink reflex. Because the cauda equina syndrome involves nerve roots, reflexes should be normal or decreased; hyperactive reflexes or a Babinski sign would indicate a myelopathy (see later).

Ancillary Testing

Imaging to evaluate a potential radiculopathy is similar to the evaluation for neck and back pain (see earlier). EMG can localize radicular abnormalities and their severity as well as assess possible comorbid neurologic diseases, such as diffuse peripheral or entrapment neuropathies. EMG electrodiagnostic localization can be extremely helpful in determining whether a finding on MRI is truly associated with neurologic impairment, and it has a high sensitivity and specificity for identification of acute and chronic denervation when the motor (anterior) aspect of the root is involved. However, EMG is less sensitive (about 30 to 70%) if only the sensory (posterior) limb of the root is involved by the lesion. MRI with its high sensitivity and EMG with its high specificity should be considered complementary tests.

Differential Diagnosis

Many mechanical processes can injure the spinal nerve root (see earlier, Neck and Back Pain), and most of the causes of spine pain can cause root disorders. Spinal cord compression may accompany radiculopathy.

In addition to conditions that can affect the nerve root as it leaves the spinal column, intra-column abnormalities below the level of the conus medullaris can affect the lumbar and sacral roots before they exit, thereby resulting in the cauda equina syndrome. Most commonly, the cauda equina syndrome is caused by extrinsic compression of the caudal sac by a mass, such as a large and centrally herniated lumbar disc, metastatic tumor, abscess, or epidural hematoma, but arachnoiditis or chronic meningitis must be considered.

Disorders of the brachial or lumbosacral plexus can cause pain radiating down a limb in a radicular or polyradicular pattern. Painful peripheral neuropathies (Chapter 428) can also resemble a radiculopathy. Non-neurologic disorders, such as fibromyalgia (Chapter 282) and polymyalgia rheumatica (Chapter 279), can cause axial pain that mimics a radiculopathy. Cervical radiculopathy also can be mimicked by acromioclavicular joint arthropathy, shoulder bursitis, and the shoulder impingement syndrome; lumbar radiculopathy can be mimicked by hip arthritis, trochanteric bursitis, iliotibial band syndrome, and hamstring tendinitis (Chapter 264).

TREATMENT Rx

Acute neck and back pain, even with radicular symptoms, is usually self-limited and resolves. If radiculopathy is associated with an underlying non-structural lesion, such as infection or tumor, treatment should be directed toward that underlying lesion (see also later, Metastatic Spinal Cord Compression). If symptoms or neurologic dysfunction progresses or persists for more than 6 weeks, interventional options should be considered.

In *cervical radiculopathy,* either foraminal or epidural corticosteroid injection may be of benefit.[10] A series of injections, usually between one and three, provides short-term relief of radicular symptoms, with an acceptable adverse event profile. Although minor events, such as increased neck pain, headache, and vasovagal reactions, are relatively frequent (5 to 20%), serious events, such as epidural hematoma or abscess, are uncommon (<1%). In cervical spondylopathy with radiculopathy, surgery provides more rapid pain relief than does physiotherapy but little additional benefit in the long term.[11] Anterior cervical discectomy, with or without fusion, is beneficial.[1] Cervical anterior discectomy and arthroplasty result in a lower risk of postoperative dysphagia compared with discectomy and fusion,[12] but more complicated surgeries are not of established benefit.

In *lumbar radiculopathy,* transforaminal epidural steroid injections provide short-term symptom relief,[13] but there are no clear guidelines on how many injections or on the indications for continuing the series. Chemonucleolysis of a lumbar disc is moderately superior to placebo but inferior to surgery.

For symptomatic radiculopathy associated with a herniated disc, either open surgical discectomy or microdiskectomy is superior to nonsurgical therapy for at least 3 months.[1] If the condition is isolated to a single disc and no significant degenerative changes are present, longer periods of benefit are more likely. Systematic reviews suggest that conservative discectomy allows a quicker return to work and has less long-term back pain than does more aggressive surgery, but with the downside of an increased risk of recurrent disc herniation. Video 407-7 demonstrates a right L4-5 hemilaminectomy with removal of a herniated disc fragment. The presurgical magnetic resonance images show the position and extent of the disc herniation.

DISORDERS OF THE SPINAL CORD

DEFINITION AND GENERAL OVERVIEW

A disorder of the spinal cord itself is termed a myelopathy. A myelopathy can be intramedullary, as the result of a disorder intrinsic to the cord, or extramedullary, as the result of an abnormality that is extrinsic to the cord but compressing it.

EPIDEMIOLOGY AND PATHOBIOLOGY

Spinal cord disorders can be caused by a wide range of conditions (Table 407-7).

The functional elements of the spinal cord (Fig. 407-6) include descending tracts largely to motor and autonomic neurons, motor neurons, autonomic neurons, and sensory ascending tracts. The anterior horn cell motor neuron is the cell body for the axon that will become the anterior nerve root and

continue directly to innervate the muscle. The cell bodies for the primary sensory neurons reside in the dorsal root ganglion outside the spinal cord itself.

CLINICAL MANIFESTATIONS

The clinical manifestations of myelopathy result from the spinal level of the lesion. The majority of signs will be bilateral, but asymmetry, or even unilaterality, does not exclude a spinal cord lesion.

In general, the three major functions affected are motor, sensory, and autonomic, especially bowel, bladder, and erectile function. If anterior horn cells are involved at the lesion level, the corresponding myotome will exhibit lower motor neuron function (hypotonic weakness), and reflexes may be decreased at that level. Below the lesion, however, patients will have hypertonic weakness that can progress to spastic paralysis, hyperreflexion, and Babinski sign. Sensation will be decreased from the level of the lesion and distally. Because increased tone and spasticity often develop over time, they may not be dramatic at the initial clinical presentation. If the posterior columns are compromised, patients may lose joint position sense and develop ataxia, especially of gait. If the posterior columns of the cervical cord are impaired, patients may have *pseudoathetosis* of the fingers, manifested as unconscious athetotic movements of the fingers of the outstretched arm when the eyes are closed.

The *anterior cord syndrome* is manifested as lower motor neuron weakness at the level of the lesion (anterior horn); upper motor neuron weakness and spasticity below the lesion (corticospinal tracts); autonomic dysfunction below the level of the lesion (lateral horn), most often bowel and bladder dysfunction; and loss of pain and temperature sensation below the level of the lesion (spinothalamic tract). Vibration and joint position sense remain intact (posterior columns). The major causes of this syndrome are vascular, such as an anterior spinal artery, or an anteriorly impinging mass lesion, such as disc or vertebral body mass.

The *central cord syndrome* is manifested as lower motor neuron signs and symptoms at the level of the lesion (anterior horn cells) and upper motor neuron signs and symptoms below the lesion (corticospinal tracts), urinary retention, and a band of loss of temperature and pain sensation at the level of the lesion (anterior white commissure decussation of these fibers). In the midcervical level, this syndrome is typical of syringomyelia (Chapter 426). Other major causes include intramedullary tumors (Chapter 195) and post-traumatic cervical injury (Chapter 406) in patients with disc herniation or preexisting cervical spondylosis.

The *posterior cord syndrome* is manifested as complaints of imbalance, especially in the dark or with eyes closed, and an examination notable for ataxia, presence of Romberg sign, and loss of vibration sense and proprioception below the level of the lesion (posterior columns), with preservation of pain and temperature sensation. Patients are seldom weak. Posterior compression may be caused by spondylotic disease, but other major causes include deficiencies of vitamin B_{12} or vitamin E (Chapters 225 and 425), syphilis (Chapter 327), AIDS-associated vacuolar myelopathy (Chapter 401), and nitrous oxide inhalation (Chapter 425).

The *Brown-Séquard (cord hemisection) syndrome* combines features of these syndromes. At the level of the lesion, patients exhibit *ipsilateral* lower motor weakness (anterior horn) and loss of all sensation (posterior root entry zone). Below the level of the lesion, patients have *ipsilateral* upper motor weakness and spasticity (corticospinal tract) and *ipsilateral* loss of vibration sense and proprioception (posterior columns), with *contralateral* loss of pain and temperature (spinothalamic tract, the fibers of which have crossed from the opposite side through the anterior white commissure). The Brown-Séquard syndrome is often caused by trauma (Chapter 406) or eccentric compression.

TABLE 407-7 CAUSES OF MYELOPATHY

Trauma/compression	Neoplastic
Direct ± vertebral spine disease	Metastatic cord compression
Spondylotic myelopathy/stenosis	Spinal tumors
Post-traumatic syrinx	Paraneoplastic
Arachnoid cyst	Infectious
Vascular	Epidural abscess
Cord infarction	Syphilis
Dural arteriovenous malformation	Lyme disease
Inflammatory/autoimmune	Tuberculosis
Multiple sclerosis	HIV infection
Devic's disease	Tropical spastic paraparesis
Acute disseminating encephalomyelitis	Herpes zoster
Adrenomyeloneuropathy	Toxic/metabolic
Systemic lupus erythematosus	Post-radiation myelopathy
Sjögren's syndrome	Vitamin B_{12} deficiency
Mixed connective tissue disease	Vitamin E deficiency
Postinfectious/postvaccination	Heroin
Arachnoiditis	Epidural lipomatosis
	Congenital/hereditary
	Chiari malformation
	Syringomyelia

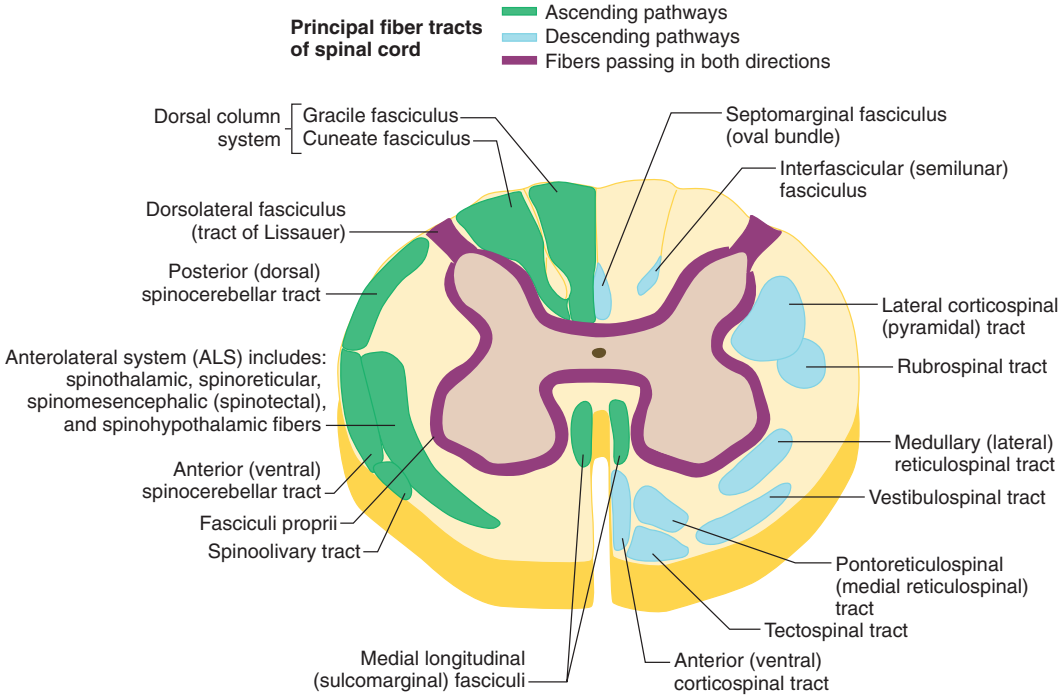


FIGURE 407-6. Principal fiber tracts of spinal cord.

The *conus medullaris syndrome* refers to dysfunction of the distal-most tapered portion of the spinal cord, which anatomically lies at approximately the T12-L1 vertebral spine level. The arms are normal; weakness in the legs is variable but often symmetrical when it is present. The main signs and symptoms are sexual dysfunction, loss of bowel and bladder control, and perianal anesthesia with loss of the anal wink reflex. The major causes are disc herniation, lumbar stenosis, and neoplasm.

DIAGNOSIS

Symptoms of bilateral involvement of the arms or legs suggest a myelopathy, although bilateral leg involvement can be seen in lumbar spinal stenosis and the cauda equina syndrome. Complaints of leg stiffness or incoordination suggest spasticity from myelopathy. Other symptoms include a recent change in bowel or bladder function, erectile dysfunction, imbalance (especially in the dark or with eyes closed), and catching of feet when walking. These central symptoms can also reflect lesions of the brain stem and higher, so the patient should be queried about cortical and brain stem symptoms (e.g., cognitive function, vision, facial strength, sensation, and swallowing). Focal back pain supports a myelopathy.

Examination for a potential myelopathy must include an evaluation of anal tone and perineal sensation. The patient should be examined in a gown to allow inspection of the spine as well as the overlying skin. A *sensory level,* which represents a point where distal (inferior) sensation is altered, should also be sought, but a spinal cord lesion rarely causes a sharp line of sensory demarcation. Joint position sense can be diminished if the posterior columns are involved. A tandem gait will assess possible gait ataxia. Finally, the patient should be examined for distal hypertonicity, if not frank spasticity, by assessment for hyperreflexia and Babinski signs. *In acute spinal cord lesions, however, a state of "spinal shock" can cause hyporeflexia or even a flaccid paralysis.*

Ancillary Testing

MRI is the test of choice because it provides anatomic detail of the spine and subarachnoid space as well as the spinal cord. MRI may also show evidence of demyelinating or metastatic disease. Plain films are not adequate to evaluate the spinal cord. If the MRI is normal, lumbar puncture is sometimes useful for evaluation of conditions that resemble myelopathy: Guillain-Barré syndrome (Chapter 428), infectious or carcinomatous meningitis (Chapter 420), arachnoiditis, and transverse myelitis.

Differential Diagnosis

The many causes of myelopathy (see Table 407-7) can typically occur at any spinal level, but certain conditions predominate at specific spinal levels.

Any lesion that has an upper *cervical* location must be evaluated for disorders of the craniocervical junction, especially disorders that can produce atlantoaxial instability, such as rheumatoid arthritis (Chapter 272); after trauma, cervical or odontoid fracture must be excluded. Disorders at the base of the skull, such as Chiari I and other congenital malformations (Chapter 426), can sometimes affect the upper cervical cord. Syringomyelia (Chapter 426), which may or may not be associated with Chiari malformation, also has a predilection for the cervical cord.

The *thoracic* cord is relatively protected from all but direct trauma, but it is the most common site for metastatic cord compression. Transverse myelitis is most commonly thoracic, and the thoracic cord also is particularly vulnerable to a watershed ischemic myelopathy due to severe hypotension. Epidural lipomatosis often is most symptomatic at the thoracic level.

The *lumbar-conus* region is the most common site for disc herniations. In addition, ependymomas are relatively more common in this region, as are metastases from more caudal locations and compression from arachnoiditis.

The rapidity of onset helps in diagnosis. *Acute or relatively acute myelopathy* suggests vascular causes, trauma, demyelinating lesions, or sudden decompensation of a preexisting lesion, such as a pathologic fracture. In a young person, with no other comorbid illnesses, a demyelinating illness, such as multiple sclerosis (Chapter 419) or acute disseminated encephalomyelitis (Chapter 422), is suggested; other central nervous system lesions separated in space with white matter signal abnormalities on MRI would increase the likelihood of this diagnosis. In older persons or patients with known vascular risk factors, hypotension, or an onset in the immediate postoperative period, a spinal cord infarction is possible. Sudden, sharp back pain suggests mechanical disorders (e.g., pathologic fracture, sudden worsening spondylolisthesis) or spinal cord infarction, whereas demyelinating lesions are often painless.

Myelopathy developing *subacutely,* especially accompanied by back pain, can be caused by metastatic disease (Chapter 195) and abscesses (Chapter 421). Both of these conditions must be evaluated and treated as true emergencies to prevent permanent paralysis. *Subacute* or *chronic* myelopathies include vitamin B_{12} deficiency (Chapter 425), although nitrous oxide inhalation may cause an acute expression of the disorder; syringomyelia (Chapter 426); and more slowly growing tumors, such as meningiomas (Chapter 195), lipomas, and neurofibromas (Chapter 426).

In the setting of known malignant disease or unexplained weight loss, metastatic cord compression (Chapter 195) must be considered. Weight loss, back pain, and fever can be seen in infection (Chapter 421) and occasionally spondyloarthropathies (Chapter 273). Infectious causes also include tropical spastic paraparesis (HTLV-1, Chapter 386). Syphilis (Chapter 327) is the cause of tabes dorsalis; patients may have other signs and symptoms, such as lancinating pains, ataxia, depressed leg reflexes, and Argyll Robertson pupils. Myelopathies that follow an infectious illness include acute disseminated encephalomyelitis and progressive necrotizing myelopathy. Transverse myelitis can follow viral infections, such as herpes zoster (Chapter 383). Myelopathy accompanied by evidence of multifocal cortical dysfunction would likely be multiple sclerosis or acute disseminated encephalomyelitis (Chapter 419). An accompanied peripheral neuropathy is seen in vitamin B_{12} deficiency myelopathy (Chapter 425), which tends to cause gait ataxia. Rheumatoid arthritis (Chapter 272) causes progressive loss of cartilage and bone destruction, potentially leading to atlantoaxial instability and cervical subluxation. Other systemic illnesses, such as systemic lupus erythematosus (Chapter 274), Behçet's syndrome (Chapter 278), and sarcoidosis (Chapter 95), can also cause myelopathies. In patients with exogenous or endogenous hypercortisolemia (Chapter 234), epidural deposition of unencapsulated fat can cause epidural lipomatosis that compresses the spinal column. Patients with a distant history of trauma might be evaluated for post-traumatic syringomyelia. Patients with a history of lumbar puncture, surgery, or intrathecal injections can develop arachnoiditis.

Younger patients are more likely to be symptomatic from congenital disorders, ankylosing spondylitis, or multiple sclerosis. In patients older than 55 years, cervical spondylytic myelopathy is the most common cause of myelopathic symptoms.

TREATMENT AND PROGNOSIS

Rx

Acute traumatic spinal cord lesions are treated with high-dose steroids (Chapter 34). Steroids should also be used in cord compression from metastatic tumors (Chapter 195). Steroids are also frequently used in transverse myelitis, although no controlled trials have been performed.

Patients with spinal cord lesions must be assessed emergently for any potential complications. With high cervical spine lesions, paresis or paralysis of the diaphragm and respiratory depression can occur. Although not emergent, higher cervical or medulla extension of inflammatory myelopathies can cause distressing hiccups and nausea. In lesions at the thoracic level or above, interruption of the lateral column autonomic pathways can lead to autonomic instability, including altered blood pressure responses. At almost any level, but especially at the conus and cauda equina, acute urinary retention may require catheterization. Long-term complications of spinal cord injury include osteoporosis (Chapter 251), orthostatic hypotension (Chapters 50 and 62), and chronic neuropathic pain (Chapter 428), all of which may require specific therapy. Other aspects of treatment and prognosis depend on the specific cause.

Specific Causes of Myelopathy

VASCULAR MYELOPATHIES

The central nervous system tissue of the spinal cord is as intolerant of ischemia as the brain is. Vascular myelopathy occurs when there is loss of blood flow to the spinal cord, whether it is acute or chronic and whether the cause is ischemic or hemorrhagic.

The blood supply to the spinal cord comes from the anterior and posterior spinal arteries that run longitudinally along the length of the spinal cord (Fig. 407-7). The paired posterior spinal arteries are derived in their most rostral origin as branches of the vertebral arteries at the level of the medulla and then run inferiorly along the posterolateral surface of the spinal cord. Along their course, they are fed by a series of small arteries that enter the spinal canal through the intervertebral foramina. Inside the canal, they anastomose extensively to provide redundancy. The anterior spinal artery is formed superiorly when branches of the vertebral artery join to form a single anterior spinal artery, which then runs down the midline of the anterior surface of the spinal

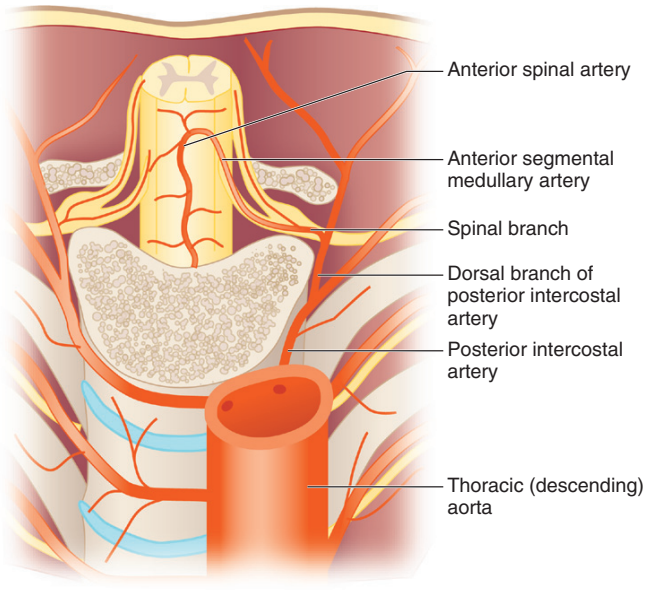


FIGURE 407-7. Blood supply of the spinal cord: section through thoracic level, anterosuperior view.

cord. It also receives feeders along its length, but not to the same extent as the posterior segmental branches do. A large anterior radicular artery at C5-6 supplies the cervical enlargement. The main caudal anterior blood supply, however, is from the large artery of Adamkiewicz that enters the spinal canal between the cord levels of T9 and L2 and serves as the main blood supply to the anterior spinal artery, which supplies the lumbar enlargement, the lower thoracic cord, and the conus medullaris.

Compromise of the microvascular supply to the cord underlies the gliotic changes in many slowly progressive myelopathies, such as spondylotic myelopathy. Ischemic causes include general hypotension, atherosclerotic disease, embolic events, vasculitis, and vascular steal; hemorrhagic events usually result from rupture of abnormal vascular malformations.

Severe global hypotension or aortic dissection or surgery can cause ischemic myelopathy, especially in watershed areas of the spinal cord, notably the thoracic region. Atherosclerosis, especially of the artery of Adamkiewicz, can lead to ischemic infarction of the cord by either decreased perfusion or thromboembolic events. Ischemia has also been reported to be a result of compression of the anterior spinal artery by a centrally herniated T12-L1 disc.

Embolic events and local thrombosis can occur in pregnancy and sickle cell disease (Chapter 166). During decompression sickness (Chapter 94), nitrogen bubbles cause microvascular emboli and ischemia. Vasculitis affecting the spinal cord is rare, but granulomatous angiitis of the central nervous system and polyarteritis nodosa (Chapter 278) can lead to infarction.

Spinal dural arteriovenous fistulas are the most common type of vascular malformation of the spinal cord. Arteriovenous malformations are most common in the thoracic cord, especially in patients older than 30 years. Vascular malformations can cause myelopathy by being mass lesions that compress local structures, by interfering with normal venous drainage, by diverting blood as part of a vascular steal with exercise of muscles that compete for blood flow, or by hemorrhage.

Spinal cord hemorrhage, which is rare, can occur intramedullary in the cord itself or in subarachnoid, subdural, or epidural locations. Intramedullary hemorrhage is most often caused by trauma, although bleeding can also occur into a tumor or from an intramedullary vascular malformation. Bleeding from a malformation that enters the subarachnoid space can cause back pain and headache. Epidural hematomas, which cause extramedullary cord compression, can occur as a complication of surgery, myelography, or lumbar puncture, particularly in patients with bleeding diatheses.

CLINICAL MANIFESTATIONS

Occlusion of the artery of Adamkiewicz usually presents with signs of thoracic watershed ischemia—paraplegia with relative sparing of the sacral roots. Infarction in the anterior spinal artery distribution results in dysfunction of the anterior two thirds of the cord, including the anterior horns, the spinothalamic tracts, and the corticospinal tracts; patients usually present with acute paraparesis and impaired bowel and bladder function. Sharp and sometimes circumferential pain at the level of the infarct is often described. Below the level of the lesion, temperature and pain sensation are lost, but vibration and position sense (posterior columns) are preserved.

Infarction of the posterior arteries is less common because of their better collateral circulation. Clinical manifestations, which are less dramatic, include loss of vibratory and position sense, ataxia, gait coordination problems, and Romberg sign; reflexes may be depressed at the level of the infarction.

The central cord vasculature syndrome is similar clinically to a traumatic central cord syndrome (Chapter 406). It may occur as a watershed lesion between the territories of the anterior and posterior spinal circulation and is most common in the cervical cord in older patients with preexisting cervical spondylotic disease.

Vascular malformations most often have a chronic progressive clinical course. Pain is common. Arteriovenous fistulas, commonly in the thoracic cord, present as progressive paraplegia. Patients may have exacerbations of symptoms with exercise and certain postures, and sudden worsening usually indicates hemorrhage.

DIAGNOSIS

Vascular malformations are initially evaluated by MRI, which also can assess the health of the surrounding tissue. When the vascular malformation is connected to the dura (arteriovenous fistula), myelography can occasionally detect lesions that are not seen or are poorly defined by MRI. If embolization or surgery is being considered, spinal angiography is needed to identify feeding and draining vessels, although the test carries a small risk of infarction. Intramedullary arteriovenous malformations are more commonly found in the cervical and thoracic levels and may require angiography to be visualized.

TREATMENT AND PROGNOSIS

Rx

Prognosis for most cases of spinal cord infarct is poor unless blood flow is restored rapidly. Treatment options are limited and include reversal of the cause of ischemia, for example, by correcting hypotension (Chapter 106) or treating for emergent sickle crisis (Chapter 166).

Arteriovenous fistulas are treated by occluding the shunt with embolization or surgery. Successful treatment may arrest and occasionally improve symptoms. Patients with suspected epidural hematomas (Chapter 406) require emergency treatment and surgery if there is progressive neurologic dysfunction.

INFLAMMATORY AND METABOLIC MYELOPATHIES

Transverse myelitis, multiple sclerosis, and other demyelinating diseases are considered in Chapter 419. Metabolic myelopathies can be caused by vitamin B_{12}, vitamin E, and copper deficiencies (Chapter 225).

Acute disseminated encephalomyelitis is mostly a monophasic disorder of demyelination of the spinal cord and brain. If it is isolated to the spinal cord, it might best be termed transverse myelitis. Parainfectious or postvaccination causes account for at least 75% of cases. Postvaccination acute disseminated encephalomyelitis is associated with measles-mumps-rubella vaccinations and diphtheria-tetanus-polio vaccinations as well as with vaccinations for influenza, hepatitis B, pertussis, and Japanese B encephalitis.

Connective tissue diseases can infrequently be a cause of myelopathy. Systemic lupus erythematosus (Chapter 274), with or without antiphospholipid antibody, can include myelitis in 1 to 3% of patients. Sjögren's syndrome (Chapter 276), Behçet's syndrome (Chapter 278), sarcoidosis (Chapter 95), ankylosing spondylitis (Chapter 273), mixed connective tissue disease (Chapter 278), and systemic sclerosis (Chapter 275) can be associated with inflammatory myelitis.

Human T lymphotropic virus type 1 (HTLV-1)–associated myelopathy/tropical spastic paraparesis (Chapter 386) is a chronic progressive myelopathy that causes leg weakness, spasticity, loss of vibratory sense, and bladder dysfunction. More than 90% of infected people remain asymptomatic, with transformation to a symptomatic condition thought to be largely related to the host's inflammatory response. Other neurologic dysfunctions associated with HTLV-1 infection include mild cognitive impairment, sensory neuropathy, and erectile dysfunction. There is no effective therapy.

DIAGNOSIS

In general, diagnosis of the inflammatory myelopathies is based on the clinical examination. MRI often shows a high T2 signal focal enlargement of the cord.

TREATMENT AND SECONDARY PREVENTION

Rx

Intravenous corticosteroid infusions (e.g., methylprednisolone, 1 g intravenously daily for 5 days) are usually the mainstay for treatment of acute attacks of inflammatory myelopathies.

In patients who do not respond to corticosteroids, plasma exchange is effective in the acute treatment of central nervous system demyelinating disorders[14]; about 60% of patients show improvement at 6 months. Factors predicting improvement are initiation of treatment within 15 days of the onset of symptoms and evidence of early improvement.

METASTATIC SPINAL CORD COMPRESSION

When metastatic cancer invades the spine or epidural space, the resultant destruction and growth compress the spinal cord and lead to a myelopathy. The prevalence of metastatic spinal cord compression may be as high as 5% in patients with cancer, depending on the type of malignant neoplasm and its tendency to metastasize to bone. Prostate (Chapter 207), breast (Chapter 204), and lung (Chapter 197) cancers each account for approximately 15 to 20% of cases, and non-Hodgkin's lymphoma (Chapter 191), renal cell cancer (Chapter 203), and multiple myeloma (Chapter 193) account for about 5 to 10% each.

Most metastatic disease causes compression as a result of an extradural lesion, although a smaller number of metastatic lesions can be intradural-extramedullary disease. Intramedullary metastases are rare. Symptoms can be caused by direct compression of the cord and roots in the epidural space as the result of direct extension from hematogenous metastasis to the vertebral body. However, some tumors, such as lymphomas, may grow through the intervertebral foramen without causing significant bone destruction; the accompanying edema can compromise the local vasculature and cause ischemic damage in addition to direct compression. Vertebral destruction can make the spine unstable and cause pathologic fractures, which can lead to cord and root damage.

CLINICAL MANIFESTATIONS

About 90% of patients present with pain that is classically worse on lying down and increases with the Valsalva maneuver. If the nerve root is involved, the pain will have a radicular component; if there is bone collapse, pain can be made worse by movement. Muscle weakness is present in 35 to 75% of patients at the time of diagnosis; sensory deficits are present in 50 to 70% of patients and autonomic dysfunction in 50 to 60% of patients. The range of signs will depend on the level of compression.

DIAGNOSIS

Spinal cord compression, which must be suspected when any patient with cancer complains of spine pain even in the absence of neurologic signs or symptoms, is a neurologic emergency. MRI is the test of choice because plain films, which might recognize bone metastases and vertebral collapse, will miss soft tissue tumors that are in the epidural space and yield no information about the spinal cord itself. Conventional myelography should be used if MRI cannot be performed because of availability or the presence of metallic implants in the patient. Because up to 35% of patients have more than one site of metastasis, care should be taken to image the entire spine by MRI, myelography, or isotope bone scanning.

Differential Diagnosis

For extradural lesions, the differential diagnosis includes lipomas, fibromas, meningiomas, and chordomas as well as vascular malformations and abscesses. Intradural-extramedullary lesions include neurofibromas (Chapter 426), neurinomas, meningiomas, vascular malformations, and, less often, metastases. Arachnoid cysts, although benign, can cause compression through pressure effect. Finally, intramedullary lesions that can present as myelopathy and must be considered in the differential of metastatic cord compression include intramedullary vascular malformations, ependymomas, astrocytomas, and syringomyelia.

TREATMENT

Rx

Prompt initiation of corticosteroids (e.g., dexamethasone, loading dose of 10-16 mg followed by tapering over 10 to 14 days) and radiation therapy are the mainstays of initial therapy. Surgical decompressive surgery plus radiation therapy is better than radiation therapy alone for maintaining ambulation[15] in patients who have a radioinsensitive tumor, have displacement of the spinal cord on MRI, have a single site of cord compression, and have not been totally paraplegic for more than 48 hours.

PROGNOSIS

Metastatic spinal cord compression usually occurs in the setting of metastases to multiple locations, and the expected survival prognosis is generally less than 6 months. Prognosis is improved in patients with malignant neoplasms that are sensitive to steroid therapy (especially lymphoma and leukemia) or are radiosensitive (e.g., multiple myeloma, small cell lung cancer). Patients who are ambulatory at the time of diagnosis, have a single site of compression, and had a less rapid onset of symptoms also generally have a better prognosis.

Grade A

1. Chou R, Fu R, Carrino JA, et al. Imaging strategies for low-back pain: systemic review and meta-analysis. *Lancet*. 2009;373:463-472.
2. Gross A, Miller J, D'Sylva J, et al. Manipulation or mobilization for neck pain. *Cochrane Database Syst Rev*. 2010;5:CD004249.
3. Chow RT, Johnson MI, Lopes-Martins RA, et al. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. *Lancet*. 2009;374:1897-1908.
4. Vas J, Perea-Milla E, Mendez C, et al. Efficacy and safety of acupuncture for chronic uncomplicated neck pain: a randomized controlled trial. *Pain*. 2006;126:245-255.
5. Hagen KB, Jamtvedt G, Hilde G, et al. The updated Cochrane review of bed rest for low back pain and sciatica. *Spine*. 2005;30:542-546.
6. Chou R, Huffman LH, American Pain Society, American College of Physicians. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med*. 2007;147:492-504.
7. Chou R, Atlas SJ, Stanos SP, et al. Nonsurgical interventional therapies for low back pain. A review of the evidence for an American Pain Society Clinical Practice Guideline. *Spine*. 2009;34:1078-1093.
8. Peul WC, van Houwelingen HC, van den Hout WB, et al. Surgery versus prolonged conservative treatment for sciatica. *N Engl J Med*. 2007;356:2245-2256.
9. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonsurgical therapy for lumbar spinal stenosis. *N Engl J Med*. 2008;358:794-810.
10. Benyamin R, Singh V, Parr AT, et al. Systemic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician*. 2009;12:137-157.
11. Nikolaidis I, Fouyas IP, Sandercock PA, et al. Surgery for cervical radiculopathy or myelopathy. *Cochrane Database Syst Rev*. 2010;1:CD001466.
12. McAfee P, Cappuccino A, Cunningham B, et al. Lower incidence of dysphagia with cervical arthroplasty compared with ACDF in a prospective randomized clinical trial. *J Spinal Disord Tech*. 2010;23:1-8.
13. Roberts ST, Willick SE, Rho ME, et al. Efficacy of lumbar transforaminal epidural steroid injections: a systematic review. *Phys Med Rehabil*. 2009;1:657-658.
14. Weinshenker BG, O'Brien PC, Patterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol*. 1999;46:878-886.
15. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. *Lancet*. 2005;366:643-648.

SUGGESTED READINGS

Chou R, Qaseem A, Owens DK, et al; for the Clinical Guidelines Committee of the American College of Physicians. Diagnostic imaging for low back pain: advice for high-value health care from the American College of Physicians. *Ann Intern Med*. 2011;154:181-189. *Clinical guidelines.*

Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? *JAMA*. 2010;303:1295-1302. *Review of the risk factors associated with the development of chronic pain.*

Deyo RA, Mirza SK, Martin BI, et al. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *JAMA*. 2010;303:1259-1265. *Complications increase with the invasiveness of surgery.*

Graber J, Nolan C. Myelopathies in patients with cancer. *Arch Neurol*. 2010;67:298-304. *Review of the diagnosis and treatment.*

Klineberg E. Cervical spondylitis myelopathy: a review of the evidence. *Orthop Clin North Am*. 2010;41:193-202. *A review of clinical trial data, including current controversies.*

408 REGIONAL CEREBRAL DYSFUNCTION: HIGHER MENTAL FUNCTIONS

DAVID S. KNOPMAN

DEFINITION

Higher mental function is at the core of what defines competent, independent individuals. Impairment of higher mental function can be broadly classified into four categories. Mental retardation is a form of cognitive impairment that is present from infancy. Acquired forms of cognitive impairment are delirium, dementia, and focal cognitive disorders. Delirium (Chapter 27) is defined by its acute or subacute onset and coexistent alterations in alertness. Dementia (Chapter 409) represents an acquired cognitive impairment that is usually gradual in onset and not associated with alterations in alertness. Focal cognitive disorders involve only one aspect of cognition: memory, language, visuospatial cognition, or executive cognitive functioning, each of which is supported by a different cerebral region.

For the majority of patients in a non-neurology practice, a global description such as "normal mental function" or "cognitively impaired" will suffice. "Cognitive impairment" then becomes a diagnosis that subsumes all forms of altered higher mental function regardless of which domains are affected or how severely they are affected.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

An informal conversation with a patient lacks sensitivity for detecting cognitive impairment. If cognitive impairment is suspected from the patient's history, formal assessments such as the Mini-Cog Test (see Table 26-4) should be performed. Bedside evaluations of orientation, memory, language, reasoning, and visuospatial function can be used to derive an overall view of cognitive function but do not automatically translate into diagnoses because alertness, cooperation, education, native language, sensorimotor function, and mood must be taken into account. Although scores on bedside mental status examinations correlate strongly with severity and prognosis, they provide only rough guides to cognitive ability and cannot localize a cognitive deficit anatomically in the brain. If cognitive dysfunction is discovered in the course of the bedside examination, further exploration of individual cognitive domains must be undertaken.

MEMORY FUNCTION AND AMNESIC DISORDERS

DEFINITION

Human memory operates over a wide time range, from seconds to decades, and with quantities of information ranging from a single word to a lifetime's experience. Each neural system that achieves this monumental dynamic range has its own brain localization (Table 408-1).

Declarative memory describes the type of learning and retrieval of facts and information that occur with conscious attention and intent; examples include remembering conversations, events, and intentions. Declarative memory has semantic and episodic components. Semantic memory refers to the brain's storehouse of knowledge, words, and facts. Episodic memory refers to learning and recall of specific events. Retention of information for more than a few seconds, in the face of exposure to additional facts, details, or events, requires declarative episodic memory to store and organize the information suitable for later recall. It is this declarative, episodic memory system that is assessed as "memory" in the clinical setting. Anterograde amnesia is the clinical manifestation of disturbances in declarative episodic memory. "Anterograde" refers to failure to learn and hence recall new information on an ongoing basis. Most disorders of memory also exhibit retrograde amnesia, a disturbance of the ability to retrieve information from the past.

Immediate recall of information with zero delay and zero intervening information is a very short-term declarative memory function. Immediate memory is capable of storing an image of an auditory message in exact form, but only a small amount and for a short period. The fidelity of immediate memory recall accuracy drops off dramatically over seconds, particularly if intervening sensory stimuli attract attention. A comparable system exists in the visual modality in that the memory acts like a photograph that fades rapidly. From a clinical perspective, immediate memory is separate from declarative episodic memory. Immediate recall is generally used as a marker of attention and alertness and not memory per se. Loss of immediate recall is not usually indicative of memory loss.

PATHOBIOLOGY

The hippocampal formations are the anatomic structures of importance for the declarative episodic memory system. The hippocampal formations are imaged well with magnetic resonance imaging (MRI) (Fig. 408-1). The principal input to the hippocampus comes through the entorhinal cortex from multimodal association areas in the frontal, parietal, and temporal neocortex. A second important input is a cholinergic pathway that originates in the septum of the medial-orbital frontal lobe. There are two principal output circuits of the hippocampal formations. One is via the subiculum back to multimodal association areas. The other hippocampal efferent pathway projects via the fornix to the mammillary bodies. The projection from the mammillary bodies passes through the medial thalamus to the ventral anterior nucleus of the thalamus, then to the posterior cingulate, and then back to the entorhinal cortex. The hippocampal circuit is believed to facilitate the formation of memory in association neocortices. The hippocampus does not store a particular learned fact, but rather it enables the appropriate region in a multimodal association cortical region to do so.

Lesions in one hippocampal formation will not generally have as devastating an impact on episodic memory as bilateral lesions will. However, in older people who may have subclinical bilateral hippocampal pathology, a unilateral lesion, particularly in the dominant hemisphere, may produce a dense

TABLE 408-1 DESCRIPTION OF MEMORY SYSTEMS

TYPE OF MEMORY FUNCTION	REGIONAL LOCALIZATION	LEARNING EFFICIENCY	TIME SPAN UNTIL EFFECTIVE RETRIEVAL	CAPACITY	CLINICAL TESTING TECHNIQUES	EXAMPLES IN DAILY LIFE
Declarative episodic memory	Hippocampus, medial thalamus	Single exposure	Decades	Very large, with rehearsal and elaboration	Recall of 3-4 words after 5 minutes	Recall of recent events and conversations
Declarative semantic memory	Temporal-parietal association cortices	Capable of single exposure; enhanced with repetition	Decades	Very large, perhaps limitless	Confrontation naming, general knowledge	Vocabulary, knowledge of life events from remote past
Attention span, "immediate memory"	Primary auditory or visual cortex	Single exposure only	Seconds	Very small: 7 ± 2 digits (auditory)	Digit span	Dialing a telephone number after hearing it or reading it
Working memory	Lateral frontal cortex	Single exposure only	Seconds	Small	Digits backward	Supporting many mental activities, such as mental arithmetic, abstract reasoning
Procedural memory	Basal ganglia, probably association neocortices	Requires extensive training	Decades	Moderate	Experimental laboratory methods only	Retention of motor skills, e.g., riding a bicycle or typing

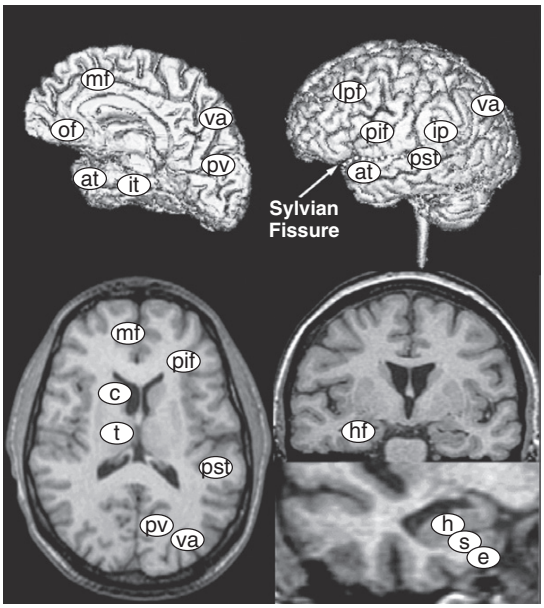


FIGURE 408-1. Magnetic resonance images of a normal brain. Upper left, Midsagittal view; **upper right,** left lateral view; **lower left,** axial view through the head of the caudate and body of the thalamus; **lower right,** coronal view through the mammillary bodies, with a magnified view of the medial temporal lobe. at = anterior temporal; c = caudate nucleus; e = entorhinal cortex; h = hippocampus; hf = hippocampal formation; ip = inferior parietal cortex; it = inferior temporal; lpf = lateral prefrontal cortex; mf = medial frontal cortex; of = orbital frontal cortex; pif = posterior inferior frontal cortex (Broca's area); pst = posterior superior temporal; pv = primary visual cortex (area 17); s = subiculum; t = temporal; va = visual association cortex (areas 18 and 19). (Courtesy Maria Shiung and Clifford Jack, MD.)

anterograde amnesia. Lesions in the columns of the fornix, mammillary bodies, and medial thalamus have also been linked to anterograde amnesia.

CLINICAL MANIFESTATIONS

Patients with anterograde amnesia have poor or no recollection of events, conversations, or observations. Family members report that patients repeat themselves in conversation or re-ask the same questions over the course of a few minutes to hours. Patients will generally forget important events and conversations, even when they were fully engaged in them. They will lose track of the date and time of day. They will forget appointments, even with reminders. Generally, patients with anterograde amnesia will fail to encode most events and happenings around them. The consequences of such memory failure are usually more evident to the family and acquaintances of patients with the disorder than they are to the patients themselves. Anosognosia (lack of awareness) for the deficit of anterograde amnesia is very common, though not universal. Patients who most vehemently complain of memory loss are often suffering from depression rather than focal cognitive dysfunction.

Because some degree of forgetting is ubiquitous in human experience, it is challenging to distinguish between "everyday" forgetting and forgetting that is pathologic. All adults occasionally misplace important items, overlook an appointment, or forget some part of a conversation. In cognitively normal individuals, distraction, preoccupation, inattention, exhaustion, sleep deprivation, or other major life stressors inevitably produce some instances of excess forgetting. Pathologic forgetting as a result of a brain disorder produces a much greater degree of forgetting than occurs in the course of normal daily life, but there is no formulaic description of the boundary at which normal forgetting ends and pathologic forgetting begins.

DIAGNOSIS

The diagnosis of anterograde amnesia begins with a complaint of memory impairment from the patient or from someone close to the patient. Testing of memory can be performed at the bedside in alert patients. The patient is asked to learn three or four words and recall them after 1 or 2 minutes. A patient with severe anterograde amnesia will recall none or at most one of the words, whereas individuals with normal memory can recall all of the words or all but one.

In patients with questionable memory difficulties, assessment by an experienced neuropsychologist is often a necessary part of the evaluation. Standardized tests of memory have greater precision and reliability and involve the use of lengthier material to be remembered and a longer delay between learning and recall.

Determining the Cause

Alzheimer's disease is the most common disorder in which anterograde amnesia occurs (Chapter 409). In Alzheimer's disease, anterograde amnesia is usually the dominant cognitive symptom, particularly early in the illness. Hippocampal atrophy is common (see Fig. 409-3). Anterograde amnesia also occurs in other dementing illnesses, such as vascular dementia and dementia with Lewy bodies.

Strokes can damage regions involved in episodic memory. Occlusion of the medial temporal branch of the posterior cerebral artery causes infarction of the hippocampus. Infarction in the territory of penetrating branches of the tip of the basilar artery causes bilateral medial thalamic infarcts.

Anterograde amnesia may be a major residual deficit after herpes simplex encephalitis (Chapter 382). Herpes simplex encephalitis has a predilection for damaging structures at the base of the cerebral hemispheres; frequently, the temporal lobes are severely damaged. Korsakoff's syndrome, the residual of the encephalopathy of thiamine deficiency (Chapter 425), is characterized by profound anterograde amnesia. Hemorrhagic necrosis of the mammillary bodies occurs in Korsakoff's syndrome. Survivors of closed head injuries (Chapter 406) may have anterograde amnesia because the medial temporal lobes are vulnerable to trauma as a result of their close proximity to the temporal bone. Survivors of an episode of anoxic-ischemic encephalopathy may also have dense anterograde amnesia. The pyramidal neurons of the CA1 region of the hippocampus are particularly vulnerable to hypoxic injury.

The syndrome of transient global amnesia involves anterograde amnesia, but the duration of the amnesia is a matter of 6 to 12 hours rather than the weeks or months seen in post-traumatic amnesia or the permanent deficits in patients with Alzheimer's disease or Korsakoff's syndrome. Transient global amnesia generally affects middle-aged or elderly individuals. Its cause is not known, although it is not usually due to typical cerebrovascular disease or epilepsy. Electroencephalography is typically not specifically abnormal, but diffusion-weighed MRI often shows distinctive abnormalities of the hippocampus a day or more after the onset of transient global amnesia.

THE APHASIAS

DEFINITION

Aphasia is a disorder of language at the conceptual level. Aphasics may have difficulty producing language, comprehending language, or both.

PATHOBIOLOGY

In more than 99% of right-handed individuals, language is localized to the left hemisphere. In left-handed individuals, language is also predominantly localized to the left hemisphere, although varying degrees of bilateral or rarely right hemispheric dominance may be seen. The hemisphere involved in language is referred to as the dominant hemisphere. Anatomic differences in the temporal and parietal lobes of the dominant hemisphere versus the other hemisphere also reflect its specialization for language.

In clinical practice, lesions in the dominant hemisphere's auditory association areas cause receptive language dysfunction. The critical regions are located in the superior temporal lobes adjacent to the primary auditory cortex and in the adjacent supramarginal and angular gyri of the inferior parietal lobule, an area known as Wernicke's area. Lesions in the dominant hemisphere's lateral inferior posterior frontal lobes, often referred to as Broca's area, result in expressive language deficits. Loss of access to one's vocabulary for either understanding spoken language or expressing oneself results from lesions in any portion of the region of the dominant hemisphere around the sylvian fissure, including the lateral posterior inferior frontal lobe, the inferior parietal lobule, and the superior and middle temporal gyri. Coronal and axial MRI scans give a detailed view of the critical language regions (see Fig. 408-1).

CLINICAL MANIFESTATIONS

The language comprehension difficulties in persons with aphasia must be distinguished from hearing disorders (Chapter 436), and the motor speech dysfunction in aphasia must be distinguished from dysarthria. Errors of articulation in persons with aphasia reflect altered conceptual selection of what is to be said. In aphasia, mispronunciation of a sound within one word may be followed by perfect pronunciation of the same sound in a different

word. In dysarthria, by comparison, the errors in articulation or phonation are consistent.

Aphasia has three principal components: impaired verbal comprehension, disordered verbal expression, and impaired naming. Disorders of reading, writing, and sentence repetition are additional elements of the aphasia syndrome. The disordered verbal comprehension may range from profound to mild. When profound, patients are unable to grasp the meaning of single words. In milder forms of disordered comprehension, patients may be able to follow one-step, but not two- or three-step commands. Usually, the comprehension difficulty involves both spoken and written language, but each can be affected separately. Anomia, which is an inability to produce names of people or objects, is common in almost all aphasic syndromes.

In expressive aphasic syndromes, written material and spoken speech are most often affected in parallel. Speech is labored in the expressive aphasias, and it lacks the normal melody and variation in intonation that characterize normal speaking. Melody and intonation are referred to as the prosody of speech. Speech is often grammatically impoverished. The number of words per utterance is greatly reduced, thus giving the speech a choppy, staccato character. These features are referred to as speech apraxia. Nonfluency is a related term that describes the reduced number of words and the terseness of verbal output. In some aphasic syndromes, speech is often degraded by anomia and paraphasic errors (word or syllable substitutions), even when fluency, melody, and intonation are preserved.

Specific Aphasic Syndromes

Specific, common aphasic syndromes exhibit various combinations of receptive and expressive difficulty (Table 408-2).

WERNICKE'S APHASIA

In Wernicke's aphasia, verbal comprehension of both written and verbal language is severely impaired. Patients with Wernicke's aphasia have difficulty understanding the meaning of individual words and may not be able to follow any command consisting of greater than one step. Their speech is fluent but marred by paraphasia and anomia. Wernicke's aphasics tend to lack awareness of the extent of their communicative difficulties and are often unaware that the words they are uttering are fundamentally incorrect. The location that typically causes Wernicke's aphasia is the dominant posterior superior temporal lobe or inferior supramarginal gyrus (see Fig. 408-1).

BROCA'S APHASIA

Broca's aphasia is a syndrome in which expressive language is prominently affected. Patients with Broca's aphasia have nonfluent, labored speech. The location of the lesion that typically causes Broca's aphasia is the dominant posterior inferior frontal lobe (see Fig. 408-1). Patients with Broca's aphasia have largely preserved comprehension and, as a result, are acutely aware of their difficulties and become frustrated with them. Depression is common in Broca's aphasics.

GLOBAL APHASIA

Global aphasia occurs when both expressive and receptive problems are present. Global aphasia often appears acutely after a major infarction, hemorrhage, or traumatic brain injury involving the dominant hemisphere.

ANOMIA

Anomia is at the milder end of the spectrum of language disorders. Some anomic aphasics also have difficulty with sentence repetition, even in the presence of relatively preserved comprehension and verbal expressive abilities. There is some controversy whether this latter syndrome, called conduction aphasia, represents a disconnection between the perisylvian centers for comprehension and expression or whether it represents a lesion in the cortical auditory areas involved in immediate auditory memory.

IDEOMOTOR APRAXIA

Ideomotor apraxia is a disorder at the interface between comprehension and execution of facial or limb motor actions. Patients with ideomotor apraxia have no paresis of the face or limb musculature and are able to carry out simple tasks, but they are unable to execute more complex tasks or commands. For example, in a woman who is able to name a comb and use her right hand to point to parts of her body, ideomotor apraxia can be demonstrated if she is unable to indicate through her actions how she would use the comb.

DIAGNOSIS

The diagnosis of aphasia is made by listening to the patient speak and by examining comprehension, naming ability, reading, and writing in a standardized fashion. Frequently, the diagnosis of aphasia is made during attempts to obtain a history from the patient. It is helpful to prompt patients to speak about a neutral topic, such as what they had for their last meal or what they did the previous day. Listening to their spontaneous speech allows the examiner to characterize its fluency, grammatical form, articulation, melody, and intonation, as well as difficulty finding words, the presence of paraphasias, and the overall information content.

Comprehension should be examined formally by asking the patient to perform tasks that range from one to at least three steps. Naming can be tested by asking the patient to name a series of common objects, such as the parts of the hand and arm (e.g., thumb, palm, knuckles, wrist, elbow). In general, the more commonly a word is used in the language, the easier it will be to name, whereas infrequent words are harder for aphasics. Reading and writing should also be tested.

Portions of the dominant perisylvian cerebral cortex may be damaged by infarction (Chapters 414 and 415), hemorrhage, and other space-occupying brain lesions such as neoplasms (Chapter 195) and abscesses (Chapter 421). Aphasia secondary to stroke has an abrupt onset, usually with some subsequent improvement. Recovery from aphasia after a stroke may occur as ischemic zones around an infarction eventually regain function. Regions remote from the infarction may also be synaptically depressed acutely after a stroke ("diaschisis") but eventually regain function. Finally, regions in the nondominant hemisphere may become more active over the course of recovery. Aphasia that has a gradual and slowly progressive onset occurs in the degenerative dementia syndromes of progressive aphasia and semantic dementia (Chapter 409).

TREATMENT

Rx

Speech therapy may be helpful for patients in the first few months after a brain injury that causes aphasia.

TABLE 408-2 MAJOR APHASIC SYNDROMES

APHASIA SYNDROME	REGIONAL LOCALIZATION	SPONTANEOUS SPEECH ABNORMALITIES	AUDITORY COMPREHENSION	CONFRONTATION NAMING	SENTENCE REPETITION
Broca's aphasia	Lateral inferior frontal lobe	Nonfluent, labored, agrammatic	Preserved	Poor	Poor
Wernicke's aphasia	Posterior superior temporal-parietal supramarginal gyrus	Fluent, many paraphasic errors, very little information content	Very impaired	Poor	Poor
Global aphasia	Major portions of the frontoparietal operculum and superior temporal lobe	Nonfluent or virtually absent	Very impaired	Poor	Poor
Anomic aphasia	Small lesion somewhere in the perisylvian region	Fluent, may contain some paraphasias	Normal or mildly impaired	Poor to moderately impaired	Preserved or impaired

CORTICAL DISORDERS OF VISUAL FUNCTION AND HEMISPATIAL NEGLECT

DEFINITIONS

Cortical disorders of vision and spatial cognition are caused by lesions in the occipitoinferotemporal or occipitoposteroparietal lobes. The principal disorders of cortical visual functioning are alexia (impaired reading), object agnosia (impaired recognition of visual forms), and prosopagnosia (impaired face recognition). The principal disorders of spatial cognition are simultanagnosia (impaired integration of complex visual scenes), dressing apraxia, and visual hemispatial neglect (lack of awareness of the personal or extrapersonal hemispace). Diagnosis of a cortical visual disorder requires integrity of primary visual function from the cornea to the lateral geniculate nuclei.

PATHOBIOLOGY

Higher visual function is localized to a network centered in the occipital lobe and includes the inferior temporal and posterior parietal lobes (see Fig. 408-1). From area 17, processing of visual information passes to visual association areas 18 and 19. From there it proceeds in several directions. Disorders of higher visual function can be related to a ventral or to a dorsal pathway. The ventral pathway from the visual centers to the medial temporal lobe links visual information to meaning ("What is the object?"). The dorsal visual processing pathway, which links the visual centers to the parietal lobes, is concerned with locating objects in space and determining spatial relationships among objects in order to grasp a complete visual scene ("Where is the object?"). Cortical control of the extraocular muscles in the parietal lobes is an integral part of the process whereby the eyes are directed to various elements of a visual scene so that the individual elements are synthesized into a coherent ensemble.

Alexia occurs as a result of lesions in the ventral pathway of the dominant hemisphere. Object agnosia may also occur with lesions, usually bilateral, in the ventral pathway. Simultanagnosia, dressing apraxia, and hemispatial neglect are syndromes caused by lesions in the dorsal pathway. Simultanagnosia usually requires bilateral posterior parietal lesions. Dressing apraxia and hemispatial neglect arise from unilateral lesions, most often in the nondominant hemisphere. Cortical blindness is a consequence of bilateral occipitoparietal pathology.

CLINICAL MANIFESTATIONS

Alexia may occur as an isolated deficit, or it may occur in the context of other evidence of aphasia. Patients may be able to recognize individual letters but are unable to recognize a string of letters as a word. In pure alexia, auditory comprehension of words and sentences is preserved. Patients with object agnosia may be unable to identify objects visually, but they will be able to recognize the object based on its characteristic sound or how it feels to touch. In simultanagnosia, patients may be able to identify small objects easily if they happen to appear within the narrow viewing area at the center of their visual field. At the same time, such patients will fail to grasp the bigger visual picture. They may appear to be functionally blind. This clinical picture is referred to as Balint's syndrome.

Patients with cortical disorders usually have difficulty with visuoconstructional tasks such as copying figures or drawing simple objects such as a flower, a house, or a clock. Dressing apraxia represents a deficit of practical significance in which patients are unable to comprehend the orientation of articles such as a shirt or a blouse and to manipulate them.

The most severe form of a cortical disorder of visuospatial processing is cortical blindness. In this condition, in which the anterior visual pathways can be reasonably believed to be intact, patients appear functionally blind. On occasion, they also exhibit anosognosia for the blindness and claim that they can see. This latter condition is referred to as Anton's syndrome.

Hemispatial neglect occurs in the setting of acute strokes involving the nondominant perisylvian region. Even when there is no hemianopia as measured by single visual stimuli, presentation of double simultaneous stimuli to the patient reveals unawareness in the nondominant field. Hemispatial neglect can be demonstrated at the bedside with a task such as drawing a clock. A patient with hemispatial neglect will fail to place the numbers on the nondominant side (i.e., the left side in a right-handed person). Patients with hemispatial neglect may sometimes deny that their paretic limb belongs to them.

DIAGNOSIS

Information about visual functioning can be obtained from the history. The patient or the patient's informant may report that the patient cannot read, cannot read a clock, or cannot find objects when asked to get something off a table or out of a cupboard. There is often a history of motor vehicle accidents in which the patient failed to see another vehicle, the curb, or the side of a garage. Patients may report difficulty recognizing people's faces, even though they are able to recognize them by their voices or by other cues.

Bedside tests that screen for visuospatial deficits include either copying a simple geometric design or drawing an object. Intersecting pentagons and a cube are objects used clinically. Clock drawing is a brief, but informative exercise. Reading of words or commands and naming of objects can be done at the bedside as well. Face recognition is more difficult to assess at the bedside. Formal testing of visuospatial function in the neuropsychology laboratory involves the use of specially designed instruments to characterize visual processing.

The etiology of lesions that cause deficits in cortical vision and spatial cognition ranges from focal cerebrovascular disease, neoplasms, infectious processes, and brain trauma to neurodegenerative disorders. When a stroke causes a disorder of cortical visuospatial processing or hemispatial neglect, it is usually abrupt in onset. Space-occupying brain lesions such as neoplasms or brain abscesses that cause cortical visual disorders do so on a subacute basis. Disordered visuospatial function may also appear insidiously when caused by the degenerative disorder posterior cortical atrophy.

EXECUTIVE COGNITIVE DYSFUNCTION AND CONTROL OF PERSONAL BEHAVIOR

DEFINITIONS

Integrative abilities that are broadly referred to as executive cognitive function include mental agility, abstract reasoning, and problem solving. Executive cognitive function represents processes that support mental flexibility, adaptability, focus, and tenacity. Control of personal actions and regulation of interpersonal relationships are also closely related to executive cognitive dysfunction. The term "comportment" denotes how a person behaves, particularly toward other people.

PATHOBIOLOGY

The anatomic basis of executive cognitive function and comportment is a network of brain regions anchored by the prefrontal and anterior temporal lobe neocortex (see Fig. 408-1). These regions receive input from multiple cortical and subcortical regions. The caudate nucleus is the site of a major frontal lobe efferent pathway. The medial thalamus is a major afferent source to the frontal lobes. The anterior temporal lobes are also part of the same integrative circuitry as the prefrontal regions. Lesions in the lateral prefrontal regions are associated with slowing of cognitive processing, difficulty with set shifting (switching from one idea or task to another), difficulty initiating tasks, and loss of mental flexibility. The frontal and anterior temporal lobes are involved in the modulation of personal behavior and interpersonal relationships. Patients with lesions in the medial prefrontal lobes are often apathetic and lack initiative. Patients with lesions in the orbital frontal or right anterior temporal lobe may exhibit disinhibition, impulsivity, and a striking loss of ability to interpret or predict the feelings of others.

Traumatic brain injury (Chapter 406) is a common cause of frontal lobe and anterior temporal damage. The orbital frontal, frontal polar, and anterior temporal regions are particularly vulnerable to contusions because of their proximity to the skull. Patients with traumatic brain injuries may also suffer diffuse white matter damage as a result of shear injuries. Disconnection of the frontal and anterior temporal lobes from other parts of the brain can produce executive cognitive dysfunction and altered control of personal behavior.

CLINICAL MANIFESTATIONS

Executive cognitive functioning and control and regulation of behavior are usually affected concurrently. Patients with executive dysfunction are deficient in goal-oriented behavior; they lose the ability to predict the consequences of their actions or words. Patients with executive dysfunction also exhibit poor mental agility and inflexibility in their thinking and control of their actions. They are easily distracted and exhibit a tendency to perseverate, in which the answer to a prior question is repeated in response to subsequent questions. They are disinhibited; as a consequence, when asked to recall a

specific event, they may glibly answer with a fabrication, a phenomenon referred to as confabulation.

Patients with lateral prefrontal pathology exhibit poor performance on tests of abstract reasoning and mental agility. In a test such as verbal similarities, they tend to be very concrete and narrowly focused. They become easily distracted and are slow in performing tasks that require sustained attention. Because of their mental rigidity and difficulty in set shifting, they do poorly on tests that require the ability to vary their response strategies, such as verbal fluency tests.

Patients with medial frontal lesions are often profoundly apathetic and lack initiative and motivation. They may be laconic and completely unable to express emotion, whether it be anger, sadness, or elation. They tend to be indifferent to their surroundings, a state referred to as "abulia." The majority of patients with substantial prefrontal or anterior temporal lobe pathology lack insight into the extent of their inappropriate behavior.

In contrast, other patients with altered comportment exhibit different manifestations of dysregulation of personal actions and interpersonal behavior. These alterations may include difficulty controlling impulsivity, poor social graces manifested as rude behavior or caustic comments, a disregard for the feelings of others (loss of empathy), and a general failure to understand what constitutes acceptable behavior in a particular social context. If the underlying disease is progressive, gross alterations in table manners and loss of interest in maintaining personal hygiene may appear. Inappropriate sexual behavior may occur. Patients with prominent disease of the frontal lobes may also exhibit hyperorality, which is a compulsion to put nonfood objects into their mouths. Hyperorality can be life-threatening, depending on the substance ingested.

DIAGNOSIS

The clinical history is essential for documenting the characteristic changes in personality, behavior, and interpersonal relationships. The history must almost always be obtained from an informant who knows the patient well because the patient may assert that there are no problems.

Mental status examination is an integral part of the diagnosis of an executive cognitive disorder. Simply interacting with the patient may be quite revealing. The patient may exhibit abulia, disinhibition, socially inappropriate behavior, or easy distractibility. Tests of executive cognitive function that are suitable for bedside use include verbal similarities and differences, the digits backward test, reciting the months of the year backward, or spelling a word backward. Verbal fluency, which is a very useful test of mental flexibility and set shifting, is tested by asking patients to produce as many words as they can that begin with a particular letter of the alphabet in 60 seconds. Frequently, a patient with a frontal lesion will quickly produce two or three words and then stop.

Bedside testing of executive cognitive dysfunction provides only a superficial view of the cognitive domain. Assessment in the neuropsychology laboratory gives a more refined estimate of the degree of executive dysfunction.

Space-occupying lesions of the frontal lobes such as neoplasms or brain abscesses can lead to the cognitive and behavioral syndromes of frontal lobe dysfunction. With these diseases, executive cognitive dysfunction and alteration of control of personal behavior develop over a period of weeks.

Neurodegenerative diseases such as frontotemporal lobar degeneration (Chapter 409) are associated with dysfunction and brain loss in the prefrontal (see Fig. 409-4) and anterior temporal lobes. These disorders may produce the entire spectrum of executive cognitive dysfunction and altered control of personal behavior over a period of a year or longer.

Some diseases that do not directly damage the frontal or anterior temporal neocortex may cause executive cognitive dysfunction and alteration of control of personal behavior because of the interconnectedness of the frontal and anterior temporal lobes with other cortical and subcortical regions. Multiple sclerosis (Chapter 419), a disorder of white matter pathways, may cause abnormalities in cognition and behavior of the frontal type. Similarly, Huntington's disease (Chapter 417) and progressive supranuclear palsy, which affect the caudate nuclei, may also resemble a frontal cognitive and behavioral syndrome and result in executive cognitive dysfunction and alterations in comportment.

TREATMENT

Rx

Cognitive-behavioral therapies offer modest, but definite benefit for patients with aphasia and for those with mild attention deficits and mild memory deficits caused by brain injury.

SUGGESTED READINGS

Bartsch T, Deuschl G. Transient global amnesia: functional anatomy and clinical implications. *Lancet Neurol*. 2010;9:205-214. *Review*.

Budson AE. Understanding memory dysfunction. *Neurologist*. 2009;15:71-79. *Clinically oriented review of memory disorders*.

Mahoney CJ, Rohrer JD, Omar R, et al. Neuroanatomical profiles of personality change in frontotemporal lobar degeneration. *Br J Psychiatry*. 2011;198:365-372. *Personality change in FTLD can be correlated with changes in regional gray matter*.

409

ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

DAVID S. KNOPMAN

DEMENTIA

DEFINITION

Dementia, which is a disorder of cognition, interferes with daily functioning and results in loss of independence (Table 409-1). The majority of dementias are of gradual onset, are progressive in course, and occur in persons with previously normal cognition. However, none of these features are necessary aspects of the definition of dementia. Some dementias, such as those caused by an acute neurologic illness secondary to stroke, encephalitis, or head trauma, may begin abruptly and then remain static for long periods. Conversely, a small subset of dementias, such as Creutzfeldt-Jakob disease (Chapter 424), have a rapid onset and a course that can run for less than a year. Dementia may also occur in persons with developmental disabilities and long-standing cognitive deficits.

EPIDEMIOLOGY

The prevalence and incidence of dementia increase with advancing age. Dementia is uncommon before 50 years of age. In individuals older than 65 years, the prevalence of dementia of all types is about 7%. In the age range of 65 to 69 years, the prevalence of dementia is only 1 to 2%, but it increases to 20 to 25% in the 85- to 89-year age range and continues to rise steadily thereafter. The incidence of new cases of dementia is about 1 per 100 per year at the age of 70 years and rises to about 2 to 3 new cases per 100 per year by about the age of 80 years. Incidence rates continue to rise into the ninth and tenth decades of life. With the dramatic increase in longevity in North America, the societal burden of dementia has risen substantially.

In absolute numbers, far more women than men have dementia because women live longer. However, men and women have an equal age-adjusted risk for the development of dementia. There are no racial or ethnic differences in the risk for dementia.

TABLE 409-1 DEFINITION OF DEMENTIA

Based on evidence from the history and mental status examination, a disorder characterized by the presence of at least two of the following: Impairment in learning and retaining new or recently acquired information (impairment in episodic declarative memory) Impairment in handling complex tasks and reasoning abilities (impairment in executive cognitive functions) Impaired visuospatial ability and geographic orientation Impaired language functions
The cognitive disturbance significantly interferes with work, usual social activities, or relationships with others
The cognitive disturbance and the consequences for daily functioning represent a significant decline from a previous level of functioning
The cognitive disturbance does not occur exclusively during the course of delirium (which includes reversibility as a criterion)
The disturbance is not better accounted for by a major psychiatric diagnosis

PATHOBIOLOGY

Dementia is the culmination of dysfunction in the cerebral hemispheres, especially the association cortices, hippocampal formations, their supporting subcortical nuclear structures such as the caudate nuclei and thalamus, and their white matter interconnections (see Fig. 408-1). Specific diseases that cause dementia do so by affecting particular parts of the cerebral cortex, subcortical nuclei, or the underlying white matter pathways linking different cortical regions.

CLINICAL MANIFESTATIONS

Any of the major domains of cognition—declarative episodic memory, executive cognitive functioning, visuospatial function, or language—may be affected in dementia (Chapter 408). Because Alzheimer's disease is the most common dementia, anterograde amnesia is typically present first and most intensely in the majority of dementia patients. In other dementing illnesses, deficits in the other cognitive domains may be dominant. A pervasive and nearly invariant aspect of dementia is a loss of insight (anosognosia) into the extent of one's cognitive and functional losses.

Neuropsychiatric symptoms are also common in dementia. Apathy and loss of initiative are almost always present. Depression and anxiety are frequent, as are irritability, paranoia, delusional thinking, and hallucinations. Daily functioning of patients with dementia is compromised. In early dementia, difficulty is likely to be present in management of finances and medications, independent travel, preparation of meals, and keeping of appointments. In more advanced disease, difficulty becomes evident in basic activities of daily living, such as bathing, dressing, toileting, and feeding oneself. Dementias secondary to cerebrovascular or Lewy body disease are often associated with specific abnormalities in strength, coordination, gait, or balance. Alzheimer's disease, the most common dementia, typically has no associated motor abnormalities.

DIAGNOSIS

Clinical Examination

Dementia is strictly a clinical diagnosis based on evidence of cognitive dysfunction in both the history and the mental status examination. The key elements of the history flow from the definition of dementia: What is the evidence for impairment in one or more domains of cognition? What is the evidence that daily functioning is affected? The mental status examination is necessary to establish that alertness is preserved (i.e., the patient does not have delirium; Chapter 27) and to determine what specific areas of cognition exhibit directly observable impairment. For diagnosis of the syndrome of dementia, no laboratory test supersedes the clinical history and the mental status examination. Laboratory testing is critical, however, to determine the cause of the dementia.

Bedside testing of mental status is based on the principles of cognitive neurology (Chapters 27 and 408). For moderate or severe dementia to be distinguished from normal cognitive states, a bedside mental status examination such as the Mini-Cog test (Table 26-4) is accurate. However, for mild dementia, bedside mental status examinations lack sensitivity (i.e., they fail to diagnose some cases of mild dementia). For patients with suspected mild dementia, neuropsychometric testing is a useful adjunct to the bedside examination. The neurologic examination is also important for evaluation of signs of specific causes of dementia, including signs of cerebrovascular disease (e.g., hemiparesis; Chapter 413) and signs of extrapyramidal disease (e.g., rigidity, bradykinesia, resting tremor; Chapter 416).

Differential Diagnosis

Dementia must be distinguished from other disorders of cognition (Fig. 409-1). Delirium (Chapter 27) also affects cognition directly; key features distinguishing it from dementia include impaired arousal and attention. Delirium is almost always of sudden onset, whereas the majority of cases of dementia are of gradual onset.

Primary psychiatric diseases (Chapter 404) such as major depression, bipolar disorder, and schizophrenia may also impair cognition. In dementia, however, the impairment in cognition is typically equivalent to or more pervasive than the changes in mood and behavior.

The principal diseases that cause dementia are three neurodegenerative diseases—Alzheimer's disease, Lewy body disease, and frontotemporal lobar degeneration—and cerebrovascular disease (Fig. 409-2). The neurodegenerative diseases that cause dementia are typically slow and insidious in onset and inexorably progressive. Dementia secondary to cerebrovascular disease may be of either sudden or gradual onset.

Many much less common secondary causes account for less than 2% of all dementias. Drug intoxication (Chapter 33), metabolic disorders (Chapter 425), central nervous system infections (Chapters 420 and 422), and brain structural lesions (Chapter 195) are typically subacute in onset; if they are diagnosed and treated early, the cognitive deficits improve or resolve completely. A number of medications such as sedatives, pain medications, corticosteroids, digoxin, and others cause mental confusion, particularly but not always at toxic levels (Chapter 110). Metabolic disorders that may also cause subacute confusion and produce a cognitive disorder include hypothyroidism or hyperthyroidism (Chapter 233), vitamin B_{12} deficiency

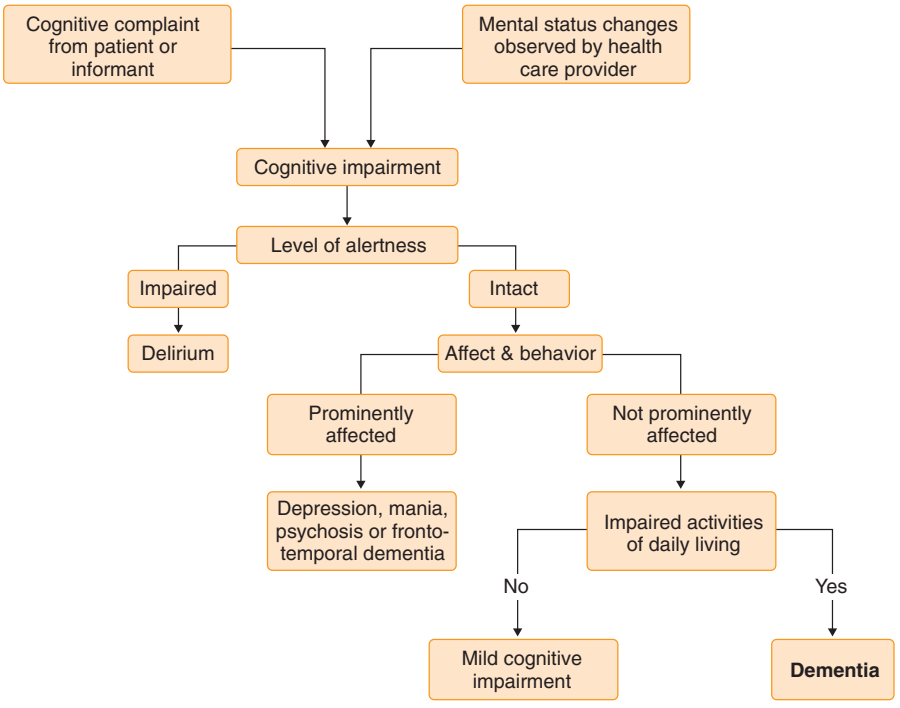


FIGURE 409-1. Flow diagram to establish the diagnosis of dementia.

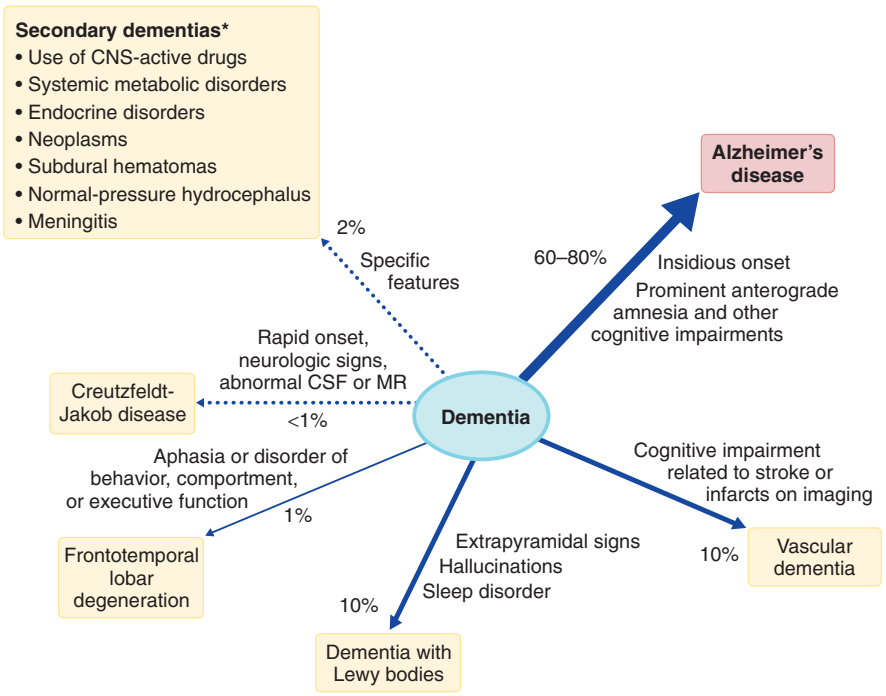


FIGURE 409-2. Flow diagram for the differential diagnosis of dementia. The percentage contributions of various diagnoses are approximate. *The list of secondary causes of dementia is not exhaustive. CNS = central nervous system; CSF = cerebrospinal fluid; MR = magnetic resonance imaging.

(Chapter 425), chronic liver disease (Chapter 156), chronic renal failure (Chapter 132), and hypocalcemia or hypercalcemia (Chapter 253). Chronic viral infections of the brain, especially human immunodeficiency virus infection, frequently cause dementia (Chapter 401). Chronic meningitides in the differential diagnosis of dementia include cryptococcal meningitis (Chapter 344), tuberculous meningitis (Chapter 332), and tertiary syphilis (Chapter 327). Finally, structural lesions of the brain, including primary and metastatic tumors (Chapter 195), chronic subdural hematomas (Chapter 406), and normal-pressure hydrocephalus (Chapter 195), can cause a syndrome resembling dementia that consists of a subacute or slowly progressive decline in cognition with few or no other neurologic symptoms or signs.

PROGNOSIS

Except for the secondary causes of dementia and the rare dementing illnesses caused by single episodes of brain injury, such as severe head trauma or anoxic encephalopathy, dementia is a condition that invariably leads to worsening of cognition and function. Almost all dementia patients progress from mild stages to severe dementia during the course of several years, if they do not die prematurely. The rate of cognitive decline is variable among individuals and, of course, also varies with the specific disease. In general, dementia can be said to decrease life expectancy by half compared with the life expectancy of nondemented individuals.

End-of-Life Care

The terminal stage and end-of-life care issues (Chapter 3) associated with the common dementias are usually similar. Dementia itself does not directly cause death, but it is strongly linked to reduced survival. Patients with dementia typically die of the same illnesses that affect debilitated individuals, such as sepsis, pneumonia, pulmonary embolism, or heart disease.

Most patients with dementia experience their terminal illnesses in hospitals or extended care facilities. Given the inexorably progressive nature of most dementing illnesses and their likelihood of producing severe and completely disabling cognitive and functional impairment, it is widely accepted that patients with end-stage dementia should receive conservative care. Feeding tubes and ventilatory support should not generally be considered.

MILD COGNITIVE IMPAIRMENT

DEFINITION

Mild cognitive impairment represents the transition between the state of normal cognition and dementia. Patients with mild cognitive impairment have abnormalities in a specific aspect of cognition to such an extent that it is clearly different from normal performance but does not interfere with daily functioning to any appreciable degree. More than one domain of cognition may be affected. The amnesic form of mild cognitive impairment, in which declarative episodic memory is impaired, is the most common. Alterations in attention, concentration, and mental agility may also be seen (Table 409-2). The term "cognitively impaired, not demented" includes patients whose mild cognitive impairment may progress to dementia but also encompasses anyone who is neither cognitively normal nor demented, such as individuals with stable, lifelong cognitive impairment.

TABLE 409-2 DIAGNOSTIC CRITERIA FOR AMNESIC MILD COGNITIVE IMPAIRMENT

The presence of a new memory complaint, preferably corroborated by an informant
Objective evidence of an impairment in episodic declarative memory (for age)
Normal general cognitive functions
No substantial interference with work, usual social activities, or other activities of daily living
No dementia

EPIDEMIOLOGY

The prevalence and incidence of mild cognitive impairment are about the same as those of dementia. Both increase with advancing age.

PATHOBIOLOGY

Mild cognitive impairment is a risk state for the subsequent development of dementia. Alzheimer's disease, followed by cerebrovascular disease and Lewy body disease, is the most common underlying cause.

CLINICAL MANIFESTATIONS

Patients with mild cognitive impairment may have more insight into their emerging cognitive difficulties than do patients with dementia. Hence, some patients with mild cognitive impairment may themselves seek medical consultation because of concern about their memory or their thinking. They or their family members may report a milder extent of many of the symptoms of dementia. Patients with mild cognitive impairment forget recent events and conversations or have trouble with mental flexibility, multitasking, problem solving, or completing mentally challenging activities at the speed that they once did. Mental status testing will sometimes corroborate the complaints, but neuropsychometric testing may be needed to document impairment. Other patients with mild cognitive impairment may have

virtually no insight into their memory loss, but the impairment is diagnosed after family members force the patient to undergo an evaluation.

DIAGNOSIS

When mild cognitive impairment is suspected, the principal alternative diagnosis is that the person is cognitively intact or that the person has dementia. The diagnosis of normal function should be straightforward when the patient and family have no complaints of cognitive impairment and the patient scores normally on bedside cognitive testing. However, a number of circumstances may cloud the issue, including very low or very high levels of prior educational and occupational achievement, instances in which English (or whatever the dominant language is) was a second language, severe hearing loss or blindness, and major alterations in mood or major motor disabilities that interfere with daily functioning. In such circumstances, the history of cognitive difficulty and the examination of cognitive status may be so confounded by these other phenomena that distinguishing between normal cognitive function and mild cognitive impairment is challenging. Conversely, distinguishing between mild cognitive impairment and dementia may be straightforward when daily functioning is obviously impaired. In other circumstances, it may be difficult to ascertain whether a person is functioning fully independently or not. For example, many older people reside in assisted living facilities that provide services such as cooking and housekeeping. In such individuals with few daily responsibilities, it is difficult to determine whether they are functionally impaired.

TREATMENT

Rx

As of 2011, no treatments have been approved for mild cognitive impairment, although a randomized trial demonstrated that donepezil therapy, 10 mg/day, significantly reduced the rate of development of dementia secondary to Alzheimer's disease at 1 year but not at 3 years. Physical activity appears to provide a modest slowing of cognitive decline.

PROGNOSIS

Mild cognitive impairment should be viewed as a risk state for the subsequent development of dementia. With use of the definition of amnesic mild cognitive impairment in Table 409-2, the rate of evolution from mild cognitive impairment to dementia is 15% per year.

ALZHEIMER'S DISEASE

DEFINITION

Alzheimer's disease is defined as a dementing illness in which anterograde amnesia is a dominant symptom (Table 409-3). The clinical diagnosis implies that the causative pathologic process is of the Alzheimer type, whereas the pathologic diagnosis rests on the findings of characteristic histopathologic features.

EPIDEMIOLOGY

Between 60 and 80% of all dementing illness is due to Alzheimer's disease. Among all individuals older than 65 years, the prevalence of Alzheimer's disease is estimated to be about 5%. As with dementia in general, the prevalence doubles in every 5-year interval after 65 years of age, and the incidence continues to rise into the 10th and 11th decades of life. Men and women may be equally affected, although on an absolute basis, far more women have prevalent Alzheimer's disease because women live longer than men do. There are no ethnic or racial differences in the predilection for Alzheimer's disease.

TABLE 409-3 DIAGNOSTIC CRITERIA FOR THE ANTEROGRADE AMNESIC SYNDROME OF ALZHEIMER'S DISEASE

Dementia (as defined in Table 409-1) with:
Major impairment in learning and retaining new information and at least one other domain of cognitive impairment:
Impairment in handling complex tasks and reasoning abilities (impairment in executive cognitive functions)
Impaired visuospatial ability and geographic orientation
Impaired language functions
The cognitive disturbance is of insidious onset and is progressive, based on evidence from the history or serial cognitive examinations
The cognitive disturbance is not better accounted for by a systemic disease or another brain disease

Risk Factors

Established risk factors for Alzheimer's disease include advancing age and a family history. Putative risk factors include diabetes mellitus, hypertension, cardiovascular disease, and head trauma; evidence for and against each of these four conditions is inconclusive, but the consensus is that at least diabetes and hypertension may play a role in the pathogenesis of Alzheimer's disease. Low educational achievement is also a consistent risk factor, but most experts believe that educational level is a proxy for some other factor, such as socioeconomic status or the early childhood medical and psychosocial environment. Protective factors have also been proposed, but their status is much debated.

PATHOBIOLOGY

The histopathologic diagnosis of Alzheimer's disease is based on the joint presence of a substantial cerebral burden of neuritic plaques and neurofibrillary tangles. Neuritic plaques consist of a core of aggregated β-amyloid peptide surrounded by degenerating neurites, which are fragments of axons and dendrites. β-Amyloid contains 39 to 42 amino acids and is proteolytically derived from a larger protein, the amyloid precursor protein. Neurofibrillary tangles are intracellular aggregations of an excessively phosphorylated form of the microtubule-associated protein tau. Neurofibrillary tangles, which are self-aggregates of tau, are thought to represent a nonspecific response to a cellular injury, which in Alzheimer's disease is triggered by β-amyloid. The altered tau protein self-aggregates and forms neurofibrillary tangles. In a low-powered microscopic section of frontal, temporal, or parietal cortex, at least six neuritic plaques and neurofibrillary tangles should be visible for the diagnosis of Alzheimer's disease to be made.

Pathophysiology

The progression of changes of β-amyloidosis follows a roughly predictable pattern in Alzheimer's disease. Positron emission tomographic imaging with ligands that bind to β-amyloid shows that β-amyloid begins to accumulate in the neocortex as long as 20 years before dementia occurs. Soluble aggregates of β-amyloid in oligomeric (consisting of a small number of monomers) forms may be the key pathogenic molecules that eventually induce neuronal injury. By the time that clinical dementia due to Alzheimer's disease is present, large numbers of β-amyloid peptide–containing deposits invariably are found in neuritic plaques in the neocortex. Neuritic plaques represent the end-stage of the Alzheimer process. Because β-amyloidosis begins well before clinical symptoms appear and probably reaches a plateau in terms of abundance, the amount of β-amyloidosis does not closely mirror the severity of dementia in Alzheimer's disease.

The regional extent of neurofibrillary tangles in Alzheimer's disease also follows a remarkably predictable pattern. The location of the earliest accumulation of neurofibrillary tangles is in the entorhinal cortex and hippocampus. At the time that clinical symptoms develop, neurofibrillary tangles are found in association neocortices of the frontal, parietal, and temporal lobes. It is only in the most severe and final stages that neurofibrillary tangles are found in the occipital lobes and primary motor and sensory cortices. The location of neurofibrillary tangles corresponds faithfully to the clinical evolution of specific symptoms and severity of Alzheimer's disease. In mild cognitive impairment, the earliest clinical manifestation of Alzheimer's disease, the most intense burden of neurofibrillary tangles is in the entorhinal cortex and hippocampi, precisely the regions that are involved in declarative episodic memory. Hippocampal atrophy is characteristic, and reductions in hippocampal volumes may be observed on magnetic resonance imaging (MRI; Fig. 409-3). Involvement of the association neocortices with neurofibrillary tangles represents the histopathologic correlate of the progression to dementia. Quantitative MRI in patients with mild cognitive impairment who later progress to dementia shows increasing atrophy of key cortical association areas, such as the lateral temporal lobes, inferior parietal lobes, posterior cingulate cortex, and lateral frontal lobes. Reflecting the spread to association neocortex, language functions, visuospatial functions, and executive cognitive functions typically become impaired some time after declarative episodic memory dysfunction occurs.

The most consistent neurotransmitter deficit in Alzheimer's disease is in cholinergic neurotransmission. The cells of origin of hippocampal and neocortical cholinergic projections are located in the septum, diagonal band, and

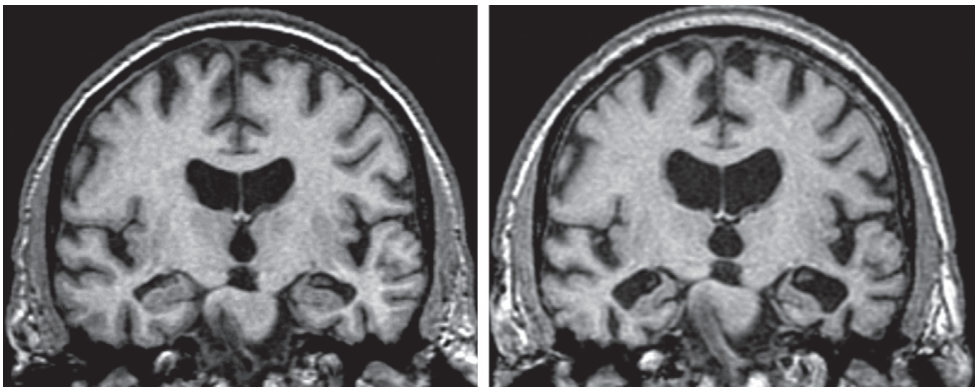


FIGURE 409-3. Serial coronal images from MRI of a patient with Alzheimer's disease. The scan on the *left* was performed when the patient was clinically normal. The scan on the *right* was performed 11 years later when the patient was demented. Hippocampal atrophy has increased dramatically from the first to the subsequent scan. (Courtesy of Maria Shiung and Clifford Jack.)

nucleus basalis. Neurofibrillary tangles accumulate in the neurons in these regions as Alzheimer's disease develops, but there is also neurochemical evidence that these neurons are stressed much earlier in the disease.

Genetics

The overwhelming majority of Alzheimer's disease is due to sporadic (not genetic) disease. However, in a very small number of instances, Alzheimer's disease occurs as an autosomal dominant disease. The three known genes involved in autosomal dominant Alzheimer's disease all are directly involved in the production of β-amyloid peptide. The first is the amyloid precursor protein (*APP*) gene, located on chromosome 21q21.3. Eighteen known mutations in this gene lead to excess production of β-amyloid and are reliably associated with a very early onset (20 to 50 years of age) of Alzheimer's disease. Another line of evidence implicating the *APP* gene in Alzheimer's disease is the invariable appearance of the pathologic process of Alzheimer's disease in individuals with Down syndrome (trisomy 21; Chapter 40), who have an extra copy of the *APP* gene as a result of the trisomy.

The other two genes associated with autosomal dominant Alzheimer's disease are the presenilin 1 and 2 genes, located on chromosomes 14q24.3 and 1q31.42. A large number of presenilin 1 mutations account for the majority of autosomal dominant Alzheimer's disease. Both genes code for a similar protein known as presenilin. Presenilin is involved in degradation of the APP molecule at the gamma cleavage site. It is believed that the Alzheimer's disease–causing mutations in presenilin 1 and 2 lead to a "toxic gain of function" that produces excess β-amyloid peptide. The presenilin mutations are also associated with early-onset (40 to 60 years of age) Alzheimer's disease.

Studies of the familial aggregation of Alzheimer's disease have shown that later-onset disease also displays genetic risks, but only one gene has been definitively linked to later-onset Alzheimer's disease. That gene, located on chromosome 19q13.2, encodes apolipoprotein E (apo E), a protein involved in lipid transport. In humans, three allelic variants of apolipoprotein gene (*APOE*) are determined by differences in the amino acids cysteine and arginine at positions 112 and 158 of the 299–amino acid protein. One of the allelic variants, with arginine at both positions, designated the ε4 variant, is strongly associated with a 14-fold increased risk for Alzheimer's disease in homozygotes and a 3-fold increase in heterozygotes. In many series, almost 50% of Alzheimer's disease patients but only about 25% of nondemented controls have at least one copy of the *APOE* ε4 allele. The presence of an *APOE* ε4 allele does not always cause Alzheimer's disease in that the disease never develops in some carriers of the genotype. The mechanism by which the *APOE* ε4 allele predisposes to Alzheimer's disease is not established, but the tertiary structure of the APOE protein with arginine at positions 112 and 158 may lead to impaired binding to β-amyloid, which in turn reduces the clearance of β-amyloid from cells.

CLINICAL MANIFESTATIONS

The early course of Alzheimer's disease is dominated by difficulties with anterograde amnesia. Some of the usual complaints include forgetting recent events and conversations, misplacing items, problems with keeping track of the date, getting lost in familiar surroundings, and problems with remembering to complete tasks. The frequency and severity of the memory lapses progress from occasional difficulty to more pervasive and consistent failure.

In mild Alzheimer's disease, declarative episodic memory function may be lost. Familiarity and access to previous knowledge may allow patients to function in their usual daily routines as long as nothing out of the ordinary is required of them. They may still retain the ability to prepare simple meals and to take walks in their neighborhood without getting lost. However, even in mild Alzheimer's disease, medication-taking errors and difficulty managing money or balancing a checkbook are likely to occur. Traveling to unfamiliar places often accentuates confusion. Changes in personality commonly accompany the cognitive losses. Apathy, loss of initiative, and loss of interest in previous hobbies and pastimes are ubiquitous in early Alzheimer's disease.

As the disease progresses, the ability to perform necessary daily tasks becomes more and more difficult to the point that the patient will need assistance preparing meals, paying bills, taking transportation, and keeping house. As the disease moves into the severe stages, assistance and supervision in basic activities such as bathing, dressing, toileting, and eating become necessary.

In the terminal stages of the disease, all communicative abilities may be lost. Mobility may still be preserved until late in the disease. Alzheimer's disease patients commonly die of illnesses that strike other debilitated elderly individuals, such as sepsis, pneumonia, and congestive heart failure.

The duration of the course of clinical Alzheimer's disease is long but variable. The time from mild dementia to death may be as short as 2 to 3 years or may be well over a decade. For patients in whom mild dementia is diagnosed, about 10% per year reach the stage of severe dementia.

Rarely, Alzheimer's disease is associated with prominent symptoms in cognitive domains other than memory. The most common of the atypical syndromes is one in which profound visuospatial deficits occur without the typical severe anterograde amnesia. This syndrome is referred to as posterior cortical atrophy.

DIAGNOSIS

The diagnosis of Alzheimer's disease, like that of dementia itself, is largely a clinical one based on the history and examination. The key elements in the history are a gradual onset and insidious progression of cognitive impairment, especially anterograde amnesia. The mental status examination should demonstrate impairment in short-term memory and other cognitive deficits. Alzheimer's disease should be thought of as a diagnosis of inclusion: if the history and examination are compatible with Alzheimer's disease and if certain exclusions can be verified, the diagnosis can be made with confidence.

No laboratory tests can confirm the diagnosis of Alzheimer's disease with sufficient sensitivity and specificity. For example, the presence of the *APOE* ε4 allele increases diagnostic accuracy only marginally after consideration of the history and physical examination. Findings on MRI, such as a decreased hippocampal volume, are useful when atrophy is present, but hippocampal atrophy is neither sensitive nor specific enough to be useful in diagnosis. Positron emission tomography with fluorodeoxyglucose or with newer amyloid-binding agents has yet to deliver the necessary precision or predictive abilities to warrant use in routine practice.

Differential Diagnosis

A number of other conditions that bear similarity to Alzheimer's disease must be excluded on clinical or laboratory grounds (see Fig. 409-2). One is dementia with Lewy bodies, which is suggested by the presence of parkinsonism, prominent visual hallucinations, and a specific sleep disorder. At autopsy, the pathologic processes of Lewy body disease and Alzheimer's disease often coexist, thus suggesting that the diagnoses overlap. Frontotemporal lobar degeneration is suggested by prominent behavioral and personality changes

or by prominent language difficulties early in the course. Hippocampal sclerosis has unique neuropathologic findings but is virtually impossible to distinguish from Alzheimer's disease by clinical features. Other neurodegenerative conditions in the differential diagnosis of Alzheimer's disease include Huntington's disease (Chapter 417), progressive supranuclear palsy, corticobasal degeneration, amyotrophic lateral sclerosis (Chapter 418), and Wilson's disease (Chapter 218); however, these diseases invariably have prominent motor manifestations early in their course.

It is particularly challenging to distinguish dementia caused by cerebrovascular disease from Alzheimer's disease (see later). The fact that Alzheimer's disease and cerebrovascular disease often coexist requires clinicians to consider both simultaneously.

PREVENTION AND TREATMENT

Rx

There are no established preventive therapies. Although a healthy diet, physical exercise, and stimulating cognitive leisure activities are sensible, they have not been shown to protect against Alzheimer's disease. Except in patients who have folate or vitamin B_{12} deficiency, vitamin B supplementation is not effective in slowing cognitive decline.[1] Treatment of diabetes (Chapters 236 and 237) and hypertension (Chapter 67) is beneficial for other reasons, but it is not clear that such treatment alters the course of Alzheimer's disease.

Once Alzheimer's disease becomes symptomatic, support for family caregivers is a critical intervention that cannot be overemphasized. Support groups through the Alzheimer's Association (available at *www.alz.org*) can benefit families coping with the disease.

Important safety issues include supervision of medications, supervision of finances, and close scrutiny of motor vehicle operation. Operation of other potentially dangerous tools, firearms, appliances, and equipment should also be carefully monitored or avoided. Patients with Alzheimer's disease often wander and can become lost long distances from home. Identification of patients can prevent tragic occurrences *(www.alz.org/Media/newsreleases/2003/033003wandering.asp)*.

Evidence-Based Treatments

Two classes of drugs are approved for the treatment of Alzheimer's disease: cholinesterase inhibitors and memantine, a glutamate receptor antagonist. The rationale for the use of cholinomimetic drugs (donepezil, 5 or 10 mg/day; galantamine, 16 or 24 mg/day; or rivastigmine, 6 to 12 mg/day) is the reduced levels of cholinergic markers in the neocortex of patients dying of Alzheimer's disease. All three agents delay the progression of symptoms to a statistically significant but clinically marginal extent at 6 to 12 months in patients with mild to moderate Alzheimer's disease, but not at 3 years.[2,3,4] Furthermore, there is no compelling evidence that they alter its biologic progression. Individual patients often do not show any clear benefits of treatment.

Memantine, which is a low- to moderate-affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist that acts on glutamate neurotransmission, also delays the progression of functional decline at a dose of 10 mg twice per day.[5] It is not clear why modulation of glutamate neurotransmission is beneficial in Alzheimer's disease, and studies of memantine in patients with mild to moderate Alzheimer's disease have not yet been published.

One study of patients with moderately severe Alzheimer's disease showed that vitamin E was effective in delaying progression, but recent studies showed no benefit in subjects with mild cognitive impairment.[6] By comparison, donepezil appears to be beneficial for severe as well as for mild disease,[7] although it has not been proven useful for the agitation that may accompany Alzheimer's disease.[8]

PROGNOSIS

Alzheimer's disease is inevitably progressive, and severe cognitive impairment and complete dependence on others develop in virtually all patients, unless they die prematurely. Alzheimer's disease also contributes to premature death; the mortality rate in patients with Alzheimer's disease is about 10% per year. In patients with advanced dementia, the 6-month mortality is about 55%; pneumonia, fever, and eating problems are associated with poor prognosis.

FUTURE DIRECTIONS

Intensive research on the pathogenesis of Alzheimer's disease is elucidating information on production and degradation of the β-amyloid molecule and mechanisms of induction of tau aggregation. Research is also focusing on the development of biomarkers, cerebrospinal fluid (CSF) markers, and imaging techniques for the early diagnosis of Alzheimer's disease. A number of therapeutic agents are also being studied.

TABLE 409-4 DIAGNOSTIC CRITERIA FOR THE SYNDROME OF DEMENTIA CAUSED BY CEREBROVASCULAR DISEASE (VASCULAR DEMENTIA)

Dementia as defined in Table 409-1
Clinically important cerebrovascular disease is demonstrable by *either* of the following:
Onset of the cognitive disturbance *or* dramatic worsening of an existing disturbance that occurred within 3 months of a stroke, where stroke is defined as a focal neurologic deficit of acute onset in which the symptoms and signs persist for more than 24 hours
Neuroimaging evidence of bilateral brain infarctions rostral to but including the thalamus

VASCULAR DEMENTIA

DEFINITION

Vascular dementia is a dementing illness in which the underlying cause is cerebral infarction. For a cognitive disorder to be attributed to cerebrovascular disease from a neuropathologic perspective, there must be sufficient cerebral infarction in locations known to be responsible for the cognitive deficits in the absence of other neurodegenerative neuropathologic changes (Table 409-4). When cerebrovascular disease produces cognitive impairment that is not severe enough to meet the criteria for dementia, it is referred to as vascular cognitive impairment.

EPIDEMIOLOGY

In clinical studies, as many as 20% of dementia patients have cerebrovascular disease. Like Alzheimer's disease, it is less common in patients younger than 65 years and increases steadily thereafter. In neuropathologic studies, about 25% of all cases of dementia have some vascular component. Roughly half that number are relatively pure vascular dementia; the remainder consists of vascular disease mixed with Alzheimer's disease. Men and women are equally affected.

Risk Factors

Risk factors for vascular dementia include cardiovascular disease, diabetes, and hypertension. There are no known protective factors other than treatment of these risk factors. Populations with high rates of generalized vascular disease should have higher rates of vascular dementia, but competing mortality from cardiovascular disease may obscure part of the relationship. In the first year after a stroke, the risk for development of dementia is about 9-fold higher than the rate in persons without a stroke; the risk remains about 2-fold higher in subsequent years.

PATHOBIOLOGY

The majority of vascular disease causing cognitive impairment is due to atherosclerosis. One mechanism is through large infarctions, such as those secondary to occlusive disease in major cerebral vessels, including the carotid arteries and the anterior, middle, and posterior cerebral arteries (Chapter 413). A second mechanism of infarction is at the arteriolar level, with lacunar infarctions in the thalamus, basal ganglia, and subcortical white matter. Both these processes can be detected by brain MRI. Infarcts in the hippocampal formations, medial thalamus, caudate nuclei, and parietal association areas are highly likely to produce cognitive impairment but not necessarily dementia. Microinfarcts, which are small zones of infarction that are not visible to the naked eye but can be observed with light microscopy, may also contribute to the dementia. The simultaneous presence of Alzheimer's disease is common in vascular dementia.

There are other uncommon causes of vascular dementia. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a very rare inherited disease that usually becomes clinically evident between the ages of 30 and 50 years and causes severe white matter disease, headaches, and dementia. The cause of CADASIL is mutations in the *notch3* gene on chromosome 19q12. Cerebral amyloid angiopathy, a β-amyloidosis in which the β-amyloid peptide accumulates in the media of small to medium-sized arteries in the leptomeninges and superficial cortex, causes cerebral hemorrhages that may lead to dementia if it occurs in sufficient number and in critical locations. Cerebral amyloid angiopathy is also seen in Alzheimer's disease, but its hemorrhagic manifestations may occur in

individuals with little evidence of Alzheimer's disease clinically and modest evidence pathologically. Cerebral vasculitis (Chapter 278) is a very rare cause of dementia.

CLINICAL MANIFESTATIONS

The spectrum of cognitive changes in patients with cerebrovascular disease is broad. The more common cognitive syndromes in cerebrovascular disease include mild cognitive impairment, a dementia with prominent anterograde amnesia, and a dementia with prominent changes in personality and executive function. Some patients with vascular cognitive impairment without dementia may have deficits in only one domain (Chapter 408). A number of aphasia syndromes are a result of cerebral infarction or hemorrhage in the perisylvian regions of the dominant hemisphere. Infarction or hemorrhage in the occipitotemporal or occipitoparietal regions may produce one of the disorders of visual cognition, such as alexia or visual agnosia. Infarcts in the caudate nuclei, particularly if they are bilateral, may produce a cognitive syndrome that includes both amnesia and disordered executive function, thus mimicking dementia. Large infarcts in the right parietal lobe can also produce dementia. Infarcts in the medial thalami or in the hippocampal formations can produce isolated amnesia.

The evolution of symptoms in vascular dementia does not follow a stereotypical pattern. In some, the dementia syndrome may remain static. In others, new strokes may lead to substantial declines in cognition and function. Some patients with vascular dementia may experience a gradually declining illness. Patients with vascular cognitive impairment without dementia or vascular dementia may also have other neurologic signs typical of patients with cerebrovascular disease, such as hemiparesis, hemianopia, hemisensory changes, or cranial nerve abnormalities.

DIAGNOSIS

The diagnosis of vascular dementia is based on the neurologic history and examination. Brain imaging, preferably with MRI, is essential to establish the presence of infarcts. The cardinal diagnostic features of vascular dementia are that (1) the cognitive disorder should have begun within 3 months of a clinical stroke event and (2) there should be multiple, bilateral infarcts in the cerebral hemispheres visible on brain imaging studies. A temporal link between the onset or worsening of cognitive impairment and a stroke is important in demonstrating that cerebrovascular disease is etiologically relevant to the cognitive impairment. Brain imaging of infarcts in the cerebral cortex, basal ganglia, thalamus, and cerebral white matter has obvious value for establishment of cerebrovascular disease. In contrast to actual infarcts on imaging, the presence of white matter hyperintensities without infarcts on brain MRI is much less specific.

The accuracy of the clinical diagnosis of vascular dementia is generally lower than that of Alzheimer's disease. The combination of (1) a temporal relationship between dementia and a stroke and (2) imaging evidence of bilateral infarcts is diagnostically specific for vascular dementia but is insensitive. Broader diagnostic criteria (see Table 409-4) are more sensitive but less specific. The usual alternative diagnosis is Alzheimer's disease, and there is typically no way to be certain whether and how much Alzheimer's disease is simultaneously present.

PREVENTION AND TREATMENT

Rx

Some cases of vascular dementia should be preventable. With early, lifelong aggressive treatment of diabetes (Chapters 236 and 237), hypertension (Chapter 67), and hyperlipidemia (Chapter 213), the number of cerebral infarcts should be reduced, with a corresponding reduction in the number of cases of vascular dementia. Evidence for this link comes from large-scale studies in which the treatment of hypertension reduced the frequency of strokes and incident dementia. Once vascular dementia develops, cholinesterase inhibitors have shown some benefit, but the major goal is to prevent future strokes.

PROGNOSIS

Patients with vascular dementia can often be expected to have severe cardiovascular disease and a greater likelihood of future strokes and cardiac ischemic events. Survival of patients with vascular dementia is poorer than that of patients with Alzheimer's disease.

TABLE 409-5 DIAGNOSTIC CRITERIA FOR THE DEMENTIA SYNDROME ASSOCIATED WITH LEWY BODY PATHOLOGY

Dementia as defined in Table 409-1
The cognitive disturbance is of insidious onset and is progressive, based on evidence from the history or serial cognitive examination
The presence of at least two of the following: Parkinsonism (rigidity, resting tremor, bradykinesia, postural instability, parkinsonian gait disorder) Prominent, fully formed visual hallucinations Substantial fluctuations in alertness or cognition Rapid eye movement sleep behavior disorder (see Chapter 412) Severe worsening of parkinsonism by antipsychotic drugs
The disturbance is not better accounted for by a systemic disease or another brain disease

DEMENTIA WITH LEWY BODIES

DEFINITION

Dementia with Lewy bodies is a multifaceted dementing disorder in which the underlying pathologic process includes Lewy bodies in limbic and cortical structures (Table 409-5). Some clinicians make a distinction between patients in whom parkinsonism preceded the cognitive disorder and those in whom the cognitive disorder occurred either simultaneously with or before the movement disorder. This distinction may be somewhat useful in clinical practice, but there are few clinical or neuropathologic differences based on different sequences of signs and symptoms. The diagnosis of dementia with Lewy bodies is similar in principle to diagnosis of both dementia and Parkinson's disease (Chapter 416) in the same individual, but dementia with Lewy bodies is a term with broader connotations because of other features (hallucinations, fluctuations, and sleep disorder) that may be more apparent than the movement disorder.

EPIDEMIOLOGY

Dementia with Lewy bodies is about a quarter as common as Alzheimer's disease. Lewy body disease becomes more common with advancing age, and the prevalence of dementia with Lewy bodies increases with advancing age as well. As with the other dementias, there are no known ethnic or racial differences, but dementia with Lewy bodies may be more common in men. There are no known risk factors for dementia with Lewy bodies. Dementia develops in up to 30% of patients with Parkinson's disease, and advancing age is the major risk factor.

PATHOBIOLOGY

The pathology of dementia with Lewy bodies is a mixture of Lewy body disease and Alzheimer's disease. In general, the more intense the Lewy body disease, the less abundant the Alzheimer disease. Lewy bodies, which are intraneuronal inclusions that contain α-synuclein, are found in the nucleus basalis, pars compacta of the substantia nigra, locus caeruleus, other brain stem structures, amygdala, cingulate gyrus, and neocortex. The earliest locations of Lewy bodies are the brain stem, where they affect nuclei involved in sleep and arousal, and the substantia nigra, the locus caeruleus, and cranial nerve nuclei IX and X. Typically, the nucleus basalis, transentorhinal cortex, cingulate gyrus, and neocortex become involved later.

In Lewy body disease, the α-synuclein protein becomes misfolded and aggregates intraneuronally. Mutations in the α-synuclein gene have been seen in a few families with autosomal dominant Parkinson's disease, but most cases of dementia with Lewy bodies are sporadic.

CLINICAL MANIFESTATIONS

The clinical manifestations of dementia with Lewy bodies include four major abnormalities: the cognitive disorder, the neuropsychiatric disorder, the motor disorder, and the disorder of sleep and wakefulness. The cognitive disorder may differ from Alzheimer's disease, although there is considerable overlap. In a typical patient with dementia with Lewy bodies, visuospatial deficits, impaired concentration, and impaired attention dominate the picture. In some patients, the deficits in executive functions may be similar to what is seen in frontotemporal lobar degeneration. Anterograde amnesia is usually present but milder than in Alzheimer's disease. Language deficits are not prominent. The neuropsychiatric manifestations of dementia with

Lewy bodies, including prominent apathy, loss of initiative, and depression, may be more disabling than the cognitive symptoms. The motor manifestations include bradykinesia, gait disturbances, postural disturbances, and rigidity. Rest tremor is less common in dementia with Lewy bodies in patients in whom the cognitive disorder appears before the parkinsonism. Visual hallucinations, fluctuations in alertness, and REM sleep disorders are part of a broader disorder of the regulation of sleep and wakefulness. Visual hallucinations are often graphic, detailed, and bizarre, perhaps because the sleep phenomenon of dreaming intrudes into wakefulness. Patients with dementia with Lewy bodies have large fluctuations in their alertness and arousal from day to day.

REM sleep behavior disorder (Chapter 412) is a parasomnia in which patients exhibit dream enactment behavior, often with violent, threatening overtones. Patients typically relate that they feel as though they are being chased by something or someone. Their behavior, while they are asleep, consists of excessive talking, calling out or shouting, and thrashing about, often to the point of striking a bed partner or falling out of bed. The REM sleep behavior disorder may precede the development of Parkinson's disease and dementia with Lewy bodies by years.

DIAGNOSIS

The diagnosis of dementia with Lewy bodies is based on clinical information that corroborates the presence of abnormalities in cognition, motor function, neuropsychiatric behavior, and regulation of sleep and wakefulness. Formal neuropsychological testing is often helpful in evaluating memory, executive function, and visuospatial function in a detailed manner. Neuroimaging has only a limited role in the diagnosis of dementia with Lewy bodies.

Differential Diagnosis

Other disorders that must be considered in patients with dementia and a movement disorder include progressive supranuclear palsy (Chapter 417), which can resemble dementia with Lewy bodies in terms of both the dementia and the motor disorder. In progressive supranuclear palsy, patients are much less likely to have disorders of arousal and typically have other distinctive signs and symptoms, including the characteristic supranuclear gaze palsy and other brain stem findings. The corticobasal degenerations, which are members of the family of frontotemporal lobar dementias (see later), may also produce a movement disorder and dementia. Huntington's disease (Chapter 417) is associated with dementia and a movement disorder, but the movement disorder of Huntington's disease includes prominent chorea and athetosis, neither of which is present in dementia with Lewy bodies.

Normal-pressure hydrocephalus (Chapter 195) is a rare disorder typically characterized by the triad of a gait disorder, dementia, and urinary incontinence. Normal-pressure hydrocephalus can be suspected when computed tomography or MRI shows ventricular enlargement that is out of proportion to the amount of sulcal widening. Predicting a favorable response to ventriculoperitoneal shunting in suspected normal-pressure hydrocephalus has proved to be difficult. Imaging studies that measure CSF flow through the aqueduct of Sylvius or that measure flow of radiolabeled CSF with radionuclide cisternography have not been useful. Clinical response to the removal of a high volume (e.g., 30 mL) of CSF through lumbar puncture is sometimes used to select patients for surgery, although its positive and negative predictive value is unclear. Normal-pressure hydrocephalus is very rare relative to dementia with Lewy bodies and Alzheimer's disease.

TREATMENT

Rx

Management of patients with dementia with Lewy bodies is challenging because of the simultaneous appearance of a cognitive disorder, a neuropsychiatric disorder, a motor disorder, and a sleep and wakefulness disorder. Treatment of the motor disorder is accomplished with antiparkinsonian drugs such as levodopa and dopaminergic agonists (Chapter 416). Treatment with these agents should be instituted for dementia with Lewy bodies if there are prominent gait or balance problems that threaten safety and interfere with independence. These medications may worsen hallucinations and exacerbate confusional states, but this concern should not preclude a treatment trial if the motor symptoms pose safety risks or interfere with independence. Cholinesterase inhibitors, which do not exacerbate parkinsonian symptoms, have a beneficial effect on neuropsychiatric symptoms but not clearly on the cognitive disorder.

Hallucinations and agitation impair quality of life for the patient and family and often require treatment. Some antipsychotic agents that might otherwise control these symptoms dramatically exacerbate the parkinsonism in dementia with Lewy bodies. Atypical antipsychotics are usually recommended, but there is insufficient experience from controlled clinical trials. Many movement disorder specialists prefer to use quetiapine in doses of 25 to 200 mg/day or clozapine at 6.25 to 50 mg/day because these agents appear to have the lowest rate of extrapyramidal side effects. However, it is not possible to make any strong statements about the relative efficacy of atypical antipsychotics in treating the hallucinations in dementia with Lewy bodies, especially in view of the possibility that atypical antipsychotic agents may be associated with higher than expected mortality.

The REM sleep behavior disorder (Chapter 412) can be disabling, but there are no controlled clinical trials to inform treatment. Some sleep disorder specialists typically use either melatonin, 3 to 12 mg, or clonazepam, 0.5 to 2 mg, at bedtime.

Treatment of depressive symptoms may substantially improve a patient's functioning. Use of one of the newer generation of antidepressants, such as sertraline in a dose of 25 to 100 mg/day or citalopram in a dose of 10 to 20 mg/day, may be beneficial and does not necessarily interfere with management of the other symptoms (Chapter 404).

PROGNOSIS

As opposed to patients with Alzheimer's disease, some studies show that patients with dementia with Lewy bodies have a more rapidly progressive course and poorer survival. As a result of the combination of manifestations, patients with dementia with Lewy bodies may become disabled sooner in their course.

FUTURE DIRECTIONS

Because the REM sleep behavior disorder often precedes the development of dementia with Lewy bodies, early diagnosis offers an opportunity for early intervention. Progress in understanding of the production and degradation of α-synuclein may lead to more specific therapies.

FRONTOTEMPORAL LOBAR DEGENERATION

DEFINITION

The frontotemporal lobar degenerations are a group of neurodegenerative disorders with distinctive clinical manifestations and a predilection for the prefrontal and anterior temporal neocortices. The most common clinical syndrome is a disorder of behavior and personal relationships (comportment) with a loss of executive functions (Table 409-6). This syndrome is referred to as behavior-variant frontotemporal dementia. Other syndromes in the clinical spectrum of frontotemporal lobar degeneration involve different aspects of language or motor dysfunction of the limbs.

EPIDEMIOLOGY

Unlike Alzheimer's disease, the frontotemporal lobar degenerations have a peak age at onset in the 50- to 70-year range, and the incidence declines after the age of 70 years. In patients with dementia who are younger than 70 years, frontotemporal lobar degeneration makes up 10 to 20% of cases. However,

TABLE 409-6 DIAGNOSTIC CRITERIA FOR FRONTOTEMPORAL DEMENTIA

Based on evidence from the history and mental status examination, a disorder characterized by the early *and* predominant presence of *either* of the following: Decline in regulation of personal or social interpersonal conduct (as characterized by loss of empathy for the feelings of others; socially inappropriate behavior that is rude, caustic, irresponsible, or sexually explicit; mental rigidity; impulsivity typically with poor judgment; inflexibility in interpersonal relationships or emotional blunting; apathy; disregard for personal hygiene and grooming; deviations in previous dietary preferences or habits; binge eating) Impairment in mental agility, reasoning, or handling of complex tasks out of proportion to impairment in the domains of declarative episodic memory or visuospatial abilities
The cognitive or behavioral disturbances are of gradual onset and are progressive, based on evidence from the history or serial cognitive examination
The cognitive disturbance significantly interferes with work, usual social activities, or relationships with others
The cognitive disturbance and the changes in daily functioning represent a significant decline from a previous level of functioning
Not occurring exclusively during the course of delirium
The disturbance is not better accounted for by a major psychiatric diagnosis, a systemic disease, or another brain disease

across the entire age spectrum, the frontotemporal lobar degenerations are much less common than Alzheimer's disease, dementia with Lewy bodies, or vascular dementia. Both men and women are affected equally. There are no known risk factors for the frontotemporal lobar degenerations except a family history.

PATHOBIOLOGY

The clinical syndrome in frontotemporal lobar degeneration is determined by the lobar location of the pathologic process. Right prefrontal or anterior temporal disease and brain atrophy produce behavioral syndromes like frontotemporal dementia. Left frontal involvement tends to produce progressive nonfluent aphasia. Predominant left anterior temporal lobe involvement may produce semantic dementia.

On histopathologic grounds, patients with frontotemporal lobar degeneration can be divided into three groups: those whose inclusions contain the microtubule-associated protein tau; those whose inclusions contain the TAR DNA-binding protein 43 (TDP-43); and those whose inclusions contain the fused in sarcoma (FUS) protein, another nucleic acid–binding protein. Each type includes both genetically determined and sporadic forms.

Among the tau-positive varieties are Pick's disease, in which intracellular tau-positive inclusions known as Pick bodies are seen. Several other pathologic tau-positive subtypes occur, including progressive supranuclear palsy, corticobasal degeneration, and the disorder associated with mutations in the tau gene. Nearly 50 mutations in the tau gene on chromosome 17q21 are associated with autosomal dominant frontotemporal lobar degeneration syndromes, each with a slightly different clinical and neuropathologic phenotype. The most common is a proline to leucine mutation at codon 301, located in exon 10. The tau gene undergoes alternative splicing, resulting in six isoforms of the tau protein. Pathologic mutations appear to disrupt splicing of alternative isoforms of tau protein, which in turn adversely affects the binding of tau to microtubules in neurons. Reduced binding of tau to microtubules is deleterious to microtubule function and neuronal integrity.

The TDP-43–positive frontotemporal lobar degenerations are almost equally common. Immunostaining shows that there are distinctive TDP-43–containing inclusions. Mutations in the granulin (*GRN*) gene, also located on chromosome 17q21, cause familial, autosomal dominant forms of frontotemporal lobar degeneration with TDP-43–positive inclusions. Nearly 70 different mutations in the granulin gene are linked to frontotemporal lobar degenerations. All of the mutations lead to premature degradation of the messenger RNA, a process termed haploinsufficiency. Granulin mutation carriers have an abnormally low amount of the protein progranulin. The normal function of granulin in the brain is unclear, and the pathophysiologic basis for dementia in persons with granulin gene mutations is unknown. The link between alterations in TDP-43 and *GRN* mutations is also unknown at this time.

Frontotemporal lobar degenerations that are FUS positive are much less common. At this time, all FUS-positive cases have had the behavioral variant of frontotemporal dementia.

CLINICAL MANIFESTATIONS

The clinical manifestations of the syndrome of frontotemporal dementia begin insidiously. Apathy, loss of initiative, and flattening of affect are common early symptoms. As the disease progresses, the entire spectrum of behavioral changes associated with dysfunction of the frontal and anterior temporal lobes appears. On cognitive assessments, patients may have preserved memory functions, but they typically have difficulty with tests of executive cognitive function. When frontotemporal dementia progresses to moderate or severe stages, the behavioral changes remain prominent, but the disease becomes more difficult to distinguish from other dementias such as Alzheimer's disease. The neuropathology of behavior-variant frontotemporal dementia may be either tau positive or TDP-43 positive.

In some patients with frontotemporal lobar degeneration, signs and symptoms of motor neuron disease develop, such as weakness, atrophy, and fasciculation in the limbs or the bulbar musculature (Chapter 418). In other patients with frontotemporal lobar degeneration, asymmetrical limb apraxia develops that is part of the corticobasal syndrome. Features of progressive supranuclear palsy may also appear in patients with behavior-variant frontotemporal dementia.

Frontotemporal lobar degeneration can be manifested as a progressive nonfluent aphasia in which patients experience a feeling of hesitancy in selecting words in their speech, a problem that may be difficult for others to appreciate at first. Anomia is an early sign. Gradually, the patient's speech becomes laconic and labored. Eventually, a nonfluent, apractic, agrammatic speech develops. In other cognitive domains, progressive nonfluent aphasics as well as progressive anomic aphasics often have no deficits. As the diseases progress, however, a pervasive cognitive disorder develops in some patients. Other progressive nonfluent aphasics may eventually become virtually mute, even though they may appear to have preserved memory and visuospatial functions. Patients with progressive nonfluent aphasia often have tau-positive neuropathologic findings.

Semantic dementia is a disorder that involves dissolution of the meaning of words or objects. A patient with semantic dementia may also become unable to access knowledge about objects (object agnosia) and people's faces (prosopagnosia). The most striking demonstration of the deficit in semantic dementia is when a patient can produce the name of an object—a watch, for example—but then cannot say what a watch is for when asked. Often, patients with semantic dementia have preservation of the ability to learn a list of words, even if their knowledge of the meaning of the words is diminished. Patients with semantic dementia usually have TDP-43–positive neuropathologic findings.

DIAGNOSIS

Frontotemporal lobar degeneration must first be suspected on clinical grounds, based on the appearance of one of the distinctive clinical syndromes such as frontotemporal dementia (see Table 409-6) or one of the aphasic subtypes. Neuropsychological testing can also aid in the diagnosis by detecting abnormalities in executive function and verifying that memory function is preserved, as it often is. For all of the frontotemporal lobar degeneration syndromes, MRI showing focal atrophy of the frontal (Fig. 409-4) or temporal lobes is highly likely to be diagnostic. Imaging with fluorodeoxyglucose-enhanced positron emission tomography can also be useful when the clinical diagnosis is uncertain and MRI is nondiagnostic.

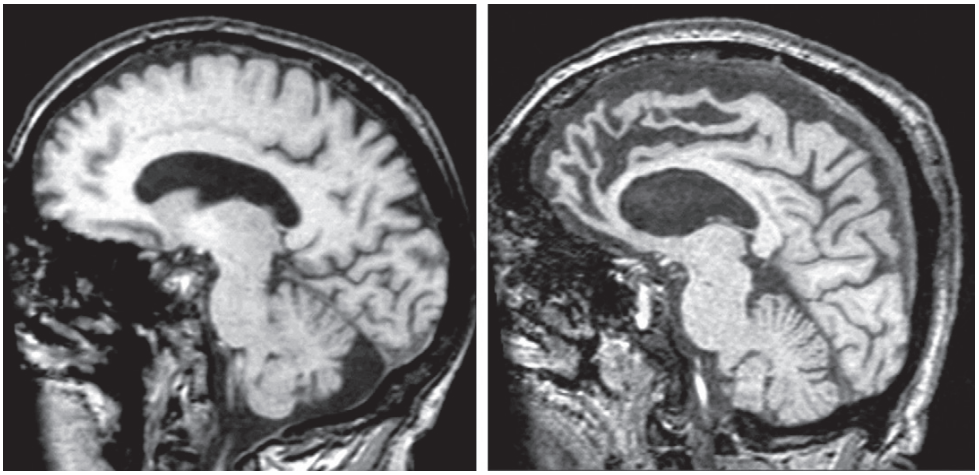


FIGURE 409-4. Parasagittal image from MRI of a patient with frontotemporal dementia *(left)*. Atrophy of the frontal lobes is dramatic compared with the brain of a normal individual *(right)*. (Courtesy of Maria Shiung and Clifford Jack.)

TREATMENT

Rx

There is no symptomatic therapy specifically for frontotemporal lobar degeneration. In patients with agitation, paranoia, delusions, or obsessive behavior, atypical antipsychotics (e.g., quetiapine, 25 to 200 mg/day) are used, but no controlled clinical trials are available. There are no preventive treatments of frontotemporal lobar degeneration.

PROGNOSIS

Specific frontotemporal lobar degeneration syndromes have dramatic differences in their clinical course and outcome. In patients with motor neuron signs and symptoms, the prognosis is usually poor, with survival of only about 2 years from the time of diagnosis. Patients with semantic dementia and progressive nonfluent aphasia have much more protracted and gradual trajectories; survival for more than 10 years is not uncommon. Frontotemporal dementia itself can also exhibit a more protracted course.

FUTURE DIRECTIONS

Drugs that delay or prevent the pathologic consequences of tau protein dysfunction could be of great value for many patients with frontotemporal lobar degeneration.

Grade A

1. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352:2379-2388.
2. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*. 2008;300:1027-1037.
3. Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. *JAMA*. 2008;300:1774-1783.
4. Courtney C, Farrell D, Gray R, et al; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet*. 2004;363:2105-2115.
5. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med*. 2008;148:379-397.
6. Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348:1333-1341.
7. Winblad B, Kilander L, Eriksson S, et al. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet*. 2006;367:1057-1065.
8. Howard RJ, Juszczak E, Ballard CG, et al. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med*. 2007;357:1382-1389.
9. Erkinjuntti T, Kurz A, Gauthier S, et al. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet*. 2002;359:1283-1290.
10. McKeith IG, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet*. 2000;356:2031-2036.

SUGGESTED READINGS

Arvanitakis Z. Update on frontotemporal dementia. *Neurologist*. 2010;16:16-22. *Review*.

Ballard C, Gauthier S, Corbett A, et al. Alzheimer's disease. *Lancet*. 2011;377:1019-1031. *Review*.

Mayeux R. Clinical practice. Early Alzheimer's disease. *N Engl J Med*. 2010;362:2194-2201. *Review*.

Plassman BL, Williams JW Jr, Burke JR, et al. Factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med*. 2010;153:182-193. *Review*.

Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med*. 2010;362:329-344. *Review*.

Yaffe K, Weston A, Graff-Radford NR, et al. Association of plasma beta-amyloid level and cognitive reserve with subsequent cognitive decline. *JAMA*. 2011;305:261-266. *A low plasma beta-amyloid level is associated with greater cognitive decline in non-demented elderly, especially those with low cognitive reserve*.

410

THE EPILEPSIES

SAMUEL WIEBE

DEFINITION

A *seizure* is defined by transient focal or generalized signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. *Focal seizures*, which originate within neuronal networks limited to one cerebral hemisphere, produce signs and symptoms corresponding to the specific region of the brain that is affected by the seizure. *Generalized seizures* rapidly affect extensive neuronal networks on both cerebral hemispheres, and their signs and symptoms are consistent with substantial involvement of both sides of the brain.

Seizures are not synonymous with epilepsy. The epilepsies should be distinguished from situations in which acute brain insults (e.g., infections, trauma, intoxication, metabolic disturbances) cause one or more seizures without a resulting chronic seizure tendency. *Acute symptomatic seizures,* or *provoked seizures*, constitute about 40% of all incident cases of nonfebrile seizures, typically respond to treatment of the provoking factor, and do not require long-term treatment with antiepileptic drugs.

The *epilepsies* are a group of conditions in which an underlying neurologic disorder results in a chronic tendency to have recurrent, unprovoked seizures. Under these circumstances, *the occurrence of two or more seizures establishes the diagnosis of epilepsy.* The causes, types, and clinical expression of the epilepsies are numerous and varied. However, some of the epilepsies conform into identifiable *epileptic syndromes*, which consist of clusters of clinical and electroencephalographic (EEG) features that have specific causes, respond to particular treatments, and may have specific prognostic implications.

EPIDEMIOLOGY

Incidence and Prevalence

Seizures are common in the general population, and about 1 in 10 people will experience a seizure in their lifetime. Most of these seizures are provoked by acute events and are not related to epilepsy. The overall annual incidence of acute symptomatic seizures, excluding febrile seizures, in developed countries is about 39 per 100,000 people. The incidence is higher in men and follows a bimodal age distribution. Incidence is at its highest peak in the first year of life (up to 300 per 100,000), reaches a nadir of 15 per 100,000 in the third and fourth decades of life, and rises again to 123 per 100,000 after 75 years of age. These differences are attributable to the high incidence of acute symptomatic seizures associated with metabolic, infectious, and encephalopathic causes during the neonatal period, and of cerebrovascular and degenerative diseases in elderly people.

The *epilepsies* are common and affect humans of any age. After headache, the epilepsies are the most frequent chronic neurologic condition seen in general practice worldwide. In developed countries, the prevalence of active epilepsy ranges from 5 to 7 per 1000 people, and the annual incidence ranges from 35 to 52 per 100,000, varying by age. The incidence of epilepsy peaks in children younger than 5 years at 60 to 70 per 100,000, decreases throughout adolescence to 30 per 100,000 in early adulthood, and rises again after the sixth decade, reaching a peak of 150 to 200 per 100,000 people older than 75 years. Overall, the incidence and prevalence of the epilepsies are higher in developing countries, largely owing to a higher frequency of perinatal insults, trauma, and infectious disorders of the brain and to suboptimal treatment. In these countries, the median prevalence of active epilepsy is 12.5 per 1000 (range, 5 to 57 per 1000), and the annual incidence ranges from 78 to 190 per 100,000. Furthermore, the patterns of age-specific incidence are quite different in developing countries, where incidence peaks in young adults, not in elderly people.

Risk Factors

Among all age groups, the top five risk factors for developing *acute symptomatic seizures* are head trauma (16%), stroke (16%), infectious disorders (15%), toxic-metabolic disorders (15%), and drug and alcohol withdrawal (14%) (Table 410-1).

The risk factors for developing *epilepsy* differ in adults and children. In childhood, excluding inherited epilepsies, the risk is increased by febrile seizures, head trauma, infections of the brain, mental retardation, cerebral palsy, and attention-deficit hyperactivity disorder. Perinatal insults do not carry an increased risk for epilepsy unless they are accompanied by mental retardation or cerebral palsy.

In adults, risk factors for developing *epilepsy* can be identified in only one third of patients, in whom head trauma, brain infections, stroke, and Alzheimer's disease are the most common. The risk of developing epilepsy is increased more than 500-fold by a history of a military head injury, 30-fold by a severe civilian head injury (Chapter 406), 20-fold each by stroke (Chapter 414) and brain infections (Chapters 420 and 422), and 10-fold each for Alzheimer's disease (Chapter 409), migraine headache (Chapter 405), and hypertension.

In Latin America, the most frequently identified risk factor is brain infection. In endemic areas, neurocysticercosis (Chapter 362) accounts for about 10% of all newly diagnosed cases of epilepsy.

Pathobiology

Pathogenesis

The pathologic substrates and mechanisms underpinning initiation and propagation differ for focal and generalized seizures. In focal seizures, an aggregate of cortical or subcortical neurons develop high-frequency bursts of sodium-dependent action potentials caused by a shift in calcium conductance, thereby resulting in the typical EEG spike discharge (Fig. 410-1). Spread of bursting activity to other neurons is normally prevented by surrounding inhibitory mechanisms, such as hyperpolarization and inhibitory interneurons. When a sufficient number of neurons are engaged in sustained bursting, further excitatory phenomena ensue, including the increased release of excitatory neurotransmitters owing to presynaptic accumulation of Ca^{2+}, depolarization of surrounding neurons owing to increased extracellular K^+, and further neuronal activation caused by depolarization-induced activation of *N*-methyl-D-aspartate (NMDA) receptors. As excitation increases and inhibition decreases, additional neurons are recruited regionally and distantly, thereby resulting in seizure propagation. The mechanisms by which neurons develop a tendency toward anomalous bursting activity include alterations in neurotransmitters, membrane receptors, ion channels, second-messenger systems, and gene expression of various proteins.

Considerably less is known about the basic mechanisms underlying generalized seizures, which depend prominently on thalamocortical circuits. In absence seizures, the classic generalized spike-and-wave discharges seen on EEG (Fig. 410-2) are related to alterations in oscillatory rhythms generated by circuits that connect the thalamus and cortex and that involve T-type Ca^{2+} channels, which are located in the reticular nucleus of the thalamus. In generalized convulsive seizures, cortical neurons exhibit prolonged depolarization during the tonic phase, followed by rhythmic depolarization and repolarization during the clonic phase. Activation of NMDA receptors increases calcium Ca^{2+} influx, thereby leading to further neuronal excitation. The initiation and modulation of generalized convulsive seizures involve cholinergic, noradrenergic, serotonergic, and histaminergic afferents from the brain stem and basal forebrain structures, which modulate excitability of hemispheric motor mechanisms.

TABLE 410-1 COMMON CAUSES OF ACUTE SYMPTOMATIC (PROVOKED) SEIZURES

METABOLIC
Hypernatremia, hyponatremia, hypocalcemia, hypoxia, hypoglycemia, nonketotic hyperosmolar hyperglycemia, renal failure
DRUG INDUCED
Theophylline, meperidine, tricyclic antidepressants, ephedra, gingko, phenothiazines, quinolones, β-lactams, isoniazid, antihistamines, cyclosporine, interferons, tacrolimus, cocaine, lithium, amphetamines
DRUG WITHDRAWAL
Alcohol, benzodiazepines, barbiturates
ENDOCRINE
Hyperthyroidism, hypothyroidism, peripartum
OTHER SYSTEMIC CONDITIONS
Sickle cell crisis, hypertensive encephalopathy, systemic lupus erythematosus, polyarteritis, eclampsia, high fever
CENTRAL NERVOUS SYSTEM DISORDERS
Trauma, stroke, intracerebral hemorrhage, encephalitis, abscess, bacterial meningitis

Genetics

Only 15% of patients have one or more first-degree relatives who also suffer from epilepsy, and of those, about 75% have just one affected relative. However, the risk is still higher in first-degree relatives of patients with epilepsy than in the general population. In a large population-based study, the cumulative incidence of epilepsy to age 20 years was 2.5-fold higher in siblings and 3.4-fold higher in offspring of patients with epilepsy.

The genetic aspects of epilepsy can be categorized in three large groups: *Conditions in which epilepsy forms part of a mendelian disorder* include over 200 rare conditions, which encompass neurocutaneous disorders (Chapter 426), neurodegenerative disorders, inherited malformations of cortical development (Chapter 426), and inherited metabolic disorders. For example, genes have been identified in progressive myoclonic epilepsies (e.g., Unverricht-Lundborg disease, Lafora's disease, and the neuronal ceroid lipofuscinosis), X-linked myoclonic epilepsy with mental retardation, and cortical malformation syndromes, such as polymicrogyria, pachygyria, and periventricular nodular heterotopia.

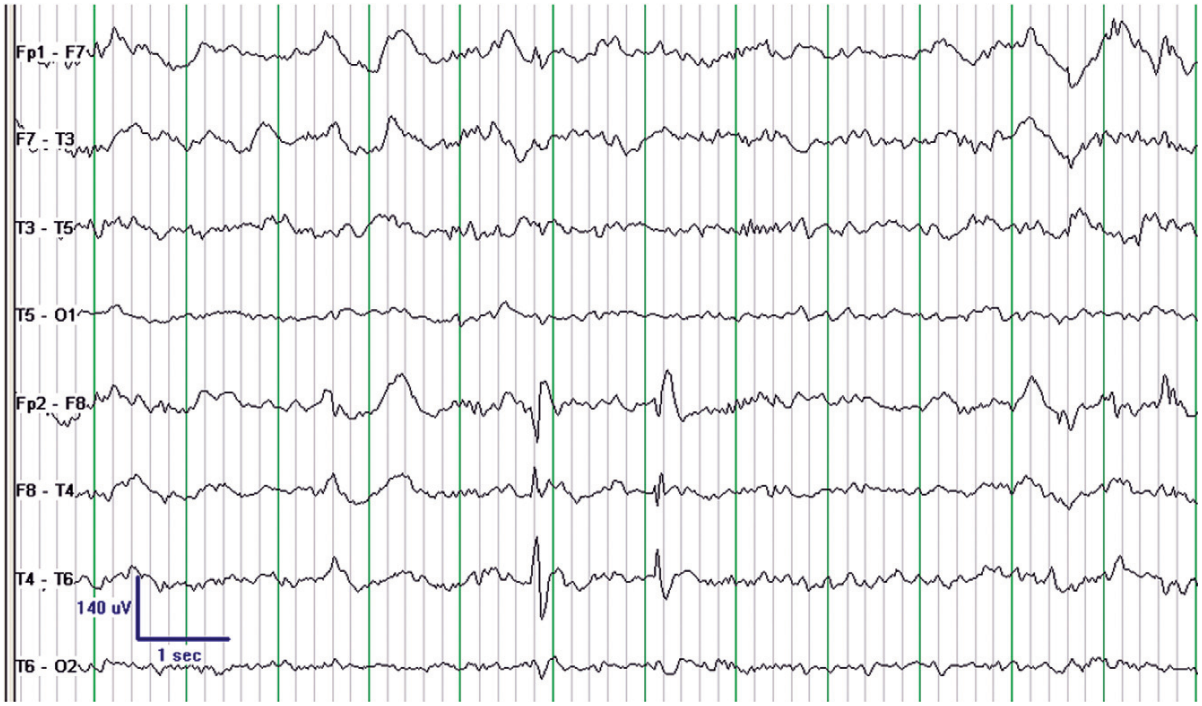


FIGURE 410-1. Selected electroencephalogram channels showing a typical right anterior temporal spike, the archetypal interictal footprint of temporal lobe epilepsy. The patient had right hippocampal sclerosis.

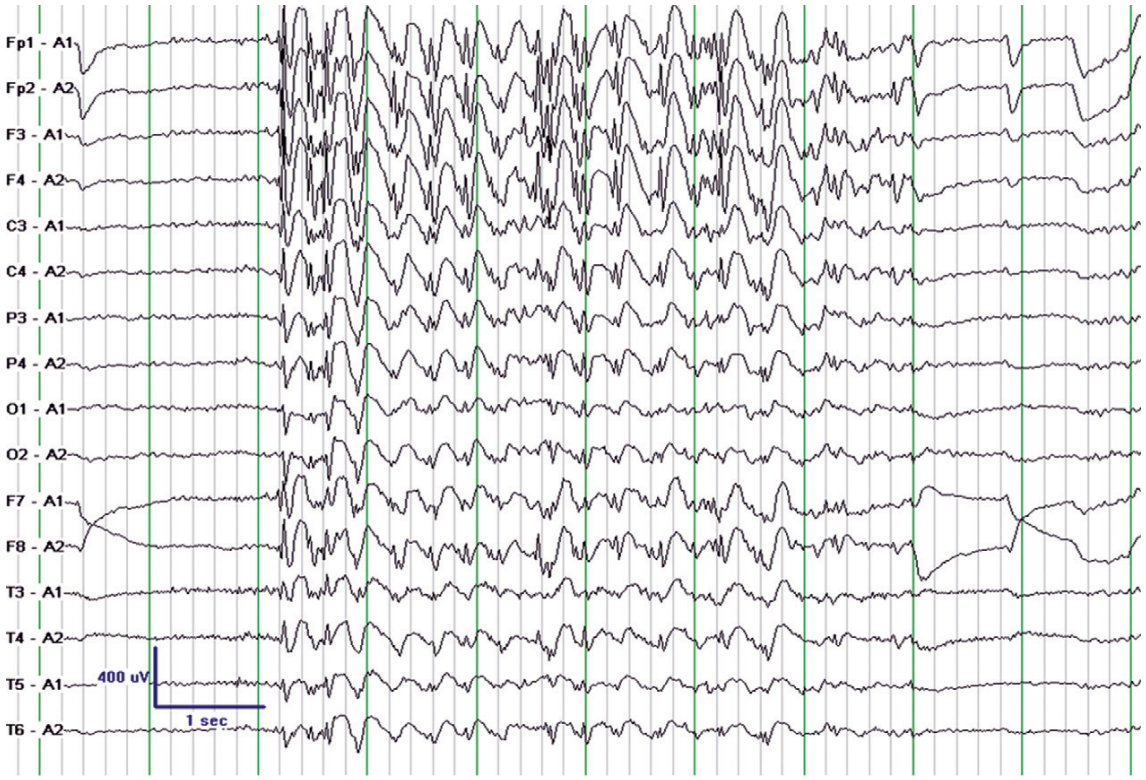


FIGURE 410-2. Electroencephalogram pattern of 3-Hz generalized spike and wave, the characteristic correlate of generalized absence seizures. This episode lasting 6 seconds had no discernible clinical manifestations.

Epilepsies that can be directly explained by simple mendelian inheritance are rare and account for only about 1% of all epilepsy cases. More than a dozen genes have been identified in the following eight autosomal dominant epilepsy syndromes, of which all but two encode voltage-gated or ligand-gated ion channels. Benign familial neonatal seizures are associated with mutations in the potassium-channel genes *KCNQ2* and *KCNQ3*. Benign familial neonatal-infantile seizures are associated with mutations in the sodium-channel *SCN2A*. Generalized epilepsy with febrile seizures plus is associated with mutations in the genes for sodium-channel subunits *SCN1A*, *SCN1B*, and *SCN2A* and the *GABRG2* subunit of the $GABA_A$ receptor. Childhood absence epilepsy with febrile seizures is associated with mutations in the *GABRG2* subunit of the $GABA_A$ receptor. Autosomal dominant juvenile myoclonic epilepsy has been associated with a mutation in the *GABRA1* subunit of the $GABA_A$ receptor and in *EFHC1*, which regulates calcium currents. Autosomal dominant idiopathic generalized epilepsy is associated with mutations in the chloride-channel gene *CLCN2*. In autosomal dominant nocturnal frontal lobe epilepsy, mutations have been found in the genes encoding nicotinic acetylcholine receptor subunits *CHRNA4* and *CHRNB2*. In autosomal dominant partial epilepsy with auditory features, mutations have been found in the *LGI1* gene, which appears to be involved in development of the central nervous system (CNS).

In some patients, the epilepsy is associated with *"complex" disease genes*. In this large group, which constitutes about 50% of all patients with epilepsy, multiple genes with individually small but additive effects act in combination with environmental factors to produce an increased risk for epilepsy.

CLINICAL MANIFESTATIONS

The clinical expression of seizures varies widely depending on the type of seizure and the areas of the brain that are involved by the epileptic activity. Accurate identification of the specific types of seizures determines the syndrome and dictates the type of drug that the patient should receive.

Focal Seizures

Focal seizures originate within neuronal networks limited to one area of one cerebral hemisphere and produce signs and symptoms corresponding to the function subserved by the area of cerebral cortex engaged by the seizure (Table 410-2). Focal seizures are now subclassified according to their clinical expression; if consciousness or awareness is predominantly impaired, they are referred to as dyscognitive seizures. For example, patients who formerly were classified as having simple partial seizures now are classified as having focal seizures with preserved consciousness.

An *aura* consists of sensory, autonomic, or psychic symptoms that are experienced at the start of an observable seizure. The aura is a focal seizure itself, and it is often missed because patients and clinicians focus on the more dramatic dyscognitive or convulsive seizure that follows. Careful inquiry about the occurrence of an aura is of crucial importance for three reasons. First, it points to a focal as opposed to a generalized onset, thereby implying an underlying focal structural or functional brain abnormality (e.g., a tumor) that requires further investigation. Second, focal seizures have important implications for therapy and for prognosis (see later). Third, the nature of the symptoms points to the area of the brain that gives rise to the seizure and that could be a target for surgical treatment.

The neuronal discharge causing the focal seizure may remain confined to the region where it began (as an aura or more objective focal event), or it may spread to involve additional brain areas. Thus, a focal seizure originating in the cortical area that represents sensation of the hand (rolandic area) may begin with contralateral hand tingling and then progress to involve additional cortical regions ipsilaterally, producing more extensive sensory symptoms as well as clonic motor signs. Seizures of rolandic origin in particular exhibit a peculiar type of propagation, in which the seizure activity "marches" from hand to arm to leg area ipsilaterally, a process referred to as a jacksonian march. After the clonic motor activity ends, patients are often weak; a postictal or Todd's paralysis may last hours or even a day or two, with gradual resolution. The seizure may also propagate to distant ipsilateral or contralateral regions along known anatomic pathways.

In dyscognitive seizures, seizure propagation sufficiently involves limbic and bilateral structures to cause alteration of consciousness. Focal seizures originating from any region can become dyscognitive seizures, and unilateral focal seizures can progress to involve bilateral brain areas and cause a convulsive seizure. Such convulsive seizures usually take the form of generalized tonic-clonic events rather than another type of generalized seizure (Table 410-3).

The evolution of the focal clinical seizure reflects the evolution of the EEG changes, which in turn reflects the pathophysiology of the process. A

TABLE 410-2 CLINICAL MANIFESTATIONS OF DIFFERENT TYPES OF FOCAL SEIZURES AND AREAS OF THE BRAIN INVOLVED

SEIZURE TYPE	AREAS OF BRAIN INVOLVED	CLINICAL EXPRESSION
Somatosensory	Postcentral rolandic; parietal	Contralateral intermittent or prolonged tingling, numbness, sense of movement, desire to move, heat, cold, electric shock. Sensation may spread to other body segments.
	Parietal	Contralateral agnosia of a limb, phantom limb, distortion of size or position of body part
	Second sensory; supplementary sensory-motor	Ipsilateral or bilateral facial, truncal or limb tingling, numbness, or pain. Often involve lips, tongue, fingertips, feet
Motor	Precentral rolandic	Contralateral regional clonic jerking, usually rhythmic, may spread to other body segments in jacksonian motor march. Often accompanied by sensory symptoms in same area
	Supplementary sensory-motor	Bilateral tonic contraction of limbs causing postural changes, may exhibit classic fencing posture, may have speech arrest or vocalization
	Frontal	Contralateral head and eye version, salivation, speech arrest or vocalization; may be combined with other motor signs (as above) depending on seizure spread
Auditory	Heschl's gyrus—auditory cortex in superior temporal lobe	Bilateral or contralateral buzzing, drumming, single tones, muffled sounds
Olfactory	Orbitofrontal; mesial temporal cortex	Often described as unpleasant odor
Gustatory	Parietal; rolandic operculum; insula; temporal lobe	Often unpleasant taste, acidic, metallic, salty, sweet, smoky
Vertiginous	Occipitotemporal-parietal junction; frontal lobe	Sensation of body displacement in various directions
Visual	Occipital	Contralateral static, moving, or flashing colored or uncolored lights, shapes, or spots. Contralateral or bilateral, partial or complete loss of vision.
	Temporal; occipitotemporal-parietal junction	Formed visual scenes, faces, people, objects, animals
Limbic	Limbic structures: amygdala, hippocampus, cingulum, olfactory cortex, hypothalamus	Autonomic: abdominal rising sensation, nausea, borborygmi, flushing, pallor, piloerection, perspiration, heart rate changes, chest pain, shortness of breath, cephalic sensation, lightheadedness, genital sensation, orgasm Psychic: déjà vu, jamais vu, depersonalization, derealization, dreamlike state, forced memory or forced thinking, fear, elation, sadness, sexual pleasure, hallucinations or illusions of visual, auditory, or olfactory nature
Dyscognitive	Usually bilateral involvement of limbic structures (see above)	Previously known as "complex partial seizures," characterized by a predominant alteration of consciousness or awareness. The current definition requires involvement of at least two of five components of cognition: perception, attention, emotion, memory, and executive function.

Note: Focal seizures may evolve into bilateral convulsive seizures.

TABLE 410-3 GENERALIZED SEIZURES: CLASSIFICATION AND CLINICAL EXPRESSION

SEIZURE TYPE	SUBTYPE	CLINICAL EXPRESSION
Absence	Typical	Abrupt cessation of activities, with motionless, blank stare and loss of awareness lasting about10 seconds. The attack ends suddenly, and patient resumes normal activities immediately.
	Atypical	Longer duration than typical absence, often accompanied by myoclonic, tonic, atonic, and autonomic features as well as automatisms
	With myoclonias	Absence with myoclonic components of variable intensity
Myoclonic	Myoclonic	Sudden, brief (<100 msec), shocklike, involuntary, single or multiple contractions of muscle groups of various locations
	Myoclonic Atonic	A sequence consisting of a myoclonic followed by an atonic phase
	Myoclonic Tonic	A sequence consisting of a myoclonic followed by a tonic phase
Tonic		Sustained increase in muscle contraction lasting a few seconds to minutes
Clonic		Prolonged, regularly repetitive contractions involving the same muscle groups at a rate of 2-3 cycles per second
Atonic		Sudden loss or diminution of muscle tone lasting 1-2 seconds, involving head, trunk, jaw or limb musculature
Tonic-clonic		A sequence consisting of a tonic followed by a clonic phase

simultaneous rhythmic, localized discharge (often in the 4- to 7-Hz range) becomes higher in amplitude and lower in frequency as the seizure continues (Fig. 410-3). Some seizures that begin in the association cortex (e.g., frontal or parietal lobes) have bizarre or extremely brief clinical manifestations, without postictal deficits, and create diagnostic challenges. The stereotyped nature of the clinical events, with the identification of EEG changes if present, may be the only way to make an appropriate diagnosis. The diagnosis can be even more challenging if the seizure spreads to different cortical regions during different seizure episodes, thereby producing variable constellations of clinical findings at different times.

Focal seizures with or without dyscognitive features can also occur as a series of single events without intervening normal behavior, thereby resulting in focal status epilepticus. Focal status epilepticus with dyscognitive seizures is characterized by prolonged confused behavior. EEG findings may be normal in a focal seizure without altered awareness, even in patients with status epilepticus, but the diagnosis is usually evident from the clinical features. In status epilepticus of focal dyscognitive seizures, EEG recordings show continuous abnormalities that are not of the same nature as seen in single seizures in that individual. The most common are a slow background with superimposed rhythmic high-amplitude sharp waves or repetitive rhythmic seizure discharges (Fig. 410-4). This type of status epilepticus is most frequent with frontal lobe seizures but can occur in temporal lobe seizures as well. The factors that precipitate status epilepticus are not well defined, nor are the implications for treatment or prognosis.

Nonconvulsive status epilepticus consists of a state of confusion or impaired mental status in patients with various neurologic diagnoses (i.e., trauma, stroke) in the acute intensive care unit setting. It also denotes a condition that can occur de novo in older adults without a precipitating cause and that is characterized by prolonged confusional episodes, which are caused by generalized slow spike-and-wave status epilepticus. Clinical suspicion should prompt an EEG study, which is essential for diagnosis (Fig. 410-5).

Generalized Seizures

Generalized seizures rapidly affect both cerebral hemispheres, and their clinical expression is consistent with substantial involvement of both sides of the brain (see Table 410-3). *Convulsive seizures,* which are also referred to as grand mal seizures, consist of excessive, abnormal muscle contractions that may be sustained or interrupted, and usually are a combination of tonic and

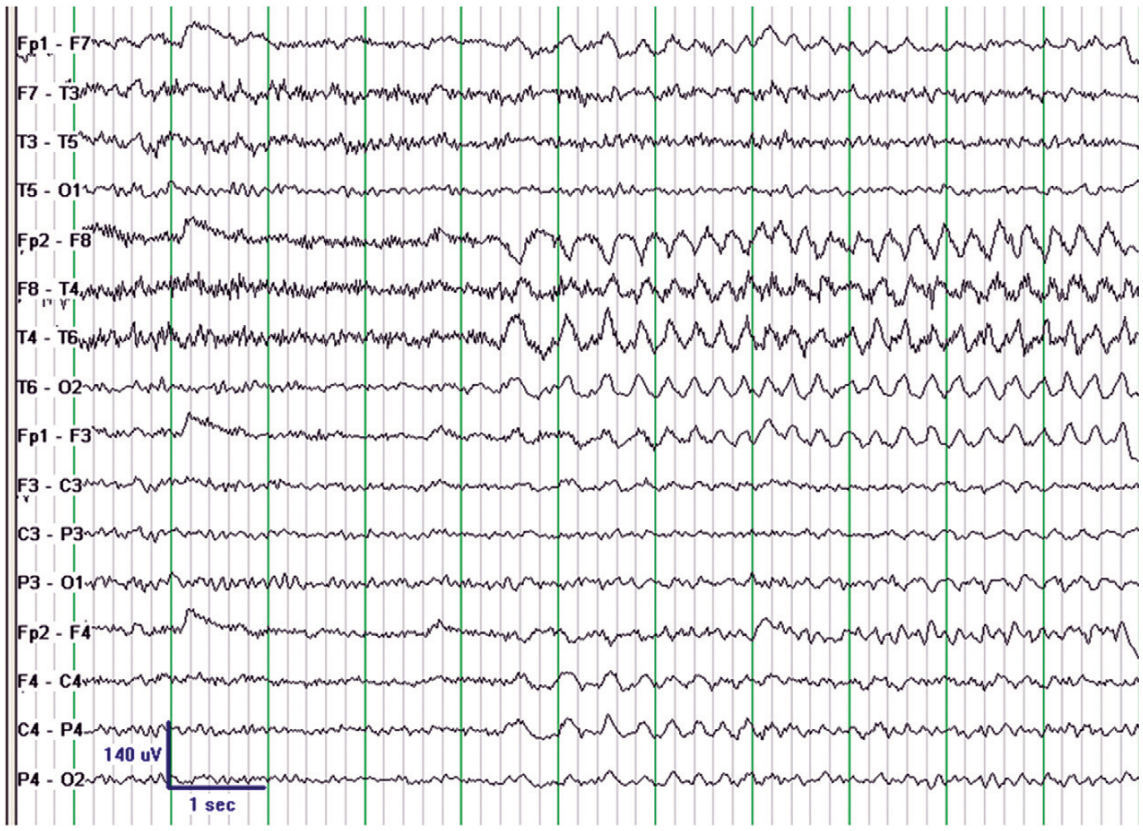


FIGURE 410-3. Right temporal lobe dyscognitive seizure in a patient with right hippocampal sclerosis. The focal onset is characteristic, with 4-Hz rhythmic waves in the right anterior temporal region.

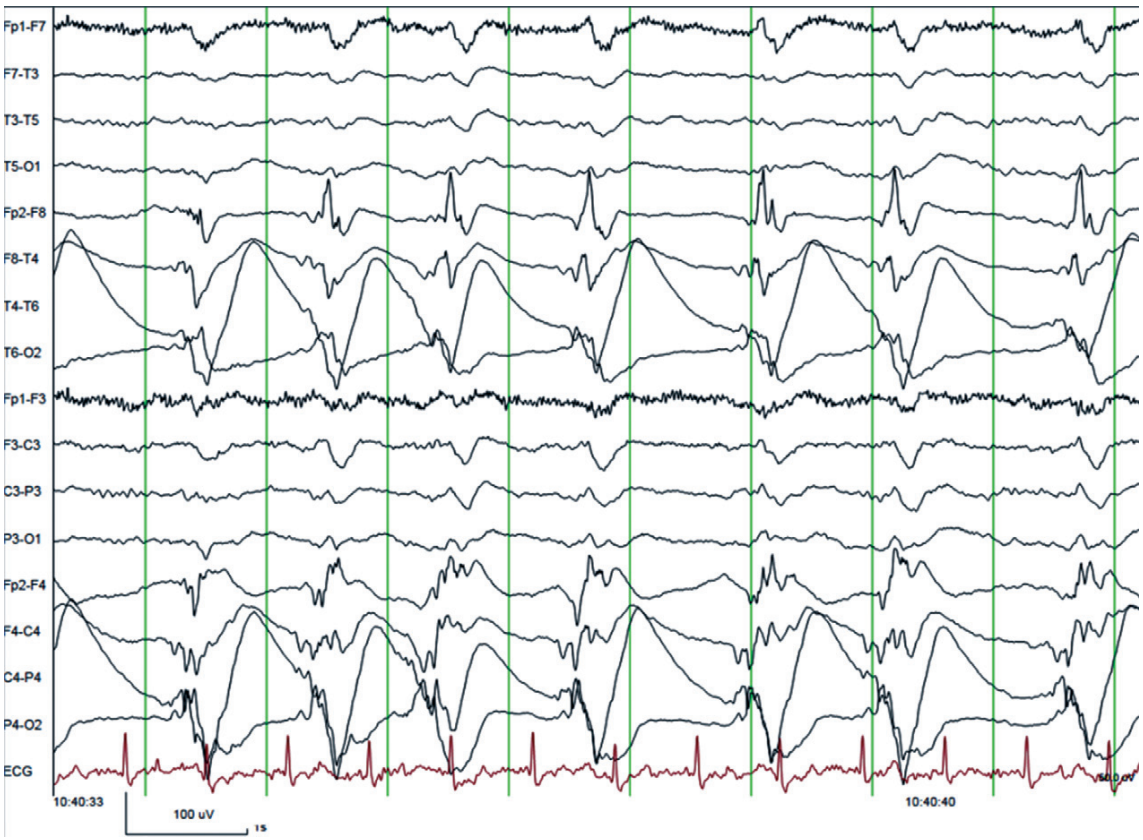


FIGURE 410-4. Focal, right hemisphere nonconvulsive status epilepticus in a comatose patient with a large right hemisphere infarct.

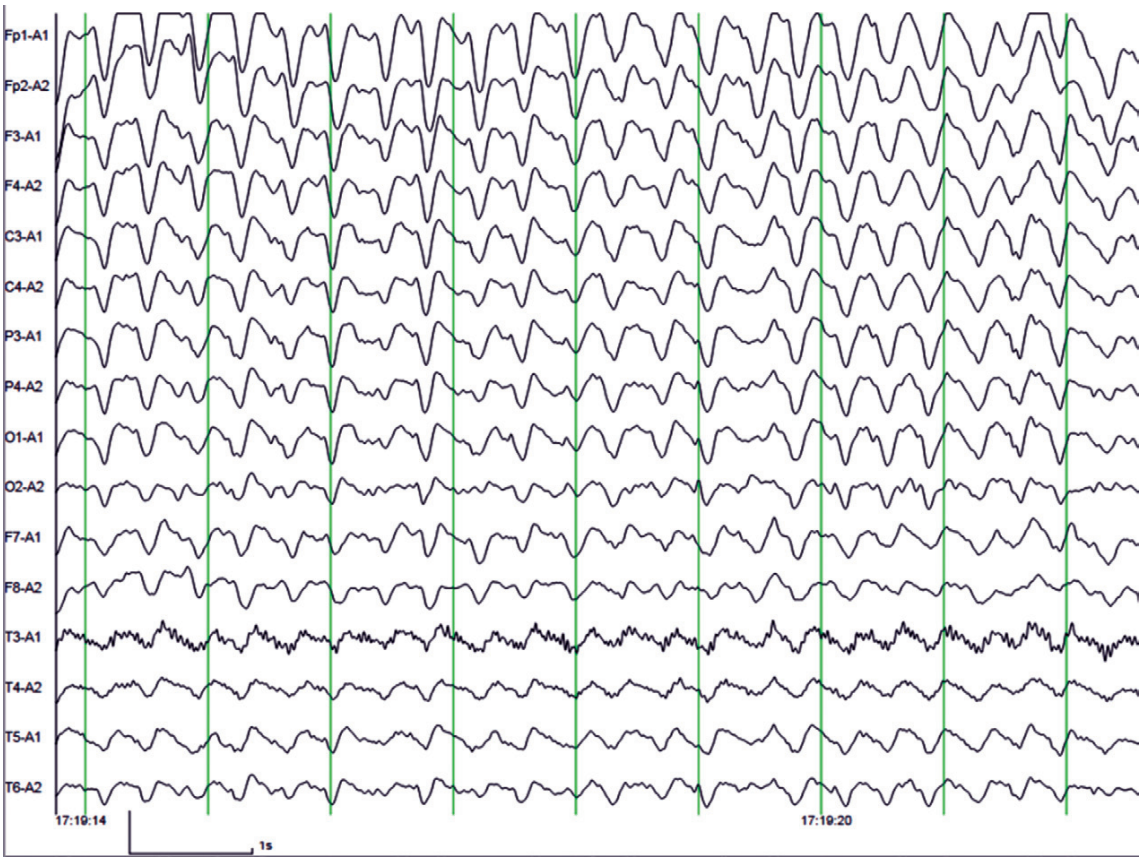


FIGURE 410-5. Generalized nonconvulsive status epilepticus in an older adult presenting with a prolonged episode of confusion and catatonic behavior.

clonic phases (generalized tonic-clonic seizures). This type of seizure may involve both hemispheres at the onset or may result from propagation of a focal seizure. These dramatic seizures often frighten witnesses and cause severe disruption of social interaction and development. They may begin with a "cry" as a result of abrupt air movement across the glottis from sudden tonic muscle contraction. The patient becomes diffusely stiff, usually with limb and body extension. Breathing is suspended, cyanosis occurs, and urinary incontinence is common. After 15 to 45 seconds, the tonic activity gives way to clonic, rhythmic, sometimes asymmetrical jerking of all four extremities. The rhythmic contractions gradually become slower in frequency until the event stops; the patient is apneic, comatose, and diaphoretic, but breathing with stridor and gasping begins within 60 seconds. Patients who have generalized tonic-clonic seizures in public often prompt bystanders to initiate resuscitation efforts, although such patients begin spontaneous respiration within 1 minute or so. Postictal stupor persists for a variable length of time. The patient generally sleeps for 2 to 8 hours and then complains of severe headache, sore muscles, a bitten tongue, and the inability to concentrate for a day or more. After generalized tonic-clonic seizures, some individuals have severe memory loss that gradually improves, sometimes over a period of weeks. Generalized tonic-clonic seizures also are a common expression of many metabolic, toxic, traumatic, or ischemic insults (see Table 410-1), but these provoked seizures do not qualify for the diagnosis of epilepsy.

Absence seizures, or petit mal seizures, are the second most common type of generalized seizure. Patients experience an abrupt onset and termination of a momentary lapse of awareness. Patients have no perception of any aspect of the event and may or may not realize that some time was lost, although individuals often lose their train of thought. Because consciousness is abruptly lost and immediately regained, there is neither an aura nor residual postictal symptoms. These seizures begin in childhood, and school teachers are often the first to notice them. Absence seizures may be accompanied by brief eye blinking or myoclonic movements (see Table 410-3), particularly if the event, as judged by EEG, extends beyond 10 seconds. These seizures can occur many times a day but are not associated with progressive neurologic disease. They can also occur in a more continuous form as nonconvulsive status epilepticus with resultant confusion (see Fig. 410-5).

Some patients with extensive bilateral brain disease have a variation of absence seizures, known as *atypical absence.* The event is similar in terms of loss of contact, but there is more motor, autonomic, or automatic activity, and the EEG demonstrates discharges that are slower than the 3-Hz spike and wave of typical absence seizures.

Myoclonic seizures consist of brief episodes of sudden motor contraction (see Table 410-3), which can be focal, with one arm involved, or bilateral and massive, with involvement of both upper extremities and the trunk. Consciousness is preserved but can be difficult to evaluate because of the brevity of these seizures. Myoclonic seizures form part of three main clinical constellations: juvenile myoclonic epilepsy, which starts in childhood or adolescence and often persists into adulthood; epilepsy with various combinations of absence and myoclonic seizures; and epilepsy in the setting of degenerative or inherited syndromes with bilateral cerebral involvement and abnormal cerebral function. Myoclonic seizures most commonly occur in the morning after awakening and often increase in frequency to culminate in a generalized tonic-clonic seizure.

Atonic and tonic seizures are brief but extremely disabling motor events that are characterized by a sudden increase or decrease in muscle tone. The result is falls and injuries with variable impairment of awareness. Such seizures frequently begin in children with diffuse CNS disease and multiple types of seizures, but they persist during adulthood.

DIAGNOSIS

The basic diagnosis of seizures is established by the clinical history. Although EEG, imaging, and laboratory studies are commonly required to determine the type of epilepsy, epilepsy syndrome, site of origin of focal seizures, and occurrence of nonepileptic seizures, the answer to the basic question of whether the patient's episodes are seizures or not rests almost entirely on a careful clinical history. Because epilepsy is defined as the occurrence of two or more unprovoked seizures, this diagnosis is also established by history.

Differential Diagnosis

The first question facing clinicians is whether the episodes under consideration are indeed seizures. The diverse clinical expression of seizures entails a

large differential diagnosis among conditions that produce episodic neurologic dysfunction (Table 410-4). Common conditions resembling seizures include syncope (Chapters 50 and 62), transient ischemic attacks (Chapter 414), migraine (Chapter 405), movement disorders (Chapter 417), and psychogenic nonepileptic seizures (see Table 410-4).

A number of historical elements dramatically change the likelihood of this diagnosis. Three essential elements help determine whether an episode is a seizure (Table 410-5) and distinguish seizures from other causes of temporary loss of consciousness, especially syncope (Chapters 50 and 62):

1. The clinical context, including medical and family history, and circumstances under which the episode occurred
2. Specific triggers or provoking factors
3. A detailed clinical description that entails four components:
   - What is the first symptom or sign (presence and type of aura, evidence of focal seizure at onset)?
   - How does it evolve after onset (what happens during the seizure proper, what are the signs or symptoms, how long does it last)?
   - How does it end (gradually or abruptly)?
   - Are there any neurologic deficits after the seizure ends?

Because patients have limited or no recall, the history from others is crucial. Observers can contribute important information about the patient's activity, responses, and appearance, including changes in color, diaphoresis, respirations, vocalization, and muscle tone. This information is often essential to characterize the type of seizure and to distinguish seizures from conditions that resemble seizures.

Migraine (Chapter 405) and focal seizures not only resemble each other but also coexist as comorbid conditions. Features that favor a diagnosis of seizures over classic migraine include an inconsistent occurrence of headache during the event, a brief duration, and the occurrence of more severe seizures. Myoclonus (Chapter 417) occurs in a variety of settings (e.g., metabolic encephalopathies) without any association with epilepsy or the EEG changes seen in myoclonic epilepsy.

Frontal lobe seizures arise predominantly during sleep and can have dramatic motor expression. They can be confused with nonepileptic psychogenic seizures, sleep disorders (Chapter 412), or movement disorders (Chapters 416 and 417). Video EEG monitoring may be necessary for diagnosis.

Patients with panic attacks (Chapter 404) can experience events that mimic focal seizures with autonomic and psychic features. However, panic attacks usually have a longer duration, do not progress to more severe seizures, and can be linked to specific circumstances. Nevertheless, focal seizures with limbic symptoms are often misdiagnosed as panic attacks.

Psychogenic nonepileptic seizures are behaviors that resemble seizures and are often part of a conversion reaction (Chapter 404) precipitated by underlying psychological distress. Psychogenic seizures can be difficult to diagnose because they can mimic almost any type of seizure, and they often coexist with epilepsy in the same patient. An erroneous diagnosis of nonepileptic seizures poses a risk for inappropriate discontinuation of medication, with resulting status epilepticus. Conversely, an erroneous diagnosis of seizures can result in iatrogenic illness owing to unnecessary therapy, excessive sedation, and cardiorespiratory depression. Features suggesting nonepileptic seizures include variable clinical manifestations across episodes, frequent and prolonged episodes, lack of response to antiseizure medication, out-of-phase upper and lower body movements, prominent pelvic thrusting, and lack of rigidity. Secondary gain is usually evident, and there is often a history of sexual abuse. Nevertheless, the peculiarities of these attacks may require continuous video EEG monitoring for diagnosis.

TABLE 410-4 DISORDERS RESEMBLING SEIZURES

VASCULAR AND PERFUSION DISORDERS
Migraine, syncope, transient ischemic attack, transient global amnesia, arrhythmia/hypoperfusion
PSYCHIATRIC DISORDERS
Psychogenic nonepileptic seizures, panic disorder, dissociative disorder
MOVEMENT DISORDERS
Tics, paroxysmal dystonia, paroxysmal choreoathetosis, paroxysmal ataxia
SLEEP DISORDERS
Night terrors, sleep walking, sleep myoclonus, narcolepsy/cataplexy, rapid eye movement sleep intrusions
METABOLIC DISTURBANCES
Alcoholic blackouts, delirium tremens, hypoglycemia, hallucinogenic drugs
OTHER
Breath-holding spells, paroxysmal vertigo, migraine with recurrent abdominal pain and cyclic vomiting

TABLE 410-5 CLINICAL FEATURES THAT HELP DISTINGUISH A GENERALIZED TONIC CLONIC SEIZURE FROM SYNCOPE

	SEIZURE	SYNCOPE
Clinical context and circumstances	Neurologic or systemic conditions that predispose to seizures, family history of seizures. Mental fatigue, sleep deprivation, alcohol use or withdrawal, systemic illness	Cardiovascular disorders, dehydration, anemia. Family history of syncope
Triggers	Usually none (unless reflex epilepsy)	Orthostatic hypotension, venipuncture, painful and noxious stimuli, emotional stress, micturition, Valsalva maneuver
Clinical features		
Onset	No warning unless there is an aura. Abrupt loss of consciousness, generalized stiffening, and fall. Occurs in any position	Tiredness, nausea, diaphoresis, tunneling of vision. Loss of consciousness over few seconds and fall. Occurs usually standing
Course	Prominent tonic phase then clonic movements lasting about 1 minute, cyanosis, labored breathing, may bite tongue or cheeks, sometimes urinary incontinence	Usually loss of tone, pallor, multifocal myoclonic jerks lasting less than 15 seconds, sometimes urinary incontinence, usually no tongue or cheek biting
Offset	Postical sleepiness and confusion lasting up to hours, headache, myalgia	Rapid recovery over seconds to less than few minutes, no confusion, headache or myalgia. May have fatigue

Diagnostic Investigations

A detailed history, EEG recordings, and magnetic resonance imaging (MRI), can lead to a definitive diagnosis of epilepsy and its cause in up to 50% of patients. In other patients, the information is insufficient or inconsistent, but the physiologic and CNS abnormalities surrounding the actual event allow it to be placed provisionally into a specific diagnostic category in about another 30% of patients. Continuous video-EEG monitoring in an inpatient epilepsy unit can increase diagnostic sensitivity.

Single Seizures

Acute symptomatic seizures (see Table 410-1) are the known consequence of an acute condition, and investigations should be directed at the possible cause of these seizures. When no known cause is readily apparent, the seizures are considered to be *unprovoked.* The evaluation of patients who present with a first unprovoked seizure includes either brain computed tomography (CT) or MRI, which reveals a possible cause in about 10% of patients. An EEG obtained after the seizure will demonstrate abnormalities with prognostic significance in 20 to 25% of these patients. Blood tests (including levels of serum electrolytes, glucose, calcium, and magnesium; tests of liver and kidney function; a complete blood cell count; and screening for suspected toxins) will reveal abnormalities in up to 15% of these patients but are often nonspecific. Lumbar puncture is indicated if CNS infections are suspected and in all patients infected with human immunodeficiency virus (HIV), even in the absence of clinical findings suggestive of infection.

Epilepsy

Electroencephalogram

The EEG is the keystone investigation in all patients with seizures and epilepsy. Between seizures, the EEG can assess overall brain function and the

type, location, and amount of epileptiform (spike) discharges. The EEG is crucial in determining the epilepsy syndrome and choosing appropriate antiepileptic drugs. In focal epilepsies, the EEG often demonstrates focal slowing and spike discharges in the area of abnormality.

The EEG can establish the definitive diagnosis of epilepsy if electrical changes consistent with a seizure are recorded during a clinical seizure. However, the EEG may fail to demonstrate electrical changes during a typical clinical seizure if the seizure focus is too small (at least 6 cm^2 of cortical involvement is needed to create an EEG epileptiform change), the seizure focus is deep or in the mesial or inferior surfaces of the brain, or the event in question may not be an epileptic seizure. The EEG is always abnormal during generalized convulsive and absence seizures.

The initial EEG is normal in up to 60% of people with known epilepsy. However, epileptiform abnormalities occur in more than 80% of individuals with focal epilepsy if three or more interictal EEG studies are performed. In generalized epilepsies, interictal epileptiform discharges are more common and are easier to capture in the EEG (see Fig. 410-2).

The type of abnormality points to the epileptic syndrome. For example, the EEG can show hypsarrhythmia in West's syndrome (see later), or the classic 3-Hz generalized spike wave in generalized epilepsies with absence seizures (see Table 410-3; see Fig. 410-2).

In some circumstances, it is imperative to record seizures, such as in the evaluation of patients for epilepsy surgery and when the diagnosis of seizures is in question. Continuous video EEG monitoring for prolonged periods has made it possible to capture these events. Continuous EEG is also used in comatose patients in the intensive care unit setting when nonconvulsive seizure or status epilepticus is suspected.

Magnetoencephalography

Magnetoencephalography measures the small magnetic fields that are generated by electrical activity in the brain and approximates their location using mathematical models. Its use is largely restricted to the evaluation of patients for epilepsy surgery, in whom it is used for mapping interictal discharges and the localization of brain function when superimposed on brain MRI.

Imaging Studies

Brain MRI, which can demonstrate lesions in most patients whose epilepsy is associated with a structural cause, should be performed in essentially all patients with new-onset seizures. The use of fluid-attenuated inversion recovery (FLAIR) sequences increases the sensitivity to detect abnormalities of cortical development as well as hippocampal sclerosis, which point to the need for chronic anticonvulsant therapy or possible surgical treatment. Functional imaging procedures such as positron emission tomography (PET) for analysis of metabolism and single-photon emission computed tomography (SPECT) for determination of blood flow are also used to help localize areas of the brain to be targeted with epilepsy surgery.

Epileptic Syndromes and Constellations

Epileptic syndromes include 27 age-related syndromes, of which all but 6 begin or occur in infancy and childhood (Table 410-6). In addition, specific clinical constellations represent diagnostically meaningful forms of epilepsy, with specific implications for treatment, especially surgery, and also categorize for structural-metabolic causes, epilepsies of unknown cause, and conditions characterized by seizures that are not a form of epilepsy (e.g., febrile seizures). The diagnosis of epileptic syndromes and constellations is based on the types of seizures, the setting in which seizures occur, the patient's neurologic and cognitive status, age at onset, family history, and results of diagnostic studies, including EEG and MRI. The selection of specific drug and surgical treatment depends on the types of seizures present (see Table 410-8, later). The need for lifelong treatment, the risk for genetic transmission, the likelihood of concurrent neurologic diseases, the risk for comorbid conditions, and the long-term prognosis are critical factors that can be addressed only with knowledge of the specific epileptic syndrome or constellation.

TABLE 410-6 EPILEPTIC SYNDROMES AND CONSTELLATIONS ACCORDING TO THE NEW INTERNATIONAL CLASSIFICATION

BY AGE AT ONSET
Neonatal Period
Benign familial neonatal epilepsy
Early myoclonic encephalopathy
Ohtahara's syndrome
Infancy
Epilepsy of infancy with migrating partial seizures
West's syndrome
Myoclonic epilepsy in infancy
Benign infantile epilepsy
Benign familial infantile epilepsy
Dravet's syndrome
Myoclonic encephalopathy in nonprogressive disorders
Childhood
Febrile seizures plus (can start in infancy)
Panayiotopoulos' syndrome
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes
Autosomal-dominant nocturnal frontal lobe epilepsy
Late-onset childhood occipital epilepsy
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike and wave during sleep
Landau-Kleffner syndrome
Childhood absence epilepsy
Adolescence-Adult
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsy with generalized tonic-clonic seizures alone
Progressive myoclonus epilepsies
Autosomal dominant partial epilepsy with auditory features
Other familial temporal lobe epilepsies
LESS SPECIFIC AGE RELATIONSHIP
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
DISTINCTIVE CONSTELLATIONS
Mesial temporal lobe epilepsy with hippocampal sclerosis
Rasmussen's syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsion-hemiplegia-epilepsy

Some Specific Seizure Syndromes and Constellations

Neonatal and Infantile Epilepsy Syndromes

Benign neonatal convulsions occur in previously healthy newborns on about day 5 as focal or generalized tonic seizures. Mutations in two potassium channel genes (*KCNQ2, KCNQ3*) have been associated with this syndrome. Potassium-channel regulation may be age dependent and therefore account for the age-related appearance of the seizures. The EEG shows rhythmic slow-wave activity or spiking with seizures. The seizures are refractory to treatment, are recurrent over a brief interval, and disappear within a month. About 90% of such infants subsequently have normal development, whereas 10% have subsequent seizures.

Generalized epilepsy with febrile seizures plus is a syndrome that consists of febrile seizures in combination with other nonfebrile types of seizures, including myoclonic, absence, atonic, tonic-clonic, and focal seizures. Mutations in at least four different voltage-gated ion channel and GABA receptors genes have been identified.

Dravet's syndrome (severe myoclonic epilepsy of infancy) starts in the first year of life with myoclonic seizures plus other seizure types, including absence, atonic, and focal. In this devastating syndrome, the seizures are resistant to treatment and are accompanied by developmental and cognitive decline. Mutations in the *SCN1A* sodium channel have been identified.

West's syndrome comprises a triad of epileptic spasms, developmental arrest, and an EEG pattern called hypsarrhythmia (a markedly abnormal EEG pattern with high-amplitude slowing and superimposed multifocal spikes, polyspikes, and spike and slow-wave complexes). It appears before the age of 12 months and ceases by 5 years of age, often to be replaced by other epilepsy syndromes such as Lennox-Gastaut syndrome. Tuberous sclerosis (Chapter 426) and hypoxia are among the common causes, but a cause may not be found. Associated abnormalities often include developmental delay, porencephaly, atrophic lesions, calcifications, and agenesis of the corpus callosum.

Childhood Epilepsy Syndromes

Childhood absence epilepsy begins before age 12 years, and its onset peaks at age 5 to 7 years, with a strong genetic tendency. It is more common in girls

than boys and is characterized by very frequent daily absence seizures (up to hundreds per day), rarely with other types of generalized seizures. It occurs in the setting of otherwise normal brain structure and function, and it is self-limited in about 40% of cases. The seizures are accompanied by a characteristic 3-Hz spike-and-wave EEG discharge, which appears in short bursts between seizures and in continuous runs during seizures. Remission usually occurs before the age of 12 years, but generalized tonic-clonic seizures occasionally may develop in adolescence.

Lennox-Gastaut syndrome is one of the most severe childhood epilepsies. It starts before age 8 years (peak from 3 to 5 years) and is characterized by a triad of mental retardation, multiple types of generalized seizures (atypical absence, generalized tonic-clonic, tonic, atonic), focal seizures that are highly resistant to treatment, and a typical EEG pattern of slow spike and wave (slower than the typical 3 Hz associated with absence seizures) and bursts of fast rhythms at 10 to 12 Hz during sleep. It often follows the resolution of West's syndrome.

Benign epilepsy with centrotemporal spikes (*benign rolandic epilepsy*) starts between 3 and 13 years of age and is characterized by almost exclusively nocturnal focal motor or sensory seizures that have a facial or oral onset and often evolve to convulsive seizures. Nearly 50% of cases have a family history of epilepsy, but most patients have no known brain abnormality. The EEG shows spiking in the centrotemporal region. In some cases, the disorder may not require treatment because it usually remits spontaneously.

Adolescence and Adult Epilepsy Syndromes and Constellations

Juvenile myoclonic epilepsy usually starts in the second decade with generalized tonic-clonic and myoclonic seizures. Mutations in GABA receptors, including *GABRG1,* can be found. Seizures typically occur in the morning, immediately after awakening. The seizures are especially linked to sleep deprivation and tend to appear in college students. A proportion of these patients have had absence seizures as well. The EEG typically shows fast (4 to 6 Hz) generalized spike and wave. Lifetime treatment is generally needed.

Mesial temporal lobe epilepsy with hippocampal sclerosis is the most common epilepsy to produce focal dyscognitive seizures in adults. It is characterized by recurrent focal limbic seizures (see Table 410-2), with and without impaired awareness, that originate in mesial temporal and limbic structures. Up to 70% of patients have a risk factor, such as lengthy and complicated seizures before the age of 4 years, frequently associated with fever or with encephalitis, meningitis, or trauma. However, the characteristic seizures generally begin some years later. Most cases are sporadic, but there are familial forms of mesial temporal lobe epilepsy.

Various components of the mesial temporal limbic network (including the hippocampus, entorhinal cortex, amygdala, neocortical areas of the frontal and temporal lobes, and dorsal medial thalamus) are probably involved in the pathogenesis of these seizures. Mesial temporal sclerosis, also called hippocampal sclerosis, is characterized by neuronal loss and gliosis, mostly in the CA1 and CA3 regions of the hippocampus, with mossy fiber reorganization that is seen as sprouting of neuropeptide Y and dynorphin interneurons into the inner third of the dentate molecular layer. Whether hippocampal sclerosis is the cause or the result of seizures (or both) is not known. The seizures of mesial temporal lobe epilepsy often begin at 5 to 15 years of age. Seizures are typically dyscognitive with limbic symptoms; they begin with an aura of a rising epigastric sensation or a feeling of déjà vu, followed by oral and alimentary automatisms and later by contralateral arm dystonia and ipsilateral arm automatisms. The seizures are lengthy (lasting several minutes), rarely generalize, and typically occur three to five times a month. Auras without subsequent seizures are common. Hippocampal atrophy and increased hippocampal signal are best seen on T2-weighted and FLAIR coronal MRI sequences, and widespread interictal hypometabolism is seen in the temporal lobe on PET. Material-specific (verbal or visual) memory impairment corresponds to primary involvement of the dominant or nondominant hippocampus. EEG recordings show temporal lobe spikes interictally as well as rhythmic 4- to 7-Hz discharges over the appropriate temporal lobe during seizures.

Seizures with Less Specific Age Relationship

Reflex seizures are triggered reliably by specific simple (e.g., flashing lights) or elaborate (e.g., reading) stimuli. The mechanisms are diverse and may involve cortical and brain stem pathways, cortical dysregulation of extracellular calcium concentrations, and an imbalance between excitatory and inhibitory neurotransmitters. Visual-sensitive seizures (triggered by light or visual patterns) are the most common type of reflex seizures. They occur most commonly in females, and their incidence peaks around puberty, when they represent up to 10% of all new cases of epilepsy. Other triggers of reflex seizures include specific thoughts, actions, reading, tactile stimuli, adopting certain positions, eating, listening to music, startle, and contact with hot water. The triggered seizures can be myoclonic, convulsive, atonic, or focal, depending on the triggering stimulus. Avoiding the offending stimulus is crucial to avoid seizures, emphasizing the importance of careful questioning about seizure triggers in patients with epilepsy.

TREATMENT Rx

The treatment of seizures and epilepsy is guided by accurate knowledge of the type of seizure and epileptic syndrome, the probability of recurrent seizures, the likelihood and severity of psychosocial or physical consequences with further seizures, and whether the benefit from treatment substantially outweighs the risks for side effects. It is important to identify and correct any environmental, physiologic, or lifestyle factors, such as sleep deprivation and irregular sleep habits, that can lower the seizure threshold and trigger seizures in patients with epilepsy.

Single Unprovoked Seizures

The decision to treat single unprovoked seizures depends on the likelihood of recurrence according to prognostic variables (see Prognosis) and on the individual patient's profile and preference. A meta-analysis demonstrated that antiepileptic drug treatment after a first seizure reduces the absolute risk of having a second seizure in the short-term by 33%, corresponding to a number needed to treat (NNT) of 3.[1] However, at least two randomized trials have shown that treatment of the first seizure with antiepileptic drugs does not prevent the development of epilepsy in the long term.[2,3] Therefore, the decision to treat the first seizure should be individualized based on the patient's preference, the risk for and impact of recurrent seizures (e.g., driving and employment), and the risk for medication side effects.

Acute Symptomatic (Provoked) Seizures

Seizures that are provoked by specific exposures are usually self-limited and not associated with an enduring seizure tendency, so the primary therapeutic consideration should be identification and treatment of the underlying disorder (see Table 410-1). If antiepileptic drugs are needed to treat seizures acutely, they usually can be discontinued after the patient has recovered from the primary illness. Some acute conditions like stroke (Chapter 414), brain infections (Chapters 420 and 422), and trauma (Chapter 406) can produce both acute symptomatic seizures and an enduring seizure tendency, so it would seem logical to use long-term antiepileptic drug treatment. To date, however, randomized controlled trials have not been able to demonstrate that antiepileptic drugs prevent the development of epilepsy in these conditions, so long-term therapy is not recommended unless epilepsy develops.

Epilepsy Syndromes with a Favorable Course

In syndromes such as benign epilepsy of childhood with centrotemporal spikes and some types of childhood occipital epilepsy, seizures are mild, infrequent, or exclusively nocturnal, and they remit spontaneously, thereby making treatment generally unnecessary. In selected cases, treatment may be desirable to prevent recurrences and to help alleviate parental concerns. In such cases, drug treatment is usually limited to 1 to 2 years regardless of interictal EEG abnormalities, which can persist long after seizures have remitted. The recommended antiepileptic drugs are those used in focal epilepsy in children, including oxcarbazepine, carbamazepine, valproate, gabapentin, lamotrigine, and topiramate (Table 410-7). Some patients with reflex seizures may require antiseizure medication, which should be chosen according to seizure type (Table 410-8).

Choice of Antiepileptic Drugs

The ultimate goal of treatment is to obtain complete freedom from seizures without side effects. Some of the newer antiepileptic drugs (see Table 410-7) are better tolerated and have better pharmacokinetics than older drugs, but there is no robust evidence to support superior efficacy of one drug over another.[4,5] The choice of medication depends on the type of seizure, thereby making a correct diagnosis crucial, and the medication's side effects, cost, and ease of use. Specific drugs are effective for specific types of seizures, and some drugs can worsen other types of seizures. Knowledge of individual drugs as they relate to age, sex, comorbid conditions, drug interactions, sedation, tolerance, mood, and withdrawal is critical in the drug selection process (see Table 410-8).[5,6] For example, ethosuximide and valproic acid are more effective than lamotrigine for the treatment of childhood absence epilepsy.[7]

Drugs that cause enzyme induction (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazepine, topiramate) or inhibition (e.g., valproic acid) can be difficult to manage when additional medications, such as oral contraceptives, are used for independent conditions. For these settings and in elderly patients, gabapentin and levetiracetam are particularly useful because they have no appreciable drug interactions.

TABLE 410-7 CHARACTERISTICS OF MAJOR ANTIEPILEPTIC DRUGS

NAME	TOTAL MILLIGRAMS PER DAY (USUAL SCHEDULE)	THERAPEUTIC RANGE (μG/mL)	PROMINENT SIDE EFFECTS	OTHER EFFECTS	OTHER ISSUES
Carbamazepine	400-1600 (bid)	4-12	Diplopia, fatigue, hyponatremia	Mood stabilizer	Enzyme inducer
Ethosuximide	750-1250 (qd, bid)	40-100	Ataxia, lethargy	Skin rash, bone marrow suppression	
Gabapentin	600-6000 (tid, qid)	2-12	Fatigue	Treatment of pain	No drug interactions
Lamotrigine	100-600 (bid)	4-18	Insomnia, headache, tremor, anxiety	Mood stabilizer	Risk for Stevens-Johnson syndrome; slow start-up
Levetiracetam	500-3000 (bid)	3-63	Mood change, irritability, lethargy		No drug interactions
Oxcarbazepine	300-2400 (tid)	6-40	Diplopia, hyponatremia, sedation	Mood stabilizer	
Phenobarbital	60-240 (hs)	15-40	Fatigue, depression, sedation	Joint pain	Enzyme inducer
Phenytoin	200-600 (bid)	10-20	Fatigue, hirsutism, gingival hypertrophy	Treatment of some pain	Enzyme inducer
Topiramate	50-600 (bid)	2-12	Anorexia, weight loss, kidney stones, speech disturbance, distal paresthesias	Headache prophylaxis, mood stabilizer	Enzyme inducer
Valproate	500-6000 (tid)	50-100	Weight gain, hair loss, tremor	Headache prophylaxis, mood stabilizer	Enzyme inhibitor, parkinsonian effects in elderly patients
Zonisamide	100-600 (hs)	10-40	Anorexia, kidney stones, dizziness, distal paresthesias	Mood stabilizer	

TABLE 410-8 ANTIEPILEPTIC DRUG SELECTION BY SEIZURE TYPE

SEIZURE TYPE	COMMONLY USED (ALPHABETICAL ORDER)	LESS COMMONLY USED (ALPHABETICAL ORDER)	*Effectiveness (Grade A Recommendation)**	
			NEW-ONSET SEIZURES	REFRACTORY SEIZURES
Focal seizures with or without dyscognitive features or evolution to convulsions	Carbamazepine (CBZ) Gabapentin (GBP) Lamotrigine (LTG) Levetiracetam (LEV) Oxcarbazepine (OXC) Phenytoin (PHT) Tiagabine (TIAG) Topiramate (TPM) Valproate (VPA) Zonisamide (ZNS)	Acetazolamide (ACZ) Clonazepam (CLN) Clorazepate (CLZ) Phenobarbital (PB) Primidone (PRM) Felbamate (FBM)	CBZ* GBP* LTG* OXC* PB* PHT* TPM* VPA*	CBZ† GBP* LAM* LEV* OXC* PB† PHT† TIAG* TPM* VPA† ZNS*
Generalized convulsive seizures (tonic-clonic seizures, tonic seizures, atonic seizures)	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Phenytoin Topiramate Valproate Zonisamide	Acetazolamide Clonazepam Clorazepate Felbamate Phenobarbital Primidone	CBZ† LEV* LTG* PHT† VPA*	CBZ† LAM* LEV* PHT† TPM* VPA*
Absence seizures	Ethosuximide (ETH) Lamotrigine Valproate Topiramate	Acetazolamide Clonazepam Phenobarbital Primidone	ETH* LTG* VPA*	
Myoclonic seizures	Clonazepam Valproate Zonisamide Levetiracetam	Phenobarbital	VPA†	LEV

*Supported by class I evidence (American Academy of Neurology).
†Often the "standard" of comparison, without evidence of effectiveness by randomized controlled trials.

In patients with newly diagnosed focal epilepsy, the underlying cause influences the response to antiepileptic drugs. The likelihood of achieving seizure freedom is higher for patients with vascular malformations, stroke, and tumors (63 to 78%), and lower for patients with hippocampal sclerosis and malformations of cortical development (40 to 50%). Among patients presenting with a new diagnosis of epilepsy, about 65% achieve seizure remission on antiepileptic drug treatment. Of these patients, about 45 to 50% achieve seizure remission with the first antiepileptic drug, 10 to 15% with the second, 1% with the third, and 3% with a combination of two or more antiepileptic drugs. Because the likelihood of achieving subsequent seizure remission is small if two drug trials fail, the 35% or so of patients who fail adequate trials of two antiepileptic drugs are considered to be *drug resistant*. In these patients, other forms of treatment, including surgery, should be considered. The first consideration in managing apparently drug-resistant patients is to ensure that the diagnosis is correct and the antiepileptic drug is appropriate. Other common issues include poor adherence to antiepileptic drugs, sleep deprivation, alcohol use, fatigue, emotional stress, systemic illnesses, use of concurrent medications, and nonepileptic seizures. After addressing these factors, patients who remain drug resistant should be considered potential candidates for surgical therapy.

Surgical Treatment

Surgical treatment entails resection or disconnection of the cerebral region that contains the seizure focus. Removal of an epileptogenic region requires accurate identification of the region as well as documentation of a lack of functional consequences after its removal. Video EEG monitoring with seizure recording from scalp electrodes, MRI protocols with special attention to areas

commonly associated with refractory seizures (e.g., the medial temporal and frontal lobes), and functional neuroimaging, including PET and SPECT, are used to make the assessment. In temporal lobe epilepsy, neuropsychological evaluation is essential to localize dysfunction and to establish the level of function in the region considered for resection. EEG localization of the region of seizure onset and mapping of brain function may require the surgical implantation of intracranial electrodes for recording and for stimulating cortical tissue. These procedures are performed by multidisciplinary teams in specialized epilepsy centers.

Epilepsy surgery interventions that have been subjected to rigorous randomized trials include temporal lobe resection compared with medical therapy for mesial temporal lobe epilepsy, comparison of different amounts of temporal lobe resection, different intensities of vagus nerve stimulation, and thalamic stimulation compared with medical therapy. The most dramatic surgical effect is seen for temporal lobe resection compared with medical therapy. In one series, 58% of surgical patients and only 8% of medical patients became seizure free (NNT of 2 at 1 year).■ As a result, patients with drug-resistant temporal lobe epilepsy should be evaluated for epilepsy surgery. Nonrandomized studies demonstrate enduring freedom from seizures at 10 years or more after hemispheric disconnection (61%), temporal lobe resection (64%), parieto-occipital resection (46%), and frontal lobe resection (27%). Palliative surgical procedures, such as callosotomy and multiple subpial transections, have lower success rates and are used when surgical resection of the seizure focus is not possible. Promising surgical therapies for epilepsy include radiosurgery and various types of electrical stimulation of the brain.

Status Epilepticus

Status epilepticus is a medical emergency in which seizures occur continuously or repeatedly without intervening resumption of consciousness for 30 minutes. However, even 5 minutes of generalized tonic-clonic seizures cause hypoxia, lactic acidosis, muscle breakdown, and neuronal damage. Most episodes of status epilepticus are caused by an acute brain insult in people without underlying epilepsy, so a cause should be sought promptly. After securing the airway and stabilizing cardiovascular function, immediate intervention with parenteral agents is needed to stop the seizures. Intravenous lorazepam (0.1 mg/kg given at 2 mg per minute) is the emergent treatment of choice, followed by intravenous phenytoin (15 mg/kg at a rate of 50 mg per minute) or fosphenytoin (15-20 mg/kg at a rate of 150 mg per minute) to provide a more long-lasting effect. If seizures continue for 10 to 15 minutes, options include phenobarbital (20 mg/kg intravenously) or continuous intravenous midazolam (0.1 to 2 mg/kg/hour), pentobarbital (0.5 to 3 mg/kg/hour), or propofol (2 to 4 mg/kg/hour), most appropriately in an intensive care setting. In refractory cases, general anesthesia for 24 hours is used.

Considerations in Women

Changes in hormone levels during the menstrual cycle may aggravate seizures perimenstrually in some women (i.e., catamenial epilepsy). The administration of oral contraceptives (Chapter 246), Depo-Provera, or acetazolamide (250 to 500 mg per day) may reduce perimenstrual seizures. Enzyme-inducing antiepileptic drugs (see Table 410-7) that reduce estrogen levels by enhancing its metabolism require patients to be treated with higher doses of estrogen or alternative methods of contraception.

Pregnancy poses challenges with regard to seizure control, teratogenesis, and outcomes of pregnancy. Nevertheless, pregnancy itself has no consistent effect on the frequency of seizures, and more than 90% of pregnancies in women with epilepsy are safe and successful. Freedom from seizures for at least 9 months preceding pregnancy is associated with a high probability of freedom from seizures during the pregnancy. Serum levels of lamotrigine, phenytoin, carbamazepine, levetiracetam, and oxcarbazepine may change during pregnancy and should be monitored. To reduce the risk for major congenital malformations, the use of valproate should be avoided if seizure control permits it. Similarly, polytherapy and high doses of antiepileptic drugs should be avoided, if possible, but antiepileptic drugs should not be discontinued. There is no increased risk for cesarean section or premature contractions, and epilepsy itself does not increase the risk for cognitive impairment in the child. Supplementation with at least 0.4 mg of folic acid daily should be given before conception and during pregnancy to reduce the risk for neural tube defects.

Discontinuing Antiepileptic Drugs

About 60% of patients have seizures that are easy to control with antiepileptic drugs. Medications may be slowly tapered over 4 to 6 months in patients who have remained free of seizures for 2 years or longer, have had few seizures before treatment started, and who have a normal neurologic examination and EEG. However, the increased absolute risk for recurrent seizures after withdrawal of medication is about 20% (number needed to harm of 5). The consequences of a recurrent seizure, the costs and side effects of drugs, and aspects such as personal preferences influence the decision to withdraw antiepileptic drugs in patients who have been free of seizures.

PROGNOSIS

The prognosis is favorable in the majority of patients who experience either unprovoked seizures or one of the epilepsies.

Prognosis after Febrile Seizures

Febrile seizures are common and usually consist of generalized tonic-clonic seizures. They are provoked by fever and therefore are not considered epilepsy. The seizures begin after 6 months of age and stop before 6 years of age. Usually, febrile seizures are left untreated because the prognosis is benign. When febrile seizures occur in the setting of a neurologic abnormality or are prolonged or complicated, the risk for later epilepsy is increased.

Prognosis after a Single Unprovoked Seizure

The risk of experiencing recurrent seizures after a first unprovoked seizure ranges from 21 to 69% at 2 years and from 34 to 70% at 5 years. The risk is lower in the general population than in hospital-based studies (36% at 1 year and 45% at 2 years). The probability of a relapse decreases with time; about 50% of recurrences occur within 6 months of the initial seizure, and 76 to 96% occur within 2 years. The two most consistent predictors of recurrence are the presence of a neurologic cause for the seizure, which is often uncovered on brain MRI or by the neurologic examination and history, and an epileptiform or slow EEG. The 2-year risk for recurrence is lowest for patients without an identified neurologic cause and with a normal EEG (about 25%), intermediate for patients with an identified neurologic cause or without a cause but with an abnormal EEG (48%), and highest for those with a neurologic cause and an abnormal EEG (about 65%). The risk rises dramatically if more than one seizure has occurred; after a second unprovoked seizure, the risk for a third seizure is 73%, and after a third seizure, the risk for a fourth seizure is 76%.

Prognosis of Epilepsy

The natural history of untreated epilepsy, mostly in developing countries, shows that 30 to 40% of patients obtain 5- to 10-year remissions without treatment. In developed countries, where treatment is generally started after two unprovoked seizures have occurred, the likelihood of 5-year remission is about 60% when patients are followed for 10 years, and about 70% when patients are followed for 20 years. The rate of 5-year remission in children is about 75%.

Conversely, the duration of active epilepsy before achieving control is one of the most powerful predictors of remission. If seizures remain uncontrolled during the first year after diagnosis, the chance of ever achieving control is only 60%. If the period of uncontrolled seizures extends to 4 years, the chance of ever achieving control is only 10%. The presence of multiple seizure types and frequent generalized tonic-clonic seizures is associated with a lower likelihood of remission. Less than 40% of patients with newly diagnosed mesial temporal lobe epilepsy will be controlled with medications, although familial cases are more easily managed medically.

Patients with epilepsy are at risk for poor psychosocial outcomes, depression, and increased mortality. The risk for death is two to three times higher in epilepsy than in the general population, and it can be up to six times higher in patients with frequent generalized convulsions and drug-resistant epilepsy. The major causes of death are underlying conditions such as stroke and pneumonia. Sudden unexpected death in epilepsy occurs in 1 per 1000 patient years and is particularly devastating because it affects young individuals with frequent, uncontrolled seizures.

Grade A

1. Wiebe S, Téllez-Zenteno JF, Shapiro M. An evidence-based approach to the first seizure. *Epilepsia*. 2008;49(suppl 1):50-57.
2. Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet*. 2005;365:2007-2013.
3. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007;369:1000-1015.
4. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007;369:1016-1026.
5. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62:1252-1260.
6. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy. Report of the Therapeutics and Technology Assessment

Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62:1261-1273.
7. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med*. 2010;362:790-799.
8. Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001;345:311-318.

SUGGESTED READINGS

Chong DJ, Bazil CW. Update on anticonvulsant drugs. *Curr Neurol Neurosci Rep*. 2010;10:308-318. *Review*.

Christensen J, Pedersen MG, Pedersen CB, et al. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort-study. *Lancet*. 2009;373:1105-1110. *The risk for epilepsy is significantly increased after skull fracture (2-fold), mild traumatic brain injury (2.2-fold), or severe brain injury (7.4-fold)*.

Geerts A, Arts WF, Stroink H, et al. Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch Study of Epilepsy in Childhood. *Epilepsia*. 2010;51:1189-1197. *Epilepsy remains active in about 30% of patients and becomes intractable in approximately 10%*.

Kahane P, Depaulis A. Deep brain stimulation in epilepsy: what is next? *Curr Opin Neurol*. 2010;23:177-182. *Review*.

Martindale JL, Goldstein JN, Pallin DJ. Emergency department seizure epidemiology. *Emerg Med Clin North Am*. 2011;29:15-27. *Review*.

Noe KH. Seizures: diagnosis and management in the outpatient setting. *Semin Neurol*. 2011;31:54-64. *Practical review*.

411

COMA, VEGETATIVE STATE, AND BRAIN DEATH

JAMES L. BERNAT

Assessment and treatment of a comatose patient are among the most challenging and critical activities in clinical medicine. Physicians must systematically and rapidly identify the cause of coma while simultaneously supporting vital systems and reversing the pathologic process. For example, resuscitation from cardiac arrest (Chapter 63) is successful only if the brain is not irreversibly damaged by a hypoxic-ischemic injury that can cause a vegetative state or brain death.

Coma, stupor, the vegetative state, and the minimally conscious state are disorders of consciousness (Table 411-1) that must be differentiated from brain death and locked-in syndrome. Human consciousness has two measurable clinical dimensions that correspond to two distinct brain neuronal systems: (1) wakefulness, which is the organism's arousal and readiness to respond to internal or external stimuli and which is provided by the reticular system of the rostral brain stem and its thalamic and forebrain ascending projections, and (2) awareness of self and environment, which is provided by a diffuse parallel network of thalamocortical and corticocortical circuits. Wakefulness is a prerequisite for awareness, but as exemplified by patients in a vegetative state, awareness may be lost despite maintained wakefulness.

Consciousness is usually considered a global brain function. Focal cerebral hemispheric lesions (Chapters 403 and 413) may disturb fragments of consciousness and produce disturbances such as aphasia, apraxia, or agnosia. Although language, praxis, and gnosis are elements of normal consciousness, their selective loss does not usually result in a diminution of the quantity of consciousness, so these focal syndromes are not classified as disorders of consciousness.

COMA

Coma is a pathologic state of eyes-closed unresponsiveness in which the patient has neither awareness nor wakefulness and from which the patient cannot be aroused to awareness or wakefulness by vigorous stimuli. Stupor is a similar disorder in which stimuli can temporarily arouse the patient to limited responsiveness but, in the absence of stimuli, the patient returns to an unresponsive state. Sleep, by contrast, is a normal state of active cyclic unconsciousness from which subjects can be fully and persistently aroused to full normal consciousness.

Coma is not a univocal state; it has levels of depth depending on the degree of reflex response to stimulation. Disorders of consciousness comprise a continuum from the mildest state of lethargy to the deepest stage of coma. Obtundation is a nonspecific term that describes any degree of altered consciousness without stipulating its depth.

EPIDEMIOLOGY

The frequencies of the various causes of coma vary widely depending on the setting. In most settings, however, post-traumatic, metabolic, anoxic, and toxic causes are the most common (Table 411-2).

PATHOBIOLOGY

Wakefulness is provided by a network of neurons and their connections in the central tegmentum of the pons and midbrain (reticular system) that receives input at each level as it ascends into the central basal forebrain, thalamus, and cerebral cortex. Damage to this neuronal network by trauma, ischemia, hypoxia, edema, or metabolic or toxic insults leads to coma because the ascending arousal mechanism is disturbed.

Awareness of self and environment requires not only wakefulness but also normal functioning of massive parallel reverberating neuronal circuits between the thalamus and multiple cortical regions to provide an integrated and unified experience. These structures and their connections can be damaged by the same pathologic conditions that affect the arousal system, but thalamic and cortical neurons are more susceptible to damage because of their higher metabolic demands. A given global brain insult, such as systemic hypoxia and ischemia suffered during cardiac arrest, can selectively damage the cortical and thalamic neurons necessary for awareness while largely sparing the phylogenetically older and less metabolically demanding neurons of the arousal network of the reticular system. This selective damage can result in the vegetative state, which is characterized by wakefulness without awareness.

Coma can be caused by (1) structural damage as a result of brain trauma, edema, inflammation, ischemia, or mass lesions or (2) diffuse metabolic and toxic effects on brain neurons. Structural lesions can affect the arousal neuronal network of the brain stem and basal forebrain directly through local neuronal damage or indirectly by downward or lateral pressure or displacement that causes local ischemia. Metabolic and toxic encephalopathies diffusely affect all brain neurons, particularly the metabolically sensitive cortical and thalamic neurons.

Structural lesions that cause coma typically produce clinically recognizable syndromes of cerebral "herniation" in which intracranial pressure shifts produce caudal displacement and ischemia of the midbrain and medial temporal lobe through the tentorial incisura and induces dysfunction of cranial nerves, breathing, and motor systems. Central transtentorial herniation from slowly expanding axial lesions is uncommon; more common is uncal herniation from rapidly expanding and laterally placed lesions that trap the ipsilateral oculomotor nerve against the uncus of the temporal lobe. Lateral displacement of brain structures can supplement or exceed downward displacement. The ascending arousal system can also be damaged directly by primary brain stem catastrophes such as pontomesencephalic hemorrhage or infarction or indirectly by downward-directed pressure waves produced by hemispheric mass lesions such as from brain trauma (Chapter 406) or supratentorial neoplasms (Chapter 195), abscesses (Chapter 421), hemorrhages (Chapter 415) or large infarctions (Chapter 414).

Metabolic encephalopathies disturb the neuronal microenvironment by altering the precise metabolic conditions necessary for normal neuronal excitability. Disturbances in the neuronal milieu can be caused by alterations in blood flow, oxygen delivery, glucose concentration, temperature, electrolyte concentrations, and intracranial pressure, as well as by meningitis, seizures, and organ failure. The depth of the resulting alteration of consciousness depends on the severity of the metabolic disturbance: mild metabolic encephalopathies can cause slowness or lethargy, whereas severe metabolic encephalopathies can produce deep coma. The rapidity of onset is of particular importance. A sudden drop in the serum sodium concentration (Chapter 118) may result in coma and seizures, whereas a slow decline to an equivalent level may not. Toxic encephalopathies can be caused by poisoning with exogenous agents such as depressant drugs or by endogenous toxins resulting, for example, from renal or hepatic failure and produce the same continuum of severity. Acute meningeal inflammation, caused most commonly by bacterial meningitis, induces coma by a combination of inflammatory and vascular changes.

TABLE 411-1 COMPARISON OF DISORDERS OF CONSCIOUSNESS*

	AWARENESS	WAKEFULNESS	BRAIN STEM/ RESPIRATORY	MOTOR	EEG	EVOKED POTENTIALS	PET/FMRI	COMMENT
Brain death	Absent	Absent	Absent	Absent	ECS	Absent	Absent cortical metabolism	Legally dead in most jurisdictions
Coma	Absent	Absent	Depressed, variable	Reflex or posturing	Polymorphic delta, burst suppression	BAER variable; cortical ERPs often absent	Resting <50%	Prognosis variable
Vegetative state	Absent	Present, intact sleep-wake cycles	Intact	Reflex, nonpurposeful	Delta, theta, or ECS	BAER preserved; cortical ERPs variable	Resting <50%; primary areas stimulatable	Prognosis variable
Minimally conscious state	Intact but poorly responsive	Intact	Intact	Variable with purposeful movements	Nonspecific slowing	BAER preserved; cortical ERPs often preserved	Reduced; secondary areas also stimulatable	Prognosis variable
Locked-in syndrome	Intact but communication difficult	Intact	Intact breathing; often brain stem signs	Quadriplegia, pseudobulbar palsy	Usually normal	BAER variable; cortical ERPs normal	Normal or nearly normal	Not a disorder of consciousness

*The table lists typical findings, which are not necessarily present in all patients.
BAER = brain stem auditory evoked response; ECS = electrocerebral silence; EEG = encephalography; ERP = event-related potential; fMRI = functional magnetic resonance imaging; PET = positron emission tomography.
From Bernat JL. *Ethical Issues in Neurology*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:292.

TABLE 411-2 CAUSES OF STUPOR AND COMA

- Traumatic brain injury*
  - Contusion
  - Intracerebral, epidural, subdural, or subarachnoid hemorrhage
  - Raised intracranial pressure
- Neoplasms and other mass lesions
- Infections
  - Meningitis
  - Encephalitis
  - Brain abscess or empyema
  - Sepsis or other infection, especially in the elderly or a demented patient*
- Cerebrovascular disease
  - Subarachnoid hemorrhage
  - Infarction in the brain stem or cerebellum or large hemispheric infarction
  - Hemorrhage in the brain stem or cerebellum or large hemispheric hemorrhage
  - Vasculitis, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura
- Seizures
  - Status epilepticus
  - Spike-wave stupor
  - Postictal state
- Metabolic encephalopathies*
  - Hypoglycemia, hyperglycemia
  - Hypercalcemia
  - Hyponatremia, hypernatremia
  - Hypoxemia, including anoxia after cardiac arrest
  - Acidosis
  - Organ system failure: hepatic, renal, pulmonary, cardiac
  - Endocrinopathy, e.g., myxedema coma
- Toxic encephalopathies
  - Drug intoxications*: alcohol, barbiturates, benzodiazepines, opioids, stimulants, salicylates, anticonvulsants, anticholinergics, psychotropic drugs, or others
  - Poisoning: carbon monoxide, industrial toxins
- Other encephalopathies
  - Hypertensive encephalopathy
  - Acute hydrocephalus
  - Pituitary apoplexy
- Other
  - Conversion, malingering, catatonia

*Most common causes.

TABLE 411-3 FOUR SCORE COMA ASSESSMENT SCALE*

EYE RESPONSE

E4 = Eyelids open or unopened, tracking or blinking to command
E3 = Eyelids open but not tracking
E2 = Eyelids closed but open to pain
E1 = Eyelids remain closed with pain stimuli

MOTOR RESPONSE

M4 = Thumbs up, fist, or peace sign
M3 = Localizing to pain
M2 = Flexion response to pain
M1 = Extension response to pain
M0 = No response to pain or generalized myoclonic status epilepticus

BRAIN STEM REFLEXES

B4 = Pupillary and corneal reflexes present
B3 = One pupil dilated and unreactive to light
B2 = Pupillary or corneal reflexes absent
B1 = Pupillary and corneal reflexes absent
B0 = Absent pupillary, corneal, or cough reflexes

RESPIRATION

R4 = Regular breathing pattern
R3 = Cheyne-Stokes breathing pattern
R2 = Irregular breathing pattern
R1 = Triggers or breathes above the ventilator rate
R0 = Apnea or breathes at the ventilator rate

*For nontraumatic coma and other disorders of consciousness.
From Wijdicks EFM. *The Comatose Patient*. New York: Oxford University Press; 2008:72a.

CLINICAL MANIFESTATIONS

A comatose patient is unresponsive and cannot be aroused to awareness or wakefulness. The level of consciousness can be assessed by loudly speaking the patient's name directly in the ear. Patients should be asked to look up and down to test for locked-in syndrome, in which vertical eye movements may be the only remaining voluntary movement. Noxious stimuli can be applied to elicit responses. Tickling the nasal hairs with a cotton-tipped swab is especially useful because it elicits primitive reflex mechanisms to protect the airway. Many painful stimuli should be avoided as unnecessary and cruel, but a sternal rub with fingers or knuckles is acceptable. Responses can be graded as voluntary movement, withdrawal, reflex posturing, and none.

Coma assessment scales are useful to describe the depth of coma, serially assess changes, and by correlation to outcomes, provide a prognosis. The widely used Glasgow Coma Scale (see Table 406-1) was devised to assess patients with traumatic brain injury. The FOUR Score scale is more useful for all causes of coma because it more accurately assesses brain stem function and quantifies awareness (Table 411-3).

DIAGNOSIS

The diagnosis of coma requires a rapid history, physical and neurologic examination (Table 411-4), laboratory tests, and neuroimaging studies, during which patient's vital functions must be supported. Immediate attention should be paid to whether the patient has signs of meningitis (e.g., fever, nuchal rigidity) or head trauma (Chapter 406) or focal findings suggestive of

a mass, lesion, bleeding, or ischemic injury. If signs of meningitis are present, a lumbar puncture should be performed without the delay of obtaining brain imaging if no marked focal signs (e.g., hemiparesis) are present. Brain computed tomography (CT) should be performed urgently in nearly every patient in coma.

The relevant history includes eyewitness accounts of any preceding headache, vomiting, confusional state, prescription and street drug use, alcohol consumption, diabetes, fever, head trauma, seizure activity, and medical illnesses, especially atrial fibrillation. The rate at which neurologic function declined can be especially helpful. On the general physical examination, assessment of vital signs, otoscopy, optic funduscopy, and inspection for head trauma, nuchal rigidity, and needle tracks can provide key findings.

TABLE 411-4 SOME INITIAL CLINICAL CLUES TO THE DIAGNOSIS OF STUPOR AND COMA

STRUCTURAL CAUSES
History
Abrupt onset of unconsciousness
Sudden headache
Vomiting
Examination
Focal neurologic signs (hemiparesis, posturing, asymmetrical reflexes)
Abnormal pupillary light reflexes
METABOLIC OR TOXIC CAUSES
History
Gradual onset of unconsciousness
Preceding confusional state
Seizures
Known cognitive impairment
Taking insulin or street drugs
Examination
Absence of focal neurologic signs
Presence of frontal release signs
Intact pupillary light reflexes
Tremor, asterixis, or multifocal myoclonus
Evidence of systemic infection
Needle tracks
MENINGITIS
History
Worsening headache
Neck stiffness and pain
Fever, chills
Progressive stupor and coma
Examination
Fever, rigors
Nuchal rigidity and signs of meningeal inflammation

Oximetry and a finger stick blood glucose assessment should be performed immediately. Emergency laboratory testing should generally include a complete blood count, serum electrolytes, a blood glucose level, tests of renal and liver function, coagulation tests, thyroid function tests, arterial blood gas analysis, a blood alcohol concentration, a urine drug screen, and an electrocardiogram.

The neurologic examination focuses on five systems whose careful assessment can distinguish structural from metabolic causes of coma and delineate the functional brain level caused by the pathologic process: the respiratory rate and pattern; the pupils' size, shape, and reactivity; eye movements and vestibulo-ocular reflexes; and motor responses to stimuli (Table 411-5).

The respiratory rate and pattern should be observed for 30 to 60 seconds. The earliest abnormalities seen in patients with altered consciousness are yawning, sighing, and posthyperventilation apnea, which occurs especially in those with metabolic encephalopathies. Stuporous patients should be asked to take five deep breaths and then be observed for the duration of subsequent apnea, which is normally less than 5 seconds. Cheyne-Stokes respiration (Chapter 86) is a periodic form of breathing whose amplitude forms a sine wave, with 5- to 45-second periods of apnea punctuating periods of hyperpnea; it is seen in the metabolic encephalopathies, especially those caused by heart failure, and during sleep. Central neurogenic hyperventilation, which is continuous hyperpnea and tachypnea that produces a pure respiratory alkalosis, occurs with lesions of the rostral brain stem tegmentum at the midbrain level; rapid, deep breathing (Kussmaul) that is compensating for a severe metabolic acidosis (Chapter 236) can look similar. Apneustic breathing, which is characterized by a prolonged inspiratory pause, is seen with pontine lesions. Ataxic breathing is an irregular and agonal sign of medullary failure.

Pupillary size and reactivity to a bright light stimulus can be assessed to evaluate the integrity of the optic and oculomotor nerves, the midbrain, and the sympathetic nerves. The reactivity of the pupils to light is an important sign that discriminates structural coma from metabolic-toxic coma. The pupils remain reactive through varying depths of metabolic-toxic coma, often until apnea ensues, whereas pupillary reflexes are lost earlier in structural coma that is caused by transtentorial herniation. The pupils are small, equal, and reactive in patients with metabolic encephalopathies. When the oculomotor nerve or the midbrain is involved, the ipsilateral pupil becomes unreactive to light because of damage to the parasympathetic pupillo-constrictors and dilates because of unopposed sympathetic pupillodilators. When herniation proceeds further, the brain stem sympathetic tracts are also damaged, so the pupil returns to midposition and becomes unreactive to light or dark. Lesions that affect only the pons and not the midbrain, such as pontine hemorrhage or infarction, can cause pinpoint pupils whose intact reaction to light can be seen with a magnifying glass. Preexisting disease (e.g., diabetes) or locally applied eye medications can also impair pupillary reflexes.

TABLE 411-5 BRAIN FUNCTIONAL LEVELS DETERMINED BY FINDINGS IN FIVE CLINICAL SYSTEMS

FUNCTIONAL LEVEL	CONSCIOUSNESS	RESPIRATION	PUPILS	VESTIBULO-OCULAR REFLEXES	MOTOR RESPONSES
CENTRAL TRANSTENTORIAL HERNIATION					
High diencephalic	Light stupor	Eupnea, yawning, posthyperventilation apnea	Small, reactive	Loss of checking component	Paratonia, grasp
Low diencephalic	Deep stupor	Cheyne-Stokes	Small, reactive	Loss of checking component	Decorticate posturing
Midbrain	Coma	Central neurogenic hyperventilation	Midposition, fixed	Loss of medial rectus function	Decerebrate posturing
Upper pons	Coma	Central neurogenic hyperventilation	Midposition, fixed	Loss of medial rectus function	Decerebrate posturing
Lower pons	Coma	Ataxic	Midposition, fixed	Absent	Flaccid
Medulla	Coma	Apnea	Midposition, fixed	Absent	Flaccid
UNCAL TRANSTENTORIAL HERNIATION					
Early third nerve	Unreliable	Normal	Ipsilateral dilated, fixed	Normal	Contralateral hemiparesis
Late third nerve	Coma	Cheyne-Stokes or central neurogenic hyperventilation	Ipsilateral dilated, fixed; contralateral dilated, fixed	Medial rectus dysfunction	Ipsilateral hemiparesis and contralateral decerebrate posturing
Midbrain-pons	Coma	Central neurogenic hyperventilation or ataxic	Midposition, fixed	Absent	Bilateral decerebrate posturing

Spontaneous eye movements may have localizing value. Conjugate horizontal eye deviation points to the side of brain lesions rostral to the brain stem (usually in the cerebral hemisphere) but to the side opposite brain stem lesions. Tonic downward eye deviation suggests acute lesions of the thalamus or dorsal midbrain. Tonic upward eye deviation is unusual but is seen in patients with hypoxic-ischemic lesions. Ocular bobbing with a rapid downward movement followed by a slow return upward suggests a pontine lesion. Reverse ocular bobbing with a slow downward and rapid upward movement ("ocular dipping") has poor localizing value but may be seen after hypoxic-ischemic insults and metabolic disorders. "Ping-Pong" gaze with alternating conjugate horizontal eye movements is nonspecific, but a slower and otherwise similar disorder, called periodic alternating gaze, is seen in those with portosystemic encephalopathy (Chapter 157). Ocular skew deviation, in which one eye is higher than the other on primary gaze, suggests a brain stem lesion.

The vestibulo-ocular reflex assesses brain stem and cerebral hemispheric function by reflexively inducing eye movements. First, the external auditory canal should be inspected to exclude perforation of the tympanic membrane and obstruction by cerumen. Ice water is then injected into the canal (10 mL for usual assessment but 50 mL for assessment of brain death), and the induced reflex eye movements are observed (see Table 411-5). In patients with normal consciousness, such as in psychogenic coma, marked horizontal nystagmus is produced. In those with stupor at a diencephalic level, such as from metabolic encephalopathy, the fast component of nystagmus is suppressed, so the patient responds with full tonic conjugate eye movements toward the injected ear. With lesions of the oculomotor or abducens nerves or lesions of the midbrain or pons, ophthalmoplegia of localizing value is observed. In brain death or total brain stem failure, no response is observed. The vestibulo-ocular reflexes may be ablated after treatment with ototoxic antibiotics.

Motor responses are observed after noxious stimulation, particularly nasal tickle, sternal rub, and ice water irrigation of the external auditory canal. In light coma from metabolic encephalopathy, symmetrical paratonia and grasp reflexes may be present. At lower functional levels of structural coma, limb posturing is often observed. Limb posturing is a unilateral or bilateral, stereotyped, tonic brain stem reflex movement induced by stimulation, especially noxious stimuli. Decorticate posturing, in which the arm is flexed and the ipsilateral leg is extended, suggests a midbrain functional level. Decerebrate posturing, in which both the arm and the ipsilateral leg are extended, suggests a pontine functional level. When the entire brain stem is destroyed, as in brain death, all limbs remain flaccid during stimulation. Metabolic-toxic encephalopathies usually produce symmetrical motor signs, whereas structural causes of coma frequently produce asymmetrical motor signs. Hypoglycemia and acute hyponatremia are exceptions in which aphasia, gaze paresis, and hemiparesis may be seen. Myoclonic seizures with continuous or intermittent rhythmic clonic movements frequently develop in patients who have suffered hypoxic-ischemic neuronal damage during cardiopulmonary arrest. Progression to myoclonic status epilepticus is a bad prognostic sign.

After the neurologic examination, screening laboratory tests, brain CT, and lumbar puncture have been accomplished, a tentative diagnosis can be made in most patients. If focal signs are present despite normal findings on CT, consideration should be given to an acute stoke involving the posterior circulation (Chapter 414). Brain CT angiography or magnetic resonance imaging (MRI) can clarify the diagnosis. If lateralizing signs are absent, metabolic and toxic causes are most likely. An electroencephalogram (EEG) is useful in patients in whom nonconvulsive seizure activity may be causing stupor or coma.

TREATMENT

Rx

Management of coma requires simultaneous diagnostic, supportive, and treatment measures (Table 411-6). Specific treatments, which depend on the causative diagnosis, include urgent attention to any head trauma (Chapter 406). Emergency stabilization of respiration and circulation and control of seizures are critical for all patients. In patients without focal findings or obvious meningitis, 50% dextrose (25 g intravenously), thiamine (50 mg intravenously), naloxone (0.4 to 2.0 mg intravenously), and flumazenil (0.2 mg intravenously) should be administered during the diagnostic assessment. If fever, nuchal rigidity, or leukocytosis is present, the patient should be treated presumptively for bacterial meningitis (Chapter 420) with intravenous antibiotics before neuroimaging and lumbar puncture.

Elevated intracranial pressure must be lowered urgently. Treatments include hyperventilation by bag or ventilator, intravenous hyperosmolar agents (Chapter 112) such as mannitol, and intravenous glucocorticoid drugs for patients with vasogenic edema from brain tumors (Chapter 195), abscesses (Chapter 421), or bacterial meningitis (Chapter 420). Intravenous barbiturate or benzodiazepine therapy remains of uncertain benefit. Therapeutically induced hypothermia for several days improves outcomes in patients who are in coma after diffuse hypoxic-ischemic neuronal damage caused by cardiac arrest.

PROGNOSIS

The prognosis is highly variable and depends on the cause, stage, degree of structural brain damage, and potential reversibility. Prediction rules for recovery apply only to a specific cause. The prognosis after traumatic brain injury is predicted by the Glasgow Coma Score (see Table 406-1). In patients who have survived cardiopulmonary arrest and resuscitation and in whom toxic and metabolic factors (e.g., sedation, neuromuscular blockade, hypothermia, organ failure, and shock) are not an issue, the likelihood for recovery of awareness is less than 1% if the following are present:

- Day 1: presence of myoclonic status epilepticus
- Days 1 to 3: bilateral absence of the N20 response of the somatosensory evoked potential
- Days 1 to 3: serum neuron-specific enolase concentration higher than 33 μg/L
- Day 3: absent pupillary or corneal reflexes; extensor or absent motor responses

If the patient remains comatose on day 3 without these findings and without a contribution from a potentially reversible metabolic or toxic encephalopathy, the probability of recovery of awareness is below 10% if there is no withdrawal response to painful stimuli and below 40% if the patient withdraws to painful stimuli but lacks spontaneous eye opening.

THE VEGETATIVE STATE

The vegetative state is a disorder of consciousness in which wakefulness is retained but awareness of self and environment is entirely absent, to the extent that it can be tested clinically. The vegetative state may be a transient stage during spontaneous recovery from coma to awareness, or it may be a chronic, unchanging state. Adjectives such as "persistent" or "permanent" should be avoided because they generate confusion by confounding the diagnosis and prognosis.

EPIDEMIOLOGY AND PATHOBIOLOGY

The vegetative state is caused by diffuse or multifocal brain lesions that disconnect the polymodal cerebral cortices from the thalami but spare the brain stem and hypothalamus. The prevalence of a transient vegetative state after brain injury is unknown. The prevalence of the chronic vegetative state is 19 per million.

Causative lesions can be located bilaterally in the thalami, diffusely in the cerebral cortex, or diffusely in the white matter that connects the thalami to the cortex. Two clinical disorders are most commonly responsible: diffuse hypoxic-ischemic neuronal damage to the thalami and cortex suffered during cardiopulmonary arrest and diffuse axonal injury from a traumatic injury

TABLE 411-6 EMERGENCY MANAGEMENT OF COMATOSE PATIENTS

1. Ensure oxygenation
2. Maintain the circulation
3. Administer 50% dextrose, 25 g IV, and control glucose
4. Lower raised intracranial pressure
5. Stop seizures with lorazepam, 1.0-2.0 mg IV
6. Search for and treat infections
7. Restore acid-base and electrolyte balance
8. Normalize body temperature
9. Administer thiamine, 50 mg IV, and multivitamins
10. Consider administration of opioid antagonists (naloxone, 0.4-2.0 mg IV)
11. Consider administration of benzodiazepine antagonists (flumazenil, 0.2 mg IV)
12. Control agitation
13. Protect the eyes
14. Consider inducing therapeutic hypothermia for diffuse hypoxic-ischemic causes

Modified from Posner JB, Saper CB, Schiff ND, et al. *Plum and Posner's Diagnosis of Stupor and Coma*, 4th ed. New York: Oxford University Press; 2007:311.

TABLE 411-7 DIAGNOSIS OF THE VEGETATIVE STATE

I. Absence of:
- Awareness of self or environment
- Purposeful or voluntary behavioral response to all stimuli
- Language comprehension or expression

II. Presence of:
- Intermittent wakefulness manifested by the presence of sleep-wake cycles
- Autonomic functions
- Cranial nerve and spinal reflexes

III. Potential behavioral repertoire:
- Breathe spontaneously
- Spontaneous roving eye movements
- Utter sounds but no words
- Grimace to pain, make facial expressions
- Yawn, make chewing jaw movements, swallow saliva
- Move limbs nonpurposefully, arch back, decorticate limb posturing
- Flexion withdrawal from noxious stimuli
- Move head or eyes briefly toward sound or movement
- Auditory startle

TABLE 411-8 DIAGNOSIS OF THE MINIMALLY CONSCIOUS STATE

Globally impaired responsiveness

Limited but discernable evidence of awareness of self and environment as demonstrated by the presence of one or more of the following behaviors that occur in a contingent relationship to relevant environmental stimuli and are not simply reflexive movements:
- Follow simple commands
- Gesture yes/no answers
- Make intelligible vocalizations or gestures in direct response to a question's linguistic content
- Reach for objects that demonstrates a clear relationship between object location and direction of reach
- Touch and hold objects in a manner that accommodates the size and shape of the object
- Sustain visual pursuit to moving stimuli
- Smile or cry appropriately to linguistic or visual content of emotional but not to affectively neutral topics or stimuli

caused by a torque force. These two disorders have different pathologies: hypoxic-ischemic injury affects cortical, thalamic, and cerebellar neurons, whereas diffuse axonal injury shears the axons at the gray matter–white matter junction in the cortex.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical features of the vegetative state (Table 411-7) are dominated by what patients do. A careful neurologic examination must be performed to search for any evidence of awareness because up to 40% of patients in whom a vegetative state is initially diagnosed are actually in a minimally conscious state (see later).

The vegetative state is a clinical syndrome with a spectrum of severity. The typical patient has diffuse slow-wave activity on the EEG, but the most severely affected patients have isoelectric EEGs. As determined by functional neuroimaging studies, an occasional patient with a clinically diagnosed vegetative state can perform ideational tasks on command, with evidence on functional MRI that they possess awareness. Such functional neuroimaging tests are not yet part of routine clinical practice but may become standard clinical assessment tools for patients who are suspected to be in a vegetative state.

TREATMENT AND PROGNOSIS

Rx

No treatments reverse or improve the vegetative state. The aggressiveness of medical treatment of patients in the vegetative state should ideally be guided by their previously stated wishes. Patients require the same medical and nursing care, physical therapy, and nutritional needs as patients in coma. Patients should be referred to specialized neurorehabilitation units when possible. Patients who are in a vegetative state from nontraumatic causes and who do not regain awareness within 3 months of the insult have less than a 1% chance of experiencing significant neurologic recovery. After traumatic brain injury, the prognosis cannot be estimated with a similar degree of certainty until after 1 year, although functional neuroimaging is a promising approach to identify patients who are destined to recover awareness.

THE MINIMALLY CONSCIOUS STATE

The minimally conscious state (Table 411-8) is a disorder of altered consciousness characterized by a profound lack of responsiveness but partial or intermittent evidence of awareness of self and environment. Patients may typically have suffered less severe injuries than patients in the vegetative state. The minimally conscious state is much more common than the vegetative state, from which it must be distinguished. When compared with patients in the vegetative state, patients in the minimally conscious state are more likely to respond to environmental and sensory stimuli, to stimulant medications such as levodopa or dopamine agonists (which stimulate thalamic dopaminergic neurons and are prescribed in the same dose ranges as for the treatment of Parkinson's disease, Chapter 416), and perhaps to deep brain electrical stimulation of the intralaminar thalamic nuclei. Patients in the minimally conscious state require the same specialized neurorehabilitation services as those in the vegetative state. There are no good prognostic data for the minimally conscious state other than for recovery after traumatic brain injury (Chapter 406).

THE LOCKED-IN SYNDROME

The locked-in syndrome, a state of profound paralysis, is not a disorder of consciousness but may be mistaken for one. In its classic form, it is produced when a large infarction or hemorrhage in the pontine tegmentum and base produces quadriplegia, pseudobulbar palsy, and paralysis of horizontal eye movements. Once the acute encephalopathy resolves, locked-in patients usually remain awake and alert, breathe spontaneously, and have normal consciousness and cognition, to the extent that they can be tested accurately. Inexperienced examiners may incorrectly diagnose locked-in patients as being comatose because of their profound paralysis, pinpoint pupils, and seeming unresponsiveness. A similar state of profound, global paralysis with intact cognition can be produced by advanced amyotrophic lateral sclerosis (Chapter 418), Guillain-Barré syndrome (Chapter 428), or critical illness polyneuropathy (Chapter 428).

Locked-in patients can be taught to communicate with voluntary vertical eye movements and eyelid movements, which are typically their only retained volitional movements because they are controlled rostral to the pons. Most affected patients die within a few months, but some otherwise healthy young patients who have become locked in as a result of basilar artery occlusion have survived for many years; occasional patients may recover function to become independent. Computerized systems can help patients communicate.

BRAIN DEATH

Brain death is the term popularly applied to the determination of human death based on tests that show irreversible cessation of all clinical brain functions. Once illness or injury has destroyed the brain or rendered its clinical functions irreversibly lost, a human being is dead. Brain death is a medically and legally accepted determination of human death throughout North America, Europe, Australia, most of the developed world, and much of the undeveloped world. Brain-dead patients serve as ideal multiorgan donors.

EPIDEMIOLOGY AND PATHOBIOLOGY

Most cases of brain death result from massive traumatic brain injury (Chapter 406), intracranial hemorrhage (Chapter 415), meningitis (Chapter 420), or diffuse hypoxic-ischemic neuronal damage secondary to cardiac arrest (Chapter 63) or asphyxia. Marked cerebral edema from the primary injury or illness produces severe intracranial hypertension. When intracranial pressure exceeds mean arterial blood pressure (or systolic blood pressure in some cases), intracranial blood flow ceases and widespread ischemic death of brain neurons ensues. Syndromes of transtentorial herniation commonly occur.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Brain-dead patients have no brain functions measurable at the bedside. The diagnosis should be suspected in any patient who is deeply comatose,

TABLE 411-9 TESTS FOR BRAIN DEATH

I. Preconditions showing irreversibility: all necessary
- Presence of a structural brain lesion sufficient to produce all the clinical signs
- Absence of reversible significant toxic or metabolic encephalopathy:
  - No depressant drug intoxication
  - No neuromuscular blockade (use electroneurography if uncertain)
  - No severe hypothermia
  - No severe hypotension
- Sequential repeated testing or one test followed by a confirmatory blood flow test

II. Signs showing complete cessation of all clinical brain functions: all necessary
- Coma: No spontaneous movements, no response to any stimuli, and no reflex movements integrated by the brain
- Apnea: No breathing or respiratory effort when the P_{ACO_2} ≥60 mm Hg while protecting the P_{AO_2}
- Brain stem areflexia: all necessary
  - Absent pupillary light and dark reflexes
  - Absent corneal touch reflexes
  - Absent facial movement to noxious stimuli
  - Absent vestibulo-ocular reflexes tested by caloric irrigation of the external auditory canal with 50 mL of ice water
  - Absent pharyngeal and tracheal reflexes to endotracheal tube suctioning

III. Confirmatory tests: optional but desirable; neuroimaging preferred
- Neuroimaging that shows complete absence of intracranial blood flow; one test
  - Intravenous radionuclide angiography
  - Transcranial Doppler ultrasound
  - Computed tomographic angiography
  - Magnetic resonance angiography or diffusion
  - Single-photon emission computed tomography
- Electrophysiologic testing (use only if intracranial pressure is not elevated)
  - Electroencephalography + brain stem auditory evoked responses + somatosensory evoked responses: all isoelectric

is unresponsive to stimuli, has absent pupillary light reflexes, and is completely ventilator dependent. The diagnosis requires a comprehensive evaluation (Table 411-9) that demonstrates both total loss of brain functions and its irreversibility as documented by at least two sequential examinations performed by an experienced physician or one examination followed by a neuroimaging test to confirm the complete absence of intracranial blood flow.

TREATMENT Rx

There is no treatment. Once the diagnosis has been made, the patient is declared dead. If the family has agreed to allow the deceased patient to serve as an organ donor, the ventilator is reattached following the apnea test, and the patient is moved to the surgical suite. If the patient is not an organ donor, the ventilator is not reattached, and all lines and monitors are discontinued. Physicians should be knowledgeable about local laws that may restrict making the diagnosis in patients belonging to certain religious groups that do not accept brain death as human death.

Grade A

1. Holzer M, Bernard SA, Hachimi-Idrissi S, et al. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med*. 2005;33:414-418.

SUGGESTED READINGS

Bernat JL. Chronic consciousness disorders. *Annu Rev Med*. 2009;60:381-392. *Reviews vegetative and minimally conscious states.*

Holzer M. Targeted temperature management for comatose survivors of cardiac arrest. *N Engl J Med*. 2010;363:1256-1264. *Review the technique, outcomes, and adverse effects of therapeutic hypothermia to protect the brain of cardiac arrest survivors.*

Wijdicks EFM, Varelas PN, Gronset GS, et al. Practice parameter update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74:1911-1918. *Clinical and laboratory approach to diagnosing brain death.*

Wu O, Batista LM, Lima FO, et al. Predicting clinical outcome in comatose cardiac arrest patients using early noncontrast computed tomography. *Stroke*. 2011;42:985-992. *Median Hounsfield units in the whole brain and the ratio in the putamen compared with the posterior limb of the internal capsule predict poor outcome.*

412

DISORDERS OF SLEEP

MARK W. MAHOWALD

DEFINITION

Wake-sleep complaints are second only to complaints of pain as the reason that patients seek medical attention. Undiagnosed and untreated wake-sleep complaints extract an enormous toll at the personal level in terms of misery and at the societal level in socioeconomic consequences. Knowledge of sleep and its disorders has expanded rapidly over the past half century, particularly with the discovery that sleep is far more than the passive absence of wakefulness. Sleep is an active brain process that includes two divergent states: non–rapid eye movement (NREM) and rapid eye movement (REM) sleep. A complex array of neurotransmitters, neuropeptides, and circulating humoral sleep-promoting factors interact with multiple areas of the central nervous system to determine wakefulness, REM sleep, and NREM sleep.

PATHOBIOLOGY

Wakefulness is controlled by the reticular activating system of the rostral brain stem, which projects to the thalamus and cortex. Inhibition of these projections, which is modulated by neurons in the pons and midbrain, results in sleep. REM sleep, during which most dreaming occurs, is generated within the tegmentum of the pons with modulation from the norepinephrine- and serotonin-containing neurons of the locus caeruleus and the dorsal raphe nucleus. Electrical events generated in the pontine reticular formation (i.e., ponto-geniculo-occipital [PGO] waves) are propagated through the oculomotor and visual system during REM sleep simultaneously with REMs. PGO waves are suppressed by norepinephrine, and the serotonin neuronal systems suppress PGO waves and REM; cholinergic neurons are stimulatory. PGO input can induce an action potential in neurons below their usual threshold. Such PGO-facilitated activity in the visual system may play a role in the random imagery of dreaming.

Hypocretins (orexins) are sleep modulatory neuropeptides made in the lateral hypothalamus with projections to the locus caeruleus and dorsal raphe, as well as to the thalamus, where they modulate the release of excitatory (glutamate) and inhibitory (γ-aminobutyric acid) neurotransmitters. Disruption of this system induces narcolepsy in animals, and hypocretin neurotransmission is deficient in most narcoleptic patients.

Stage of Sleep

Sleep stages in humans are defined electroencephalographically and behaviorally (Table 412-1). Sleep includes NREM and REM sleep. NREM sleep can be divided into four stages. In *stage I NREM sleep*, patients are drowsy and may maintain some environmental awareness. The electroencephalogram (EEG) loses its alpha rhythm (8 to 13 Hz) and develops theta (3 to 7 Hz) activity; vertex potentials (i.e., negative deflections recorded from the midline) occur, especially in response to sensory stimuli. Slow lateral eye movements take place, and spontaneous motor activity, as monitored by electromyography (EMG), is diminished. Stage I represents about 5% of normal sleep time.

Stage II NREM sleep is characterized by sleep spindles (12 to 14 Hz), vertex sharp waves, and K complexes (i.e., biphasic, high-voltage slow waves often followed by sleep spindles). Slow lateral eye movements may persist. EMG activity is further reduced. Stage II NREM sleep represents 50 to 60% of sleep and increases with age.

Stages III and IV NREM sleep are characterized by slow or delta waves (<4 Hz) and are therefore called delta sleep or deep sleep. If 20 to 50% of the EEG is delta activity, the patient is in stage III sleep; if delta activity is 50% or greater, the sleep event is called stage IV. Deep sleep constitutes 10 to 20% of sleep time (less with advancing age). EMG activity is diminished. Eye movements are not seen, and ventilation is regular.

In REM sleep, the EEG resembles that of waking, with low-voltage, mixed frequencies. Abrupt REMs and irregular ventilation and heart rate are present. Penile tumescence occurs, and muscle tone is depressed because of suppression of activity in all somatic muscles except the diaphragm. REM

TABLE 412-1 STAGES OF SLEEP

SLEEP STAGE	EEG	EYE MOVEMENTS	EMG ACTIVITY	IMAGERY
Wakefulness	Alpha and beta activity (low voltage, fast)	Random, rapid	Active, spontaneous	Vivid, external
Non-REM sleep (NREM)				
Stage I (drowsiness)	Theta activity	Slow, rolling	Attenuated, episodic	Dulled
Stage II (light sleep)	Sleep spindles, K complexes	Slow or absent	Attenuated	Nonvivid
Stage III and IV (slow wave sleep)	Delta activity	Absent	Attenuated	
REM sleep	Low amplitude, irregular	Abrupt, rapid eye movements	Absent	Vivid, bizarre

EEG = electroencephalogram; EMG = electromyogram; REM = rapid eye movement.

TABLE 412-2 CAUSES OF HYPERSOMNIA (EXCESSIVE DAYTIME SLEEPINESS*)

Sleep deprivation
Obstructive sleep apnea (Chapter 100)
Narcolepsy
Circadian rhythm disorders Shift work sleep disorder Jet lag Advanced and delayed sleep phase syndrome
Restless legs syndrome (may be associated with extreme daytime sleepiness but is always manifested as insomnia)
Drug use
Syndromes associated with subjective sleepiness but usually without true, verifiable sleepiness by objective testing Depression Chronic pain Insomnia

*Excessive daytime sleepiness is usually confirmed by objective testing.

TABLE 412-3 EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent time. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

SITUATION	CHANCE OF DOZING
Sitting and reading	
Watching TV	
Sitting and inactive in a public place (theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch (without alcohol)	
In a car, while stopped for a few minutes in traffic	
Total	

From Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14:540-545.

sleep occupies 20 to 25% of sleep time. Dreaming occurs during all stages of NREM sleep and during REM sleep.

There is some evidence that procedural (i.e., motor learning such as typing) and declarative (i.e., episodic learning such as recalling places or events) memory consolidation occurs during REM sleep. REM sleep time increases after task training. After episodic learning, memory consolidation is accomplished during slow wave sleep by rapid reactivation of the hippocampal neurons previously activated by the place or event to be remembered. Alternatively, it has been hypothesized that dream sleep functions as a random stimulator of the cortex to remove weak memories and thus permit only stronger memories to be retained.

CLINICAL MANIFESTATIONS

Most sleep complaints fall into four categories: hypersomnia (excessive daytime sleepiness), insomnia (trouble falling or staying asleep), circadian rhythm (biologic clock) disorders, and parasomnias (complex behavior arising during the sleep period).

Hypersomnia is typically manifested as the tendency to fall asleep in inappropriate or undesirable settings such as at work, while talking with others, or while driving. Sleepiness from any cause can result in impaired sustained attention, with adverse, occasionally disastrous socioeconomic consequences in the classroom, in the workplace, or on the highways. The most common cause of hypersomnia is volitional sleep deprivation for social or economic reasons. Volitional sleep deprivation can usually be diagnosed by the history or sleep diary. Nonvolitional sleep deprivation–related sleepiness is almost always due to an underlying sleep disorder, most commonly either obstructive sleep apnea or narcolepsy (Table 412-2).

DIAGNOSIS

Subjective

Sleep Diaries and Sleepiness Scales

Sleep diaries kept for a period of 2 or 3 weeks may reveal valuable information about a patient's subjective perception of wakefulness and sleep. One useful scale is the Epworth Sleepiness Scale (Table 412-3), which is frequently used as a screening tool for identifying excessive daytime sleepiness and generally correlates with other measures of sleep propensity. A score higher than 11 suggests a high probability of a sleep problem. This scale may be limited by its lack of sensitivity in that there may be a striking discrepancy between self-perceived sleepiness and the physiologic sleepiness that can be documented by formal sleep studies.

Objective

Polysomnography

Polysomnography (Chapter 100) determines states of sleep and wakefulness by recording eye movements, submental EMG activity, and the EEG. If sleep-disordered breathing is suspected, additional monitoring such as oral/nasal airflow, chest/abdominal movement, hemoglobin oxygen saturation, and transcutaneous or end-tidal CO_2 is used. A full EEG helps evaluate disorders of arousal, REM sleep behavior disorder, and nocturnal seizures.

Multiple Sleep Latency Test

The multiple sleep latency test, which assesses the tendency to fall asleep during normal waking hours, consists of five 20-minute nap opportunities at 2-hour intervals. An all-night polysomnograph is generally performed the night before to determine the quality and quantity of the preceding night's sleep. Normal, fully rested adults do not usually fall asleep in less than 10 minutes and uncommonly display REM sleep during daytime naps. Patients with narcolepsy typically fall asleep in 5 minutes or less and often display REM sleep during at least two of the daytime naps. This test is not generally performed in patients with obstructive sleep apnea because an explanation for the hypersomnia should have been identified by the preceding all-night polysomnograph.

Actigraphy

Analysis of sleep diaries may be insufficient to verify a tentative diagnosis in patients with reported insomnia or suspected abnormalities in the wake-sleep cycle. In such cases, definitive objective data may be obtained by actigraphy,

in which a small, wrist-mounted device records activity plotted against time—usually over a period of 1 to 3 weeks. There is direct correlation between the rest/activity recorded by the actigraph and the wake-sleep pattern as determined by polysomnography.

SPECIFIC SLEEP DISORDERS

Obstructive Sleep Apnea

Obstructive sleep apnea (Chapter 100), which is the most common medical disorder causing hypersomnia, affects more than 2% of adult women and 4% of adult men. It is seen primarily in overweight people who are loud snorers, but it may also occur in children and thin individuals.

Obstructive sleep apnea is characterized by collapse of the upper airway during sleep. This upper airway collapse may be associated with a fall in the blood oxygen level and results in repetitive arousal (up to 100 per hour of sleep) to re-establish upper airway airflow. These brief arousals are not perceived by the individual but result in excessive daytime sleepiness. Obstructive sleep apnea is described in detail in Chapter 100.

Narcolepsy

EPIDEMIOLOGY AND PATHOBIOLOGY

Narcolepsy affects 1 in 2000 individuals. It has a clear genetic component, with more than 90% of affected individuals carrying the HLA-DR2/DQ1 (under current nomenclature, HLA-DR15 and HLA-DQ6) gene, which is found in less than 30% of the general population. Despite a genetic component, the risk in a first-degree relative is only 1 to 2%, but this risk represents a 10- to 40-fold increase over that in the general population. Thus, the genetic component is neither necessary nor sufficient to cause narcolepsy.

Hypocretin-1 is an excitatory neuropeptide found in a very circumscribed group of neurons confined to the hypothalamic region. Patients with narcolepsy have lost hypocretin cells, possibly by an immune-mediated phenomenon.

CLINICAL MANIFESTATIONS

Narcolepsy is characterized by the tendency to fall asleep inappropriately during the daytime, particularly during sedentary or nonstimulating activities, despite having obtained an adequate amount of sleep the preceding night. Other symptoms of narcolepsy include (1) cataplexy (sudden brief spells of muscle weakness), often triggered by emotionally laden events; (2) hypnagogic (occurring at sleep onset) or hypnopompic (occurring at sleep offset) hallucinations; (3) sleep paralysis (awakening to find the entire body paralyzed—with the exception of being able to breathe and move the eyes); (4) automatic behavior; and (5) disrupted nighttime sleep.

Patients with narcolepsy do not sleep more per 24 hours than non-narcoleptics do; instead, they are unable to maintain the normal boundaries of wakefulness, NREM sleep, and REM sleep. The automatic behavior (driving past the desired freeway exit, putting clothing into the refrigerator) represents an admixture of wakefulness and NREM sleep, with enough wakefulness to perform complex behavior but not enough for conscious awareness of the behavior. Sleep paralysis and cataplexy represent the simultaneous occurrence of REM sleep–related muscle paralysis and wakefulness. If the paralysis intrudes into wakefulness, the result is cataplexy; if it persists into wakefulness from a period of REM sleep, sleep paralysis results. The waking hallucinations represent the release of sleep-related dreaming into wakefulness, and the disrupted nighttime sleep is a manifestation of the "state boundary dyscontrol" aspect of narcolepsy. Sleep paralysis and hypnagogic/hypnopompic hallucinations, but not cataplexy, are often experienced by people who do not have narcolepsy—particularly in the setting of sleep deprivation.

DIAGNOSIS

Sleep laboratory evaluation of patients with narcolepsy includes polysomnography and the multiple sleep latency test. Results of the all-night polysomnograph will usually be unremarkable. The multiple sleep latency test will demonstrate objective hypersomnolence, and REM sleep may be present during the daytime naps.

Levels of hypocretin-1 are undetectable in the cerebrospinal fluid (CSF) of most patients with narcolepsy who experience cataplexy and are HLA-DQB1*0602 positive. Absent CSF hypocretin-1 levels are not found in any conditions that could be confused clinically with narcolepsy, thus suggesting that CSF hypocretin determinations could be of value in the diagnosis of narcolepsy in difficult cases.

TABLE 412-4 CLASSIFICATION OF ADULT INSOMNIA

PRIMARY INSOMNIA
Idiopathic insomnia—Insomnia arising in infancy or childhood with a persistent, unremitting course
Psychophysiologic insomnia—Insomnia caused by a maladaptive conditioned response in which the patient learns to associate the bed environment with heightened arousal rather than sleep; its onset is often associated with an event causing acute insomnia, with the sleep disturbance persisting despite resolution of the precipitating factor
Paradoxical insomnia (sleep-state misperception)—Insomnia characterized by a marked mismatch between the patient's description of sleep duration and objective polysomnographic findings
SECONDARY INSOMNIA
Adjustment insomnia—Insomnia associated with active psychosocial stressors
Inadequate sleep hygiene—Insomnia associated with lifestyle habits that impair sleep
Insomnia caused by a psychiatric disorder—Insomnia secondary to an active psychiatric disorder, such as anxiety or depression
Insomnia caused by a medical condition—Insomnia secondary to a condition such as restless legs syndrome, chronic pain, nocturnal cough or dyspnea, or hot flashes
Insomnia caused by a drug or substance—Insomnia secondary to consumption or discontinuation of medications, drugs of abuse, alcohol, or caffeine

Reproduced with permission from *The New England Journal of Medicine*. Silber M. Clinical practice. Chronic insomnia. *N Engl J Med*. 2005;353:803-810.

TREATMENT Rx

Stimulant medications such as methylphenidate (e.g., 10 to 60 mg/day), methamphetamine (e.g., 20 to 60 mg/day), dextroamphetamine (e.g., 5 to 60 mg/day), and modafinil (e.g., 100 to 400 mg/day) are generally effective and well tolerated. Sodium oxybate (20 to 40 mg/kg per night in divided doses), alone or combined with modafinil, can reduce sleep disruption significantly. However, responses to these medications are variable among individuals, and clinical judgment is needed to titrate to an effective dose. Dependency, tolerance, or abuse of stimulant medications is uncommon in patients with narcolepsy, and there is no indication for "drug holidays." Cataplexy is often controlled by tricyclic antidepressants (e.g., imipramine, 25 to 50 mg at bedtime), selective serotonin re-uptake inhibitors (e.g., fluoxetine, 10 to 20 mg/day), or selective norepinephrine re-uptake inhibitors (e.g., venlafaxine, 25 to 37.5 mg/day). γ-Hydroxybutyrate (20 to 40 mg/kg per night in divided doses) has been used in difficult cases.

Insomnia

Insomnia (Table 412-4) is defined not simply by total sleep time but rather by difficulty in initiation and maintenance of sleep, poor quality of sleep, and a insufficient duration of sleep, such that functioning in the awake state is impaired.

EPIDEMIOLOGY

Insomnia, the most prevalent sleep complaint, affects up to 10 to 20% of the adult population and is second only to the complaint of pain as a reason to seek medical attention.

PATHOBIOLOGY

There is growing evidence that some insomniacs may be in a constant state of hyperarousal because many are actually less sleepy during the day than normal subjects are as measured by objective daytime nap studies, and some also have increased 24-hour metabolic activity.

Many people with insomnia have identifiable psychiatric or psychological problems, and untreated insomnia is a risk factor for the future development of psychiatric problems such as depression (Chapter 404) or substance abuse (Chapter 33). Importantly, the relationship between insomnia and psychiatric conditions is bidirectional: depression may cause insomnia, and insomnia may cause depression.

CLINICAL MANIFESTATIONS

Patients with insomnia complain of an inability to sleep long enough or well enough to awaken feeling rested or restored despite having an adequate amount of time to devote to sleep. Sleep deprivation as a result of inadequate time to devote to sleep is not insomnia. Many patients complain of

TABLE 412-5 COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA

STIMULUS-CONTROL THERAPY
Go to bed only when sleepy
Use the bedroom only for sleeping and sex
Go to another room when unable to sleep in 15 to 20 minutes, read or engage in other quiet activities, and return to bed only when sleepy; repeat if necessary
Have a regular wake time regardless of the duration of sleep
Avoid daytime napping
SLEEP-RESTRICTION THERAPY
Reduce time in bed to the estimated total sleep time (minimum, 5 hr)
Increase time in bed by 15 minutes every week when the estimated sleep efficiency (ratio of time asleep to time in bed) is at least 90%
RELAXATION THERAPY
Physical component: progressive muscle relaxation, biofeedback
Mental component: imagery training, meditation, hypnosis
COGNITIVE THERAPY
Education to alter faulty beliefs and attitudes about sleep, such as that a minimum of 8 hours of sleep per night is required for health
SLEEP-HYGIENE EDUCATION
Correct extrinsic factors affecting sleep, such as environmental disruption (pets or snoring bed partner); bedroom temperature; fixation on the bedside clock; use of alcohol, nicotine, or caffeine; lack of exercise or exercise too close to bedtime

Reproduced with permission from *The New England Journal of Medicine*. Silber M. Clinical practice. Chronic insomnia. *N Engl J Med*. 2005;353:803-810.

nonrestorative sleep. Daytime consequences include feeling tired or fatigued or having trouble concentrating. True excessive daytime sleepiness (inappropriate or uncontrollable sleep episodes during the day) is extremely rare in insomniacs.

DIAGNOSIS

Insomnia is a clinical diagnosis. Sleep diaries and actigraphy may be very helpful in difficult cases. Formal sleep studies are rarely indicated unless there is reason to suspect a coexisting sleep disorder such as obstructive sleep apnea.

TREATMENT Rx

Behavioral therapy for insomnia (Table 412-5) can be quite effective but may be very time-consuming. Over-the-counter sleep aids are of little, if any benefit.

Although medications used to treat depression are often prescribed to treat insomnia, there is very little evidence that they are effective in the treatment of insomnia not associated with depression. Nevertheless, if patients with insomnia are physiologically hyperaroused, a case may be made for chronic administration of sedative-hypnotic agents. Three classes of medications are approved for the treatment of insomnia: the benzodiazepines (e.g., temazepam, 15 to 30 mg at bedtime; triazolam, 1.25 to 2.5 mg at bedtime; or estazolam, 1 to 2 mg at bedtime), the newer, nonbenzodiazepines (e.g., zolpidem, 5 to 10 mg at bedtime; zolpidem controlled release, 6.25 to 12.5 mg at bedtime; zaleplon, 5 to 10 mg at bedtime; or eszopiclone, 1 to 3 mg at bedtime), and a melatonin agonist (ramelteon, 8 mg at bedtime). Combined behavioral and pharmacologic treatments are often effective. Benzodiazepines may be administered safely and effectively for longer than 3 weeks. Tolerance, abuse, and dependency can be associated with chronic benzodiazepine administration in patients with well-documented sleep disorders, but the incidence of these complications is relatively low. Melatonin is normally secreted by the pineal gland (Chapter 230) in synchronization with the light-dark cycle. Its effect on sleep is variable, and its efficacy in treating insomnia has been disappointing.

Restless Legs Syndrome

Restless legs syndrome, which is one of the most common causes of severe insomnia, is a neurologic sensory/movement disorder that affects 5 to 15% of the general population. It is described in detail in Chapter 417.

Disorders of Circadian Rhythm

DEFINITION

Most living creatures follow a relentless and pervasive daily rhythm of activity and rest that is ultimately linked to the geophysical light-dark cycle. Plants, animals, and even unicellular organisms show daily variations in metabolic activity, locomotion, feeding, and many other functions. The importance of the light-dark cycle on the human biologic clock is underscored by the fact that only a third of totally blind humans will be entrained to the environment, a third will have a 24-hour cycle that is out of phase with the environment, and the remaining third have a free-running pattern that is longer than 24 hours.

EPIDEMIOLOGY

In the absence of blindness, the etiology of primary circadian dysrhythmias is unknown. There is good evidence that genetic factors contribute in some cases.

PATHOBIOLOGY

The function of the biologic clock is to promote wakefulness. Normally, maximal wakefulness occurs during daylight hours. For reasons that are not understood, the biologic clocks of people with circadian dysrhythmias are inexorably out of synchronization with the environment, thus making it difficult or impossible to adjust to demands of the environment.

Exposure to bright light has a potent effect on the biologic clock, and exposure at strategic times during the wake-sleep cycle results in a change in the underlying rhythm. For example, evening light exposure may delay the clock, whereas morning light exposure may advance it.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The primary symptom of disorders of circadian rhythm is an inability to sleep during the desired sleep time. Once asleep, there is no abnormality of sleep per se, only an abnormality of the timing of sleep. The result is often a complaint of insomnia if sleep is attempted during the "wake" cycle of the clock or a complaint of sleepiness if wakefulness is attempted during the clock's sleep period. Wake-sleep schedule disorders fall into two categories: (1) primary malfunction of the biologic clock per se and (2) secondary malfunction as a result of environmental effects on the underlying clock. The primary disorders may be difficult to diagnose because they typically masquerade as other sleep, medical, or psychiatric disorders, such as hypersomnia, insomnia, substance (sedative-hypnotic or stimulant) abuse, or psychiatric conditions.

The diagnosis is made by the history. Most people, if asked what their wake-sleep pattern would be if they had 3 weeks of vacation without any constraints on their wake-sleep activities (meals, work, school, family activities), can provide an accurate estimate of their inherent wake-sleep pattern. Sleep diaries and actigraphy may be helpful in difficult cases. The secondary disorders (such as jet lag and shift work) are usually immediately apparent on simple questioning of the patient.

TREATMENT Rx

The mainstays of treatment of the primary circadian dysrhythmias are chronotherapy, phototherapy, and pharmacologic therapy.

Chronotherapy

In chronotherapy, the desirable total sleep time is determined by sleep logs during a "free-running" period. The patient then delays or advances the onset of sleep by a few hours every day and sleeps only the predetermined number of hours until the onset of sleep occurs at the desired time, at which point the patient attempts to maintain that time. This method requires several days of free time and can be difficult if sleeping quarters cannot be kept dark and quiet during the several day sleeps required.

Phototherapy

The timing and duration of phototherapy depend on the diagnosis and individual response. The patient sits at a prescribed distance from a bright light that furnishes an illuminance of greater than 2500 lux at that distance. The effect of light on human rhythms varies with the intensity, wavelength, timing, and duration of exposure. This intervention can be performed at home, with the timing of light exposure individualized for a given patient's complaint. Light exposure in the morning will advance the clock, whereas evening

exposure will delay the clock. Once the desired sleep period time has been achieved, continued light exposure must be maintained.

Pharmacologic Therapy

The administration of melatonin, 3 mg 4 to 5 hours before the desired time of sleep onset, may assist in advancing the timing of the biologic clock.

JET LAG, SHIFT WORK, AND PERSISTENT PRIMARY CIRCADIAN DYSRHYTHMIAS

The best way to manage jet lag is to assume the wake-sleep pattern of the destination site immediately. Sedative-hypnotic medication may reduce the sleep-onset insomnia associated with jet lag. Jet lag usually resolves at a rate of 1 day per time zone change.

Management of shift work may be difficult; options include stimulant medications and exposure to bright light at night or sedative-hypnotic medication and protection of the sleep environment during the day (or both). The biologic clocks of night shift workers virtually never completely adjust to the night shift because the drive home in the morning resets the clock every day and workers tend to sleep at conventional times during nights off.

Treatment with medications is justified in patients who have persistent symptoms despite chronotherapy and phototherapy. For example, modafinil, 100 to 200 mg during the night shift, is effective for the excessive sleepiness and loss of attention associated with shift work sleep disorder. Caffeine has modest benefits■ but is no better than napping, bright light, or modafinil.■ The administration of 3 mg of melatonin 4 to 5 hours before the desired onset of sleep may be of benefit, especially in individuals who travel across five or more time zones, particularly in an eastward direction.■

DELAYED SLEEP SYNDROME

In delayed sleep phase syndrome, the patient falls asleep late and rises late. There is a striking inability to fall asleep at an earlier, more desirable time. This syndrome may be manifested as either sleep-onset insomnia or daytime hypersomnia, particularly in the morning. Delayed sleep phase syndrome is the most common of the primary circadian dysrhythmias and may, in part, be the consequence of societal increases in opportunities for nighttime activity. Combinations of chronotherapy, phototherapy, and medications may be effective in "resetting" the clock, as for circadian dysrhythmias. Unfortunately, the treatment regimen must be maintained, or the clock will again become delayed.

ADVANCED SLEEP PHASE SYNDROME

Individuals suffering from advanced sleep phase syndrome fall asleep early and awaken earlier than desired. They are unable to remain awake until the desired time; they fall asleep in the early evening and awaken in the very early hours of the morning. This syndrome may be manifested as hypersomnia, particularly in the evening, or sleep maintenance insomnia. Patients complain of interruption of evening activities by their sleepiness. They may avoid evening social activities for fear of the intrusive sleepiness. The undesirable early morning awakenings in this condition may lead to a misdiagnosis of depression. Exposure to bright light in the evening may delay the clock to a more acceptable pattern.

OTHER ABNORMALITIES OF CIRCADIAN RHYTHM

Other, less common circadian dysrhythmias include a "non–24-hour wake-sleep pattern" in which the wake-sleep period is longer than 24 hours and sleep begins at a later time each cycle, as well as an "irregular wake-sleep pattern" characterized by a completely chaotic and unpredictable wake-sleep pattern.

Parasomnias

Parasomnias are defined as unpleasant or undesirable behavioral or experiential phenomena occurring predominately or exclusively during sleep. Initially attributed to psychiatric disease, it is now clear that parasomnias are the manifestation of a wide variety of completely different conditions, most of which are diagnosable and treatable. The common parasomnias are examples of "dissociated sleep states," which represent the simultaneous admixture of wakefulness with either NREM sleep (disorders of arousal such as confusional arousal, sleepwalking, or sleep terrors) or REM sleep (REM sleep behavior disorder). The parasomnias, like narcolepsy, support the concept that wake and sleep are not mutually exclusive states and that sleep is not necessarily a global brain phenomenon.

Isolated, often bizarre sleep-related events may be experienced by perfectly normal individuals, and most do not warrant further extensive or expensive evaluation. However, serious attention should be paid to complaints of sleep-related behavior that is potentially violent or injurious. In these cases, formal sleep studies using a full EEG montage with continuous audiovisual monitoring is indicated to establish a correct diagnosis and treatment plan.

DISORDERS OF AROUSAL

Disorders of arousal tend to arise from NREM sleep and usually occur in the first third of the sleep cycle and rarely during naps. They are common in childhood and usually decrease in frequency with increasing age.

Disorders of arousal may be triggered by febrile illness, prior sleep deprivation, physical activity, emotional stress, or medications. They are not caused by significant underlying psychiatric problems.

Clinical manifestations vary across a broad spectrum ranging from confusional arousal to somnambulism (sleepwalking) to sleep terrors. Some patients perform more specialized behavior, such as sleep-related eating and sleep-related sexual activity, without conscious awareness. Such behavior may have forensic implications.

TREATMENT Rx

Most disorders of arousal, such as simple sleepwalking or sleep terrors, require no treatment other than reassurance of their benign nature. If the behavior is bothersome or potentially injurious, medical management with benzodiazepines (e.g., clonazepam, 0.5 to 1.0 mg 30 minutes before bedtime) or tricyclic antidepressant medications (e.g., imipramine, 25 to 50 mg 30 minutes before bedtime) or behavioral treatment in the form of self-taught relaxation exercises is often effective.

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

The most common and best-studied REM sleep parasomnia is the REM sleep behavior disorder.

EPIDEMIOLOGY AND PATHOBIOLOGY

REM sleep behavior disorder predominately affects males (about 90%) and usually begins after the age of 50 years. Acute REM sleep behavior disorder is often due to undesirable side effects of prescribed medications, most commonly antidepressant medications and particularly the selective serotonin re-uptake inhibitors. Chronic REM sleep behavior disorder, which may be preceded by a lengthy prodrome of REM sleep behavior disorder, can be idiopathic or associated with neurodegenerative disorders, particularly the synucleinopathies (Parkinson's disease, multiple system atrophy, or dementia with Lewy bodies), in which it may be the first symptom and precede other manifestations of the underlying process by more than 10 years (Chapter 416). There is also a higher incidence of REM sleep behavior disorder in patients with narcolepsy, in whom this tendency may be aggravated by the tricyclic antidepressants or selective serotonin re-uptake inhibitors prescribed to treat cataplexy.

CLINICAL MANIFESTATIONS

In these patients, somatic muscle atonia—one of the defining features of REM sleep—is absent, thereby permitting the acting out of dream mentation, often with violent or injurious results. The initial complaint is vigorous sleep behavior usually accompanying vivid dreams. Such behavior may result in repeated injury, including ecchymoses, lacerations, and fractures.

DIAGNOSIS

The diagnosis may be suspected by the clinical history, but formal sleep studies are indicated. Patients with REM sleep behavior disorder will demonstrate increased EMG activity during REM sleep, thus confirming the clinical suspicion.

TREATMENT Rx

The benzodiazepine clonazepam (0.5 to 2.0 mg 30 minutes before bedtime) is a highly effective treatment of REM sleep behavior disorder, with a sustained response rate of nearly 90%, although its mechanism of action is unknown. Melatonin, 6 to 12 mg at bedtime, may also be effective.

Grade A

1. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4:487-504.
2. Drugs for insomnia. *Med Lett*. 2009;7:23-26.
3. Ker K, Edwards PJ, Felix LM, et al. Caffeine for the prevention of injuries and errors in shift workers. *Cochrane Database Syst Rev*. 2010;5:CD008508.
4. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev*. 2002;2:CD001520.

SUGGESTED READINGS

Cao M. Advances in narcolepsy. *Med Clin North Am*. 2010;94:541-555. *Review*.

Centers for Disease Control and Prevention (CDC). Unhealthy sleep-related behaviors—12 States, 2009. *MMWR Morb Mortal Wkly Rep*. 2011;60:233-238. *In the prior 30 days, about 48% of people snored, 38% unintentionally fell asleep during the day, and about 5% nodded off or fell asleep while driving*.

Sack RL. Clinical practice. Jet lag. *N Engl J Med*. 2010;362:440-744. *Case-based review recommending short-acting sleep medications and consideration of oral melatonin*.

Sullivan SS. Insomnia pharmacology. *Med Clin North Am*. 2010;94:563-580. *Review*.

Trenkwalder C, Paulus W. Restless leg syndrome: pathophysiology, clinical presentation and management. *Nat Rev Neurol*. 2010;6:337-346. *Review emphasizing the use of dopaminergic agents*.

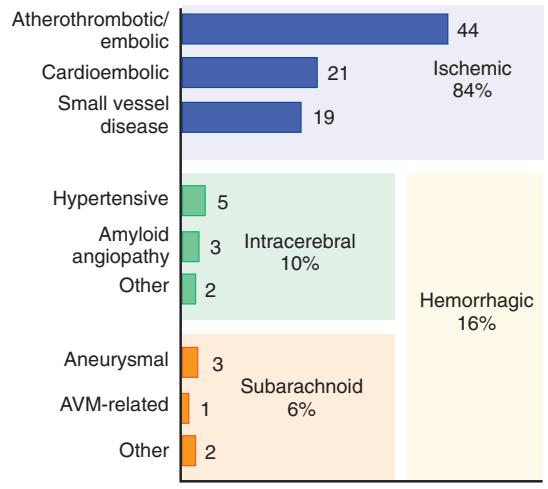


FIGURE 413-1. Classification of cerebrovascular disease. AVM = arteriovenous malformation.

413 APPROACH TO CEREBROVASCULAR DISEASES

JUSTIN A. ZIVIN

DEFINITION

Stroke is the generally preferred term for a group of diseases that are of abrupt onset and cause neurologic damage (Fig. 413-1). Approximately 85% of strokes are caused by a sudden onset of inadequacy of blood flow to some or all of the brain (Chapter 414). The remaining strokes are divided between hemorrhage (Chapter 415) into brain tissue (parenchymatous hemorrhage) and hemorrhage into the spaces surrounding the brain, most frequently the subarachnoid space. A commonly used synonym for stroke was *cerebrovascular accident*, but this term has lost favor because strokes are not really accidents. Well-established prophylactic and acute therapies are now available, and diagnostic tools have improved markedly. Management of stroke has become much more rational and successful.

EPIDEMIOLOGY

Stroke is the second leading cause of mortality worldwide and the third most common cause of death in the industrialized world (after heart disease and all types of cancer combined). It is the most common cause of adult disability in the United States. In China and Japan, stroke is the most frequent cause of death.

In the United States, the annual incidence and death rate for stroke declined steadily for most of the 20th century. In more recent years, however, the rate of decline has slowed and the incidence of stroke may be increasing. About 750,000 new strokes reach medical attention per year in the United States, and strokes cause about 150,000 deaths annually. At any given time there are about 3 million stroke survivors in the United States. Incidence rates in Western European countries are slightly higher than those in the United States, and several Eastern European countries, China, and Japan have much higher rates based at least partly on smoking and on environmental and dietary factors.

The rate of stroke approximately doubles with each decade after the age of 55. Blacks and Hispanics have about twice the risk as whites, and men have about a 40% higher incidence of stroke than women do. Hypertension increases the risk by four-fold, smoking nearly doubles the risk, and diabetes increases the risk two- to six-fold. Carotid stenosis and atrial fibrillation are perhaps the strongest risk factors. Other factors that increase risk include obesity, hypercholesterolemia, physical inactivity, alcohol abuse, hyperhomocysteinemia, drug abuse, and use of oral contraceptive agents.

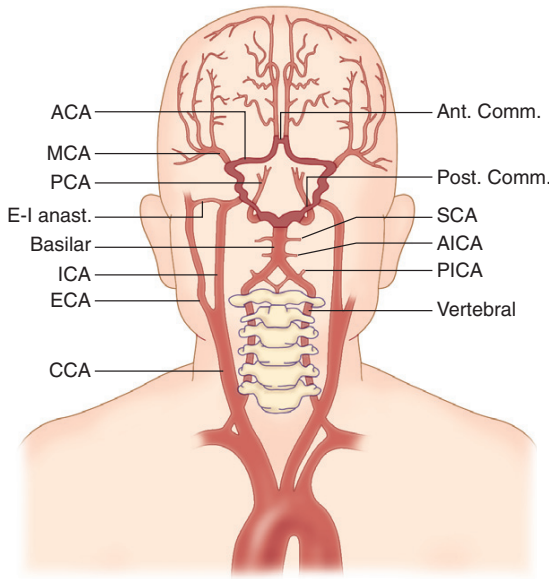


FIGURE 413-2. Extracranial and intracranial arterial supply to the brain. Vessels forming the circle of Willis are highlighted. ACA = anterior cerebral artery; AICA = anterior inferior cerebellar artery; Ant. Comm. = anterior communicating artery; CCA = common carotid artery; ECA = external carotid artery; E-I anast. = extracranial-intracranial anastomosis; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PICA = posterior inferior cerebellar artery; Post. Comm. = posterior communicating artery; SCA = superior cerebellar artery. (Modified from Lord R. *Surgery of Occlusive Cerebrovascular Disease.* St. Louis, MO: CV Mosby; 1986.)

PATHOBIOLOGY

Cerebrovascular Anatomy

Strokes are usually caused by abnormalities in the cerebral circulation. Anatomic variations are frequent, however, and the territory receiving its blood supply from a given artery is not entirely predictable; as a result, stroke syndromes may not correlate well with the location of the vascular injury. Appropriate imaging studies are needed to provide detailed information about each individual patient. In many situations, noninvasive imaging is adequate. For vascular anomalies such as stenosis, malformations, and aneurysms, angiography is crucial for diagnosis because an understanding of the anatomy is necessary to develop treatment plans.

Four major arteries supply the brain: the bilaterally paired internal carotid and vertebral arteries (Fig. 413-2). The left common carotid artery arises directly from the aortic arch, but the right originates from branches of the aorta. The right common carotid artery is a branch of the innominate artery, and the left and right vertebral arteries originate from the subclavian arteries.

Internal Carotid Arteries

In most individuals, each common carotid artery bifurcates into an internal and external carotid artery just below the angle of the jaw and approximately at the level of the thyroid cartilage. The internal carotid artery (ICA) enters the skull through the foramen lacerum and travels a short distance within the petrous portion of the temporal bone. It then enters the cavernous sinus before penetrating the dura and ascends above the clinoid processes to divide into the anterior cerebral artery (ACA) and middle cerebral artery (MCA). The portion of the ICA that lies between the cavernous sinus and the supraclinoid process forms an S shape and is sometimes termed the *carotid siphon*. The ICA gives off its first important branches at the supraclinoid level: the ophthalmic, posterior communicating, and anterior choroidal arteries, usually in that order. In some cases, the ophthalmic artery arises from the ICA within the cavernous sinus.

External Carotid Arteries

Branches of the external carotid artery sometimes form anastomoses that provide collateral circulation to the ICA. These branches include the facial artery and the superficial temporal artery. Both vessels may anastomose with the supratrochlear branches of the ophthalmic artery. In instances of ICA occlusion below the level of the ophthalmic branch, the facial and superficial temporal arteries sometimes supply blood through the ophthalmic branch to the distal ICA.

Vertebral-Basilar Arteries

Anatomic variation is considerably more common in the vertebral artery system than in the ICA. The paired vertebral arteries usually arise from the subclavian arteries, but their origins may be more proximal on the aortic arch, or they may form a common branch of the thyrocervical trunk. The vertebral arteries generally enter the foramina of the sixth cervical vertebra or, much less commonly, the fourth, fifth, or seventh vertebral foramina. The vertebral arteries ascend through the transverse foramina and exit at C1, where they turn nearly 90 degrees posteriorly to pass behind the atlantoaxial joint before penetrating the dura and entering the cranial cavity through the foramen magnum. The portion of the vertebral artery that loops behind the atlantoaxial joint is prone to mechanical deformation, and excessive rotation of the head may cause arterial narrowing and reduction of blood flow to the ipsilateral vertebral artery.

Intracranially, the vertebral arteries are lateral to the medulla oblongata and then course ventrally and medially, where they unite rostrally at the medullopontine junction to form the basilar artery. The basilar artery ultimately bifurcates at the pontomesencephalic junction to form the posterior cerebral arteries (PCAs).

In a few individuals, the right or left vertebral arteries terminate before reaching the basilar artery, which is consequently supplied, proximally, by a single vertebral artery. The vertebral arteries usually have medial branches that turn caudally and unite to form the anterior spinal artery, as well as lateral branches supplying the dorsolateral medulla and posterior cerebellum, called the *posterior inferior cerebellar arteries*.

Circle of Willis

The circle of Willis, which is at the base of the brain, is formed by the union of the right and left ACAs via the anterior communicating artery, the MCAs, and the PCAs via the posterior communicating arteries. Anomalies of the circle of Willis occur frequently; in large autopsy series of normal individuals, more than half show an incomplete circle of Willis. The most common sites for these abnormalities, which are usually manifested as hypoplasia or absence, are the posterior communicating arteries and the ACAs.

Anterior Cerebral Arteries

The ACAs travel medially above the optic chiasm and pass rostrally toward the interhemispheric fissure, where they arch caudally to lie just dorsal to the corpus callosum. In a small fraction of normal individuals, the A1 segment of the ACA (the portion between the origin at the MCA and the first major branch, the anterior communicating artery) is hypoplastic or absent, which leaves its distal portion to be supplied by the opposite ACA via the anterior communicating artery. Branches of the ACA normally supply the frontal poles, the superior surfaces of the cerebral hemispheres where their distal branches anastomose with those of the MCA, and all of the medial surfaces of both cerebral hemispheres with the exception of the calcarine cortex (Figs. 413-3 and 413-4). Cortical areas served by the ACA include the motor and sensory cortex of the legs and feet, the supplementary motor cortex, and the paracentral lobule.

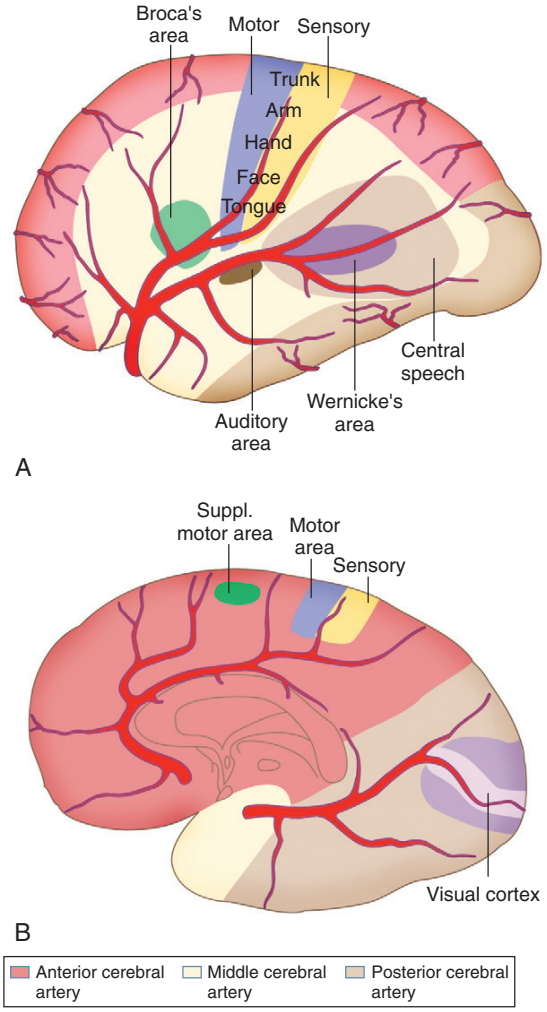


FIGURE 413-3. Surface cerebral arterial anatomy. Lateral (**A**) and medial (**B**) views of the cerebral hemisphere show the surface distributions of the anterior, middle, and posterior cerebral arteries.

The A1 and A2 segments (the portions between the anterior communicating artery and the genu of the corpus callosum) give off many small branches that penetrate the anterior perforated substance of the brain. These small penetrating branches include all of the anterior and some of the medial lenticulostriate arteries. Usually, there is a dominant medial striate vessel called the *recurrent artery of Heubner*, which commonly arises from the A1 segment of the ACA. This artery penetrates the perforated substance of the brain and, along with the other small perforators, supplies the anterior and inferior portions of the anterior limb of the internal capsule, the anterior and inferior head of the caudate nucleus, the anterior globus pallidus and putamen, the anterior hypothalamus, the olfactory bulbs and tracts, and the uncinate fasciculus.

Anterior Choroidal Artery

The anterior choroidal artery arises from the supraclinoid portion of the ICA in most people. It travels caudally and medially over the optic tract, to which it provides a few small branches, and enters the brain via the choroidal fissure. Many important brain structures receive blood flow from the anterior choroidal artery, including portions of the anterior hippocampus, uncus, amygdala, globus pallidus, tail of the caudate nucleus, lateral thalamus, geniculate body, and a large portion of the most inferior, posterior limb of the internal capsule.

Middle Cerebral Artery

The MCA provides flow to most of the lateral surface of the cerebral hemispheres and is the vessel most frequently involved in ischemic stroke. As the

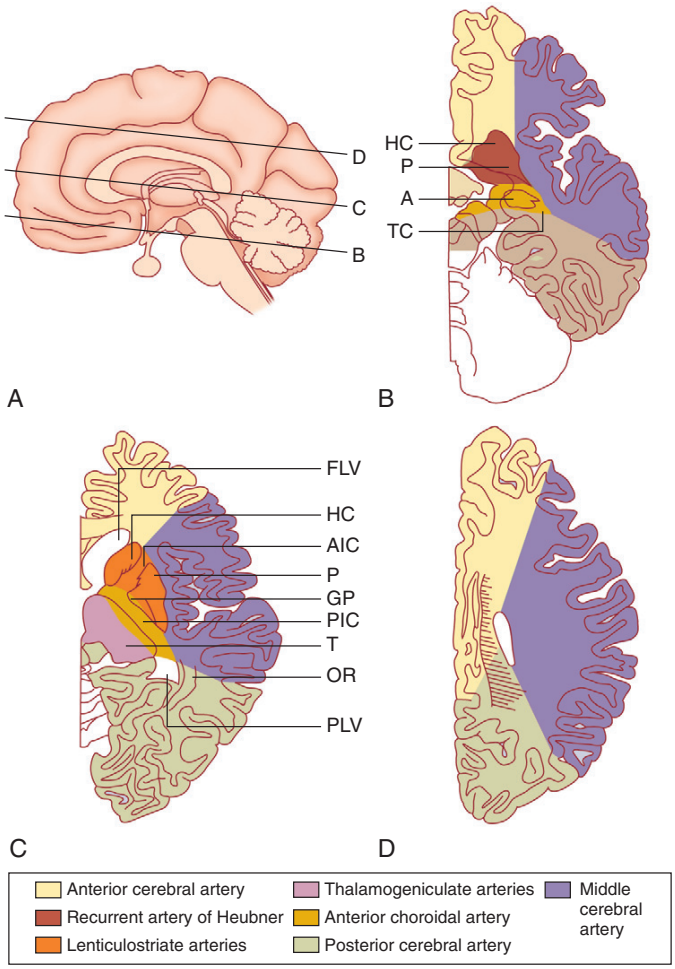


FIGURE 413-4. Arterial supply of the deep brain structures. A, Sagittal view of the brain showing the computed tomographic (CT) planes through which views **B**, **C**, and **D** were taken. **B**, CT plane through the head of the caudate nucleus (HC), putamen (P), amygdala (A), tail of the caudate nucleus (TC), hypothalamus, temporal lobe, midbrain, and cerebellum. **C**, CT plane through the frontal horn of the lateral ventricle (FLV), head of the caudate nucleus (HC), anterior and posterior limbs of the internal capsule (AIC, PIC), putamen (P), globus pallidus (GP), thalamus (T), optic radiations (OR), and posterior horn of the lateral ventricle (PLV). **D**, CT plane through the centrum semiovale. (Modified from De Armond S, Fusco MM, Dewey MM. *Structure of the Human Brain, a Photographic Atlas,* 3rd ed. New York: Oxford University Press; 1989, with permission.)

main MCA trunk passes laterally toward the sylvian fissure, it gives rise to some of the medial and all of the lateral lenticulostriate arteries. These arteries supply the putamen, the head and body of the caudate nucleus, the lateral globus pallidus, the anterior limb of the internal capsule, and the superior portion of the posterior limb of the internal capsule. The MCA extends into the sylvian fissure, where it branches into several smaller arteries grouped into a superior division, which feeds the cortical surface above the fissure, and an inferior division, which supplies the cortical surface of the temporal lobe. The territory of the MCA includes the major motor and sensory areas of the cortex, the areas for contraversive eye and head movement, the optic radiations, the auditory sensory cortex, and in the dominant hemisphere, the motor and sensory areas for language.

Posterior Cerebral Arteries

Blood flow to both PCAs is derived in most people from the basilar artery and infrequently from the ICA. Sometimes the ICA is the origin of one PCA and the other PCA originates from the basilar artery. The PCAs pass dorsal to the third cranial nerves and across the cerebral peduncles and then ascend upward along the medial edge of the tentorium, where they branch into anterior and posterior divisions. The anterior division supplies the inferior surface of the temporal lobe, where its terminal branches form an anastomosis with branches of the MCA. The posterior division supplies the occipital lobe, where its terminal branches anastomose with the ACA and the MCA. In its most proximal course along the base of the brain, the PCA gives off several groups of penetrating arteries commonly called the *thalamogeniculate*, the *thalamoperforating*, and the *posterior choroidal* arteries. The red nucleus, the substantia nigra, medial portions of the cerebral peduncles, the nuclei of the thalamus, the hippocampus, and the posterior hypothalamus receive blood from these penetrating branches.

Brain Stem Blood Supply

The ventral medial portion of the brain stem receives its blood supply from short paramedian vessels, the ventrolateral region receives its blood from short circumferential branches of the vertebral or basilar arteries, and long circumferential branches supply the dorsolateral brain stem and cerebellum (Fig. 413-5). These vessels include the posterior inferior cerebellar arteries, which arise from the vertebral arteries, and the anterior inferior and superior cerebellar arteries, which arise from the basilar artery.

The pyramids, the inferior olives and medial lemnisci, the medial longitudinal fasciculi, and the emerging fibers of the hypoglossal nerve derive blood from the vertebral arteries. Longer branches from the vertebral arteries and posterior ICAs supply the spinothalamic tracts, the vestibular nuclei, the sensory nuclei of the fifth cranial nerve, the descending fibers of the sympathetic nervous system, the restiform body, and the emerging fibers of the vagus and glossopharyngeal nerves. The most cephalad and dorsal segment of the medulla includes the vestibular and cochlear nuclei, which along with the posterior portion of the cerebellum, receive flow from the posterior inferior cerebellar artery.

The basilar artery gives rise to perforating branches as it spans the ventral midline pons and midbrain. These short perpendicular branches distribute blood to the paramedian structures, including the corticospinal tracts, the pontine reticular nuclei, the medial lemnisci, the medial longitudinal fasciculi, and the pontine reticular nuclei. The anterior ICA feeds blood to the lateral pons, including the emerging seventh and eighth cranial nerves, the trigeminal nerve root, the vestibular and cochlear nuclei, and the spinothalamic tracts. It also branches to the most dorsal and lateral of these structures on its dorsal course toward the cerebellum.

At the midbrain level, the basilar artery lies in the midline in the interpeduncular fossa. Short branches pass laterally and dorsally on both sides to supply the cerebral peduncles, the emerging fibers of the third nerve, medial portions of the red nuclei, the medial longitudinal fasciculus, the oculomotor nuclei, and the midbrain reticulum. The superior cerebellar arteries contribute to the dorsal midbrain supply, including that of the colliculi and the superior portion of the cerebellum on each side.

Venous Drainage

The veins in the brain, in contrast to those in many other parts of the body, often do not accompany the arteries. Cortical veins drain into the superior sagittal sinus, which runs between the cerebral hemispheres. Deeper structures drain into the inferior sagittal sinus and great cerebral vein (of Galen), which join at the straight sinus (Fig. 413-6). The straight sinus runs along the attachment of the falx cerebri and tentorium to join with the superior sagittal sinus at the torcular Herophili, from which the two transverse sinuses arise. Each transverse sinus passes laterally toward the petrosal bone to become the sigmoid sinus, which exits the skull into the internal jugular vein. Each cavernous sinus communicates with its contralateral twin and surrounds the ipsilateral carotid artery. Both drain into the petrosal sinuses, which drain into the sigmoid sinus.

Normal Physiology

Cerebral Metabolism and Blood Flow

Although the brain is normally about 2% of body weight in humans, it is supplied with approximately 14% of the resting cardiac output. The energy demands to support normal brain activity in conscious humans are equal, on a per-weight basis, to the demands of the most metabolically active tissues, such as the heart and kidney. Aerobic glucose metabolism in a normal, conscious human brain consumes an average of 140 μmol of oxygen and 24 μmol of glucose per 100 g of brain tissue each minute. Normal brain activities, such as thinking or sleeping, do not alter total blood flow, glucose use, or oxygen uptake in the brain, but they do change the patterns of blood supply and energy use in specific brain areas.

The brain extracts approximately 10% of available blood glucose in a single pass, yet only 80% of this glucose is used to generate energy. About 10 to 15% of the glucose is metabolized to lactate, which may be lost to the circulation; the remainder is used for the synthesis of neurotransmitters, fats, and to a

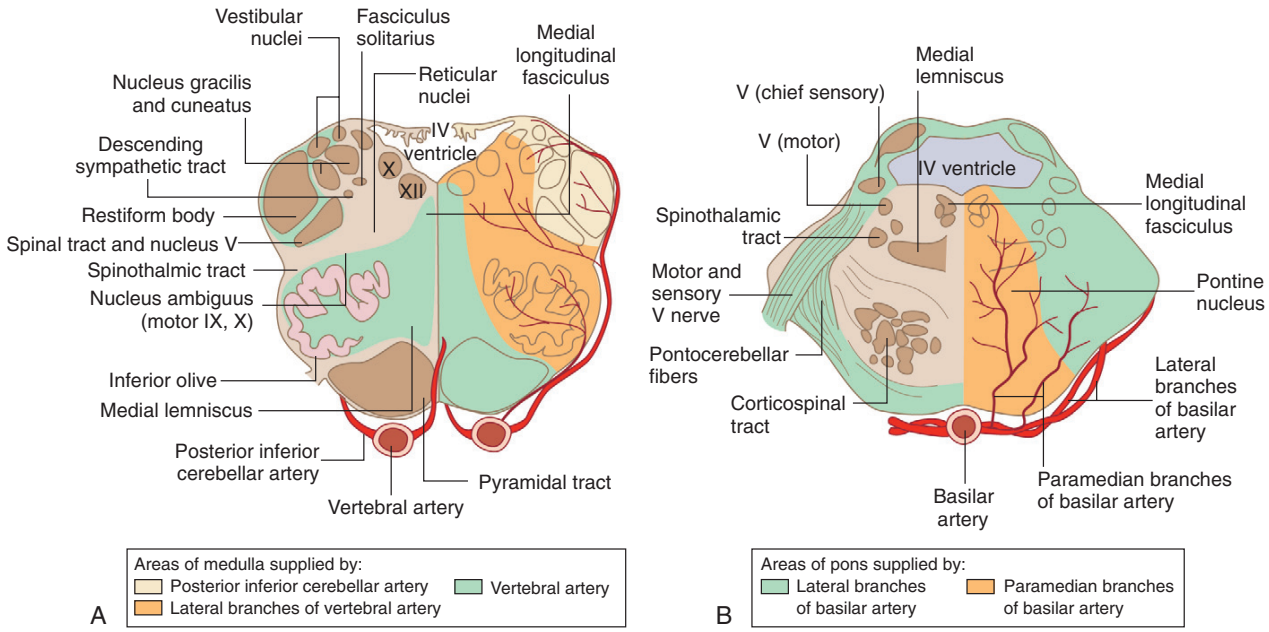


FIGURE 413-5. Brain stem blood supply. A, Cross section of the medulla oblongata at the level of the hypoglossal nuclei (cranial nerve XII). Short branches of the vertebral and anterior spinal arteries supply the medulla. Longer circumferential branches, including the posterior inferior cerebellar artery, supply the lateral portions of the medulla. **B**, Cross section of the midpons region. The medial portion receives blood supply from short, perforating basilar artery branches. More laterally, the blood supply comes from lateral basilar artery branches.

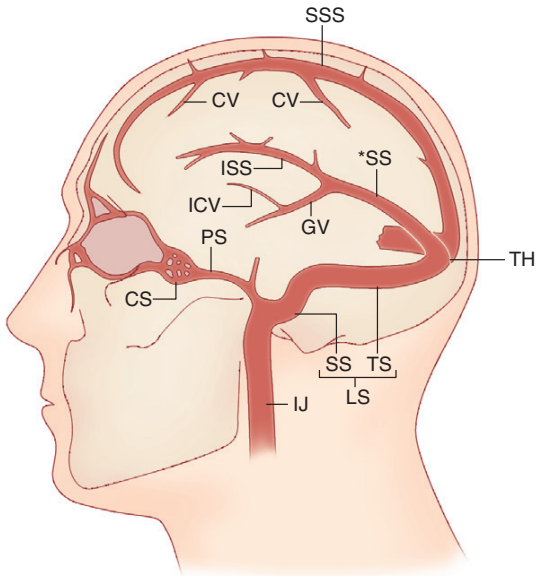


FIGURE 413-6. Venous drainage of intracranial structures. CS = cavernous sinus; CV = cortical veins; GV = great vein of Galen; ICV = internal cerebral vein; IJ = internal jugular vein; ISS = inferior sagittal sinus; LS = lateral sinus; PS = petrosal sinus; SS = sigmoid sinus; *SS = straight sinus; SSS = superior sagittal sinus; TH = torcular Herophili; TS = transverse sinus. (From Gates P, Barnett HJ, Mohr JP, et al, eds. Stroke: *Pathophysiology, Diagnosis and Management*. New York, NY: Churchill Livingstone; 1986.)

small degree, proteins. Each mole of glucose metabolized by the brain through glycolysis and the mitochondrial respiratory chain yields approximately 30 mol of adenosine triphosphate (ATP) instead of the theoretical maximum of 38 mol.

In contrast to most other tissues, the brain stores little glucose, glycogen, or high-energy phosphates (ATP, phosphocreatine) but instead relies on continuous, well-regulated blood flow to satisfy its needs for energy. Cerebral blood flow (CBF) averages 50 mL/100 g of brain tissue per minute in a normal, conscious human. In the absence of this flow, the brain has sufficient high-energy stores to support its metabolic needs for only a few minutes. The vascular reserves of oxygen and glucose are small, as illustrated by the fact that all changes in synaptic activity, whether related to thinking, talking, or directing muscular activity, are tightly coupled, temporally and anatomically, to an almost instantaneous increase in local CBF. The mechanisms responsible for this coupling of blood flow to metabolic activity have not been fully elucidated, but the relationship is well established, under normal conditions, and provides a basis for the use of imaging methods to assess regional brain activity. Regional CBF can be precisely quantified with positron emission tomography. Other less invasive techniques such as magnetic resonance imaging and single-photon emission computed tomography provide qualitative measurements of local CBF. The brain's functional activities result in a frequently and rapidly changing pattern of regional metabolic and blood flow values that reflect moment-to-moment changes in activity. On a larger scale, the low stores and high metabolic rate of the brain are responsible for the rapid loss of consciousness and subsequent irreversible damage that accompany loss of the critical energy sources of the brain, glucose and oxygen.

The coupling of CBF to regional synaptic and metabolic activity is only one of several mechanisms known to regulate normal CBF. Another is alteration of carbon dioxide. Hypercapnia dilates and hypocapnia constricts cerebral resistance vessels such that CBF shows a linear relationship to $Paco_2$ within the normal range. This physiologic response to $Paco_2$ can be exploited clinically to treat cerebral herniation. Increases in intracranial pressure (ICP) in the absence of adequate intracranial volume may force the hemispheres through the tentorium or the cerebellum through the foramen magnum. Mechanical hyperventilation to a $Paco_2$ of 20 to 25 mm Hg reduces CBF by approximately 40 to 45% and normal adult cerebral blood volume from 50 to approximately 35 mL. Though seemingly small, this reduction sometimes suffices to retard the progression of herniation and is the fastest way to reduce ICP. The response is short-lived, however, and brain and blood HCO_3^- and H^+ ions controlling blood vessel tone re-equilibrate within 30 to 60 minutes. More definitive therapy must be initiated quickly.

A complex system of neural pathways also helps control CBF. Some of these pathways participate in autoregulation, a process that maintains CBF at a constant level despite fluctuations in arterial blood pressure over a fairly wide range (Fig. 413-7). Autoregulation has upper and lower limits; at a mean arterial pressure greater than about 150 mm Hg, blood flow increases and capillary pressure rises, whereas at a mean arterial pressure of less than 50 mm Hg, CBF falls. In patients with chronic hypertension, the upper and lower autoregulatory limits are shifted toward higher systemic pressure. Consequently, a rapid therapeutic reduction in blood pressure to levels that would be normal in most people carries the risk of further lowering CBF in hypertensive patients who have ongoing cerebral ischemia. Long-term treatment with antihypertensive agents readjusts the autoregulatory curve toward more normal values. Conversely, excessive reduction of blood pressure in

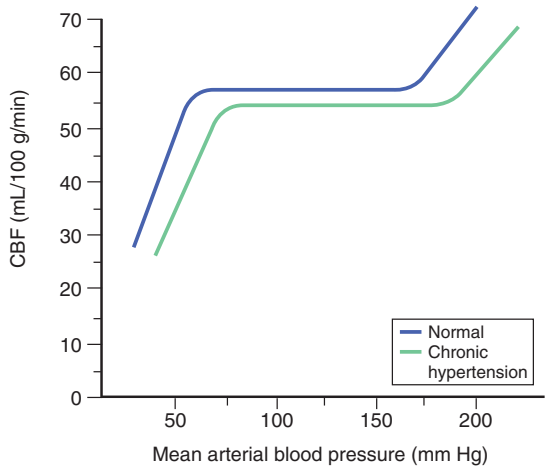


FIGURE 413-7. Autoregulatory cerebral blood flow (CBF) response to changes in mean arterial pressure in normotensive and chronically hypertensive people. Note the shift of the curve toward higher mean pressure with chronic hypertension.

previously normal patients to a mean arterial pressure of less than approximately 50 mm Hg inevitably leads to loss of autoregulation, possible expansion of an ischemic zone, or production of global cerebral ischemia. These injuries are seen in patients who are treated too aggressively with antihypertensive agents in the immediate aftermath of a stroke and in patients who are anesthetized during surgical procedures.

Blood-Brain Barrier

The brain's extracellular ionic and molecular environment is tightly regulated. Small changes in extracellular concentrations of Na^+, K^+, and Ca^{2+} ions or neurotransmitters, including glutamate, acetylcholine, and norepinephrine, alter neuronal function. Intracellular communication within the brain, perhaps its most important basic function, depends on a carefully controlled extracellular space. The blood-brain barrier (BBB), which has evolved to protect this milieu, is composed of unique endothelial cells that lack the usual transendothelial channels and closely abut one another in tight junctions. This anatomy protects the brain against the fluctuating composition of blood and reduces the entry of potentially toxic compounds. A negative consequence is that the BBB prevents the entry of polar molecules into the brain, thus limiting the utility of many drugs, small molecules, and proteins, which cannot gain entry into the brain by the oral or intravenous routes.

The entry of nutrients and egress of metabolic waste across the BBB can occur by simple diffusion, facilitated transport, or active transport. Lipid-soluble compounds can diffuse rapidly across endothelial cell membranes, whereas some polar compounds can be transported by special carrier molecules that are driven either by concentration gradients (facilitated transport) or through the expenditure of energy (active transport). Gas molecules, such as oxygen and carbon dioxide, freely diffuse across plasma membranes and rapidly equilibrate between blood and brain. Glucose, a highly polar molecule, enters the brain on a special glucose transporter. The rate of brain glucose transport is normally two to three times faster than the metabolism of glucose, but because glucose uptake depends so highly on its blood concentration, a reduction in blood glucose level to a third of normal, caused by either ischemia or hypoglycemia, may compromise normal brain energy metabolism.

CEREBRAL ISCHEMIA

Inadequate delivery of oxygen or glucose to the brain initiates a cascade of events that ultimately result in infarction. The severity of the insult, defined by the degree and duration of reduced blood flow, hypoxia, or hypoglycemia, determines whether the brain suffers only temporary dysfunction, such as a transient ischemic attack; irreversible injury to only a few of the most vulnerable neurons (selective necrosis); or cerebral infarction, in which damage occurs to extensive areas involving all cell types (pan-necrosis).

Types of Cerebral Hypoxia-Ischemia

Cerebral hypoxia-ischemia can be divided into focal ischemia caused by vascular occlusion, global ischemia as a result of complete cardiovascular failure, and diffuse hypoperfusion-hypoxia produced by respiratory disease or severely reduced blood pressure.

Focal Ischemia

Focal cerebral ischemia results most frequently from embolic or thrombotic occlusion of extracranial or intracranial blood vessels and the resulting reduction in blood flow within the related vascular territory. Blood flow to the central zone of the ischemic vascular bed is usually severely reduced but rarely reaches zero because of partial supply from collateral blood vessels. The best treatment option for this intensely ischemic region is acute restoration of blood flow. A transition zone may be present between the normally perfused tissue and the more ischemic central core. This rim of moderately deprived tissue has been called the *ischemic penumbra*. It is thought that brain cells in the penumbra remain viable for a longer time than do cells in the ischemic core. This marginally viable tissue may die if inadequate blood flow persists but may be salvaged by restoring flow or, possibly, by neuroprotective therapeutic agents. The size and duration of the penumbra are unknown in any individual patient and poorly defined by current diagnostic techniques. In more recent years, salvage of the penumbra with neuroprotective agents has been the subject of intense basic and clinical research.

Cerebral ischemia sufficient to cause clinical signs or symptoms, if severe, can produce irreversible injury to highly vulnerable neurons in 5 minutes. Progressively longer durations of ischemia increase the probability of permanent damage. If cerebral ischemia persists for more than about 6 hours, infarction of part or all of the involved vascular territory is completed, and the only strategies for therapy entail rehabilitation, such as treatment with neurotrophic factors or neural transplantation. Whether clinical evidence of permanent brain injury from ischemia is detectable depends on the location of the brain tissue involved.

Global Ischemia

Global cerebral ischemia results from cardiac asystole or ventricular fibrillation that reduces the blood flow rate to zero throughout the brain and body. Global ischemia for more than 5 to 10 minutes is generally incompatible with full recovery of consciousness in normothermic humans. If blood flow is restored in time to prevent cardiac death, selective ischemic necrosis usually involves the most vulnerable neurons in the CA1 pyramidal neurons of the hippocampus, the cerebellar Purkinje cells, and the pyramidal neurons in neocortical layers 3, 5, and 6. Anything that prevents adequate oxygen or glucose supply to the brain, such as hypoxemia, carbon monoxide poisoning, and severe and prolonged hypoglycemia, can also produce such injury. Cardiac resuscitation or other causes of prolonged hypotension may cause cerebral infarction, particularly in border zones that lie between the terminal branches of major arterial supplies, often termed *watershed zones*.

Diffuse Hypoxia

Diffuse cerebral hypoxia initially causes cerebral dysfunction but not irreversible brain injury. Individuals with cerebral hypoxia from high altitude, pulmonary disease, or severe anemia can exhibit confusion, cognitive impairment, and lethargy. The onset of coma heralds permanent brain damage. With acute changes in Pao_2 from normal to less than 40 mm Hg or a decrease in the hemoglobin concentration to less than 7 g/dL, compensatory increases in CBF become inadequate, and clinical signs and symptoms of cerebral hypoxia develop. A slower onset of reduced oxygenation, such as caused by moving to high elevations or the gradual development of anemia, permits compensation by a variety of mechanisms; if the hypoxia increases, however, the compensation ultimately fails.

Neuropathology of Cerebral Ischemia

Four general classes of histopathologic damage can occur. Cerebral infarction caused by focal vascular occlusion is characterized by destruction of all cellular elements: neurons, glia, and endothelial cells (pan-necrosis). Cerebral infarcts are initially grossly pale (anemic) or hemorrhagic (showing gross petechial bleeding). Later, necrotic tissue is removed and replaced by a glial scar or a cavity. Transient arrest of the cerebral circulation (global ischemia) can cause selective *ischemic necrosis* of highly vulnerable neurons. Using conventional stains, histologic change begins to outline the margins between living and dying neurons and glia within a few hours, although the full extent of damage may not be evident for several days. The neurologic functionality of the cells is irreversibly lost within the first 6 hours. Newer imaging techniques can reveal abnormal cell function much more rapidly than conventional histology can.

Cerebral *autolysis* is observed most frequently in brain-dead patients who are maintained on mechanical ventilators for more than a few days; it reflects enzymatic autodigestion of brain tissue. *Demyelination* of the central hemispheric white matter is usually a consequence of carbon monoxide poisoning or other prolonged periods of moderately severe hypoxemia or cerebral hypoperfusion. Development of these lesions may take several days, and the onset of neurologic dysfunction may be delayed. Patients may have a lucid interval after such an injury and subsequently manifest neurologic symptoms. Within these lesions, nerve cell axons are demyelinated, and oligodendroglial cells die.

Ischemic Cascade

In severe ischemia, energy-rich compounds become depleted within minutes. As energy-dependent membrane pumps fail, neuronal and glial cell membranes depolarize and allow the influx of Ca^{2+} ions. Elevated intracellular Ca^{2+} and other second messengers activate lipases and proteases, which release membrane-bound free fatty acids that denature proteins. Depolarization of presynaptic terminals releases abnormally high concentrations of excitatory neurotransmitters, such as glutamate, which may elevate metabolic demand at a time when energy supplies are inadequate and thus exacerbate the injury. If blood flow is restored within 5 minutes and there are no other complicating factors such as hyperglycemia, these events are completely reversible. As the duration of ischemia increases, selectively vulnerable neurons die first; if the ischemia persists for hours or longer, cerebral infarction develops. Prompt restoration of blood flow permits full functional recovery and maintenance of tissue integrity. Tissues with partial depletion of ATP and impaired calcium homeostasis may benefit from pharmacologic therapies that reduce calcium movement through voltage- and neurotransmitter-dependent ion channels. Many other neuroprotective strategies have also been shown to be effective in animal models, including prevention of the detrimental actions of excitatory neurotransmitters, inhibition of many biochemical pathways leading to cell death, and therapies that may delay the denaturation of proteins. Thus far, however, none of these therapies has proved useful in clinical trials in stroke patients.

Leukocytes

More recently, the role of leukocytes in ischemic damage has been recognized. Two proposed mechanisms of injury are (1) microvascular occlusion from direct mechanical obstruction and damage to the endothelium and (2) infiltration into central nervous system tissue and cellular cytotoxic injury. The white blood cell–mediated damage may be irreversible even if blood flow is restored.

White blood cells require considerable deformation to pass through capillaries. When activated by chemotactic substances during ischemia, their cytoplasmic stiffness increases, and they adhere to capillary endothelium. Under conditions of reduced perfusion pressure, white blood cells may obstruct the microcirculation. This leukocyte capillary plugging may be the major cause of the *no-reflow phenomenon*, which is defined as incomplete restoration of normal blood flow after a period of ischemia. Areas of parenchyma that might be viable when blood flow returns are inadequately reperfused. This phenomenon was a laboratory curiosity until the advent of thrombolytic therapy; it may now be a cause of apparent stroke in evolution or the development of increased neurologic deficits after apparently successful thrombolysis.

Leukocytes may potentiate injury by toxic damage to vascular endothelium and by transendothelial migration to the parenchyma. Release of leukocyte granule contents, which include reactive oxygen metabolites and membrane phospholipases, can injure the endothelium and is usually responsible for the removal of necrotic tissue after irreversible damage. The resultant effects include increased endothelial permeability, interstitial edema, expansion and injury of individual cells (endothelial, glial, and neuronal), vasoconstriction, and generation of substances that induce further leukocyte adhesion.

Anoxic Encephalopathy

In industrialized countries, out-of-hospital cardiac arrest (Chapter 63) occurs in 0.04 to 0.13% of the total population per year. Only a minority of these patients will survive the arrest and be discharged with a good neurologic outcome, in part because of the risk for anoxic encephalopathy. If brain stem function is preserved but the cerebral hemispheres are destroyed, the patient enters a persistent vegetative state (Chapter 411).

CEREBRAL HEMORRHAGE

Bleeding into the subarachnoid space from a ruptured aneurysm or other vascular malformation produces a chemical (sterile) meningitis and can induce vasospasm, particularly in the vessels constituting the circle of Willis. If the vasospasm is sufficiently severe, it can result in cerebral infarction and death.

Intraparenchymal hemorrhage may be relatively benign. Bleeding into a region of previous infarction, called *hemorrhagic transformation*, causes no additional functional loss. Primary parenchymatous hemorrhage damages tissue in several ways, however. If a large vessel ruptures, the amount of bleeding into the brain can be severe. The portion of the vascular distribution distal to the site of rupture is no longer supplied with blood, and infarction results. At the site of rupture, bleeding into the brain may cause traumatic injury to the exposed tissue, and blood or its breakdown products in the parenchyma damage brain tissue. In addition, the extravascular blood in the brain parenchyma increases total brain volume, and the edema, which forms rapidly in and around the site of bleeding, increases the intracranial contents. Because cranial capacity is fixed, ICP increases rapidly, and cerebral herniation may occur.

The biochemical pathology caused by exposure of brain tissue to blood has not been established. Hypertension is closely associated with intracerebral hemorrhage. Research suggests that the matrix metalloproteinases in vessel walls are activated, thereby leading to degradation of vascular tissue with subsequent bleeding.

CEREBRAL EDEMA

A pathologic increase in the water content of brain tissue (edema) eventually develops in all types of ischemic and hemorrhagic stroke. Brain swelling and raised ICP relate proportionally to the volume of accumulated water; in some instances, edema can cause neurologic deterioration and death by herniation syndromes.

The intracranial space contains the brain, which weighs approximately 1400 g, about 75 mL of blood, and approximately 75 mL of cerebrospinal fluid (CSF). An increase in the volume of any of these contents must be accompanied by a decrease in another component because the intracranial cavity is of relatively fixed size and surrounded by bone. Normally, the brain's tissue volume is constant, whereas intracranial blood and CSF vary reciprocally to maintain normal ICP. A variety of mechanisms can compensate for increased intracranial contents to a limited extent, including displacement of CSF into other cranial compartments, reduction of venous blood volume, reduction of normal cerebral interstitial fluid, and chronic cerebral atrophy. If there is a rapid increase in extravascular blood, reduced venous outflow, blockage or resorption of CSF, or cerebral edema, ICP increases markedly.

Brain edema is categorized on the basis of pathophysiologic and anatomic criteria as intracellular or interstitial. Intracellular edema, also called *cytotoxic edema*, develops as energy-dependent membrane ion pumps fail; as a result, Na^+ and other osmoles enter the cell and draw water in from the interstitial and vascular compartments. This process can begin within a few hours after the onset of ischemia. Cell swelling occurs predominantly in astrocytes, but neurons, oligodendroglial cells, and endothelial cells are also involved.

Interstitial edema, also called *vasogenic edema*, occurs later than the intracellular form. Damage to endothelial cells of the BBB allows macromolecules, such as plasma proteins, to enter the cerebral interstitial space accompanied by osmotically bound water. Interstitial edema after cerebral infarction progressively worsens for about 3 days after a stroke. Fluid accumulation within the vicinity of damaged endothelial cells and the zone of infarction can raise the local water content of brain by 10%. The osmolality of ischemic brain increases from 310 to approximately 350 mOsm. The intracellular accumulation of water increases from a normal value of approximately 79 to 81% of brain weight.

If the cerebral circulation is re-established before permanent brain injury develops, the intracellular edema resolves without permanent sequelae. A large increase in the brain's volume can, however, lead to transtentorial herniation of the cerebral hemispheres or to cerebellar herniation. These syndromes can result in irreversible global ischemia of the hemispheres or crushing of the brain stem, loss of cerebral control of the circulation, and death from respiratory arrest. The edema-induced increase in ICP usually reaches a maximum about 3 days after the onset of a stroke. If a patient has a large stroke and survives after the third day, the patient is unlikely to die as a result of that stroke.

SUGGESTED READINGS

Butcher K, Emery D. Acute stroke imaging. Part I: fundamentals. *Can J Neurol Sci*. 2010;37:4-16. *Review*.
Gorelick PB, Ruland S. Cerebral vascular disease. *Dis Mon*. 2010;56:39-100. *Review*.
Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. *JAMA*. 2011;305:913-922. *Antihypertensive medications decrease the risk of stroke even in people without hypertension*.

414

ISCHEMIC CEREBROVASCULAR DISEASE

JUSTIN A. ZIVIN

DEFINITION

Ischemic stroke is caused by insufficient blood flow to part or all of the brain. *Focal stroke* is defined as an infarction in a part of the brain as the result of reduced blood flow in an artery that supplies that part of the brain. During the early phases of a stroke, when acute therapy is potentially beneficial, it is impossible to predict whether an individual patient will recover because the treatment is effective only if given before it is known whether the symptoms will resolve spontaneously.

The important distinction between a transient ischemic attack (TIA) and a stroke is whether the ischemia has caused brain infarction, a difference that may not be possible to distinguish within the first few hours after the onset of symptoms but commonly becomes apparent retrospectively. With a stroke, symptoms usually persist for more than 24 hours, but clinical deficits that persist for more that 1 to 2 hours commonly are associated with permanent brain damage, often demonstrable by computed tomography (CT) or magnetic resonance imaging (MRI), despite complete recovery. Many events that were defined as TIAs in the era before neuroimaging were actually infarcts. By comparison, the symptoms of TIAs usually do not persist for more than 1 to 2 hours and do not cause permanent damage on neuroimaging studies. Patients with TIAs are at considerably increased risk of having a stroke within hours to days after a TIA.

Ischemic strokes are differentiated from hemorrhagic strokes (Chapter 415) by the lack of extravasated blood in the brain parenchyma. There are two main classifications of ischemic stroke. *Thrombosis* and *embolism,* which are caused by arterial occlusion with either a thrombus that forms locally at the site of an atherosclerotic plaque or an embolic clot, are responsible for 65% of all strokes. Emboli are produced when a piece of a larger clot breaks off from a mural thrombus in the heart or a more proximal artery and lodges downstream at a point where the diameter of the vessel has decreased in size so that the clot can no longer pass through the arterial lumen. It is often impossible to distinguish a thrombus from an embolus by imaging methods or histopathologic material, so the two processes are classified together. *Small vessel strokes,* commonly called *lacunes,* are caused by occlusion of small arterioles and account for about 20% of strokes. The histologic lesion in blood vessels in these strokes is classically called lipohyalinosis, which does not help in identifying the cause of these strokes. Some of these strokes are caused by local vascular abnormalities, but others are almost certainly caused by small emboli. The other 15% or so of strokes are caused by hemorrhage (Chapter 415).

EPIDEMIOLOGY

Hypertension is the most important risk factor for ischemic and hemorrhagic stroke (Chapter 67). The incidence of stroke increases directly in relation to the degree of elevation of systolic and diastolic arterial blood pressure above threshold values. More important, there has been conclusive evidence for more than 30 years that control of hypertension prevents strokes. Meta-analyses of randomized controlled trials confirm an approximate 30 to 40% reduction in stroke risk with lowering of blood pressure.

Approximately 7 to 10% of men and 5 to 7% of women older than 65 years have asymptomatic carotid stenosis of greater than 50%. Epidemiologic studies suggest that the rate of unheralded stroke ipsilateral to a stenosis is about 1 to 2% annually.

Nonvalvular atrial fibrillation (Chapter 64) carries a 3 to 5% annual risk for stroke, with the risk becoming even higher in the presence of advanced age, previous TIA or stroke, hypertension, impaired left ventricular function, and diabetes mellitus.

In epidemiologic studies, the risk for stroke in smokers is almost double that in nonsmokers, but the risk becomes essentially identical to that of nonsmokers by 2 to 5 years after quitting. The relative risk for stroke is two to six times greater for patients with insulin-dependent diabetes (Chapter 236). Patients with sickle cell disease (Chapter 166) have a markedly increased risk for stroke. Hyperlipidemia also increases the risk for stroke, and reduction of low-density lipoprotein (LDL) cholesterol levels with statins reduces this risk. Some evidence suggests that abdominal obesity in men and obesity and weight gain in women are independent risk factors for stroke. Weight reduction in overweight people is recommended, but weight loss has not been proved to reduce the risk for stroke.

Epidemiologic studies have found that consumption of fruits and vegetables is associated with a lower risk for stroke, but no randomized trials have proved the value of changing dietary habits. Heavy alcohol consumption may be a risk factor for ischemic and hemorrhagic stroke.

Postmenopausal hormone replacement therapy has been shown to increase the risk for stroke. The absolute risk for stroke remains low, however, in otherwise healthy, low-risk patients. Meta-analysis suggests an increase in the relative risk for stroke in women taking oral contraceptives, but the absolute risk for stroke is small. Women who smoke, are hypertensive or diabetic, have migraine headaches, or have previously suffered thromboembolic events may be at increased risk for stroke when taking oral contraceptives.

PATHOBIOLOGY

The precise signs and symptoms of ischemic stroke depend primarily on the region deprived of blood flow. The tempo with which deficits develop has important clinical implications.

Pattern of Development of Strokes

Shortly after the onset of vascular occlusion, it is common for symptoms and signs to fluctuate and either to improve or to deteriorate, often rapidly. Some patients may be in denial and anticipate that their symptoms will resolve, thereby resulting in delay in seeking medical care until sufficient time has elapsed that acute therapy is useless.

If the symptoms resolve completely in 1 or 2 hours, the patient has had a TIA. The basis for this resolution is unclear. Possibilities include dissolution of an embolus with subsequent restoration of normal regional blood flow, decrease in vasospasm, and improvement in perfusion secondary to increased collateral flow.

Ischemic episodes that ultimately develop into infarction often fluctuate for several hours after onset. Early in the course it is impossible to predict what will happen. Recovery may stop suddenly, and deficits may plateau or increase. Persistence of any neurologic deficit beyond 2 hours, even if the patient subsequently recovers fully, is nearly always accompanied by some degree of tissue destruction.

Hours to days after the abnormality becomes stable, increased neurologic deficits may develop, a deterioration termed *stroke in evolution.* Probable reasons include reperfusion injury, clot extension, or a new stroke in the same vascular distribution. Compromised cardiac output and systemic hypotension resulting from myocardial ischemia, cardiac arrhythmias, or heart failure may also contribute in some cases. Patients may appear to have stroke in evolution because of systemic disorders, such as electrolyte imbalances or glucose abnormalities that initially appear to be exacerbations of a stroke but are really comorbid problems that do not cause extension of the infarct. Cerebral edema may increase neurologic deterioration in large strokes by causing herniation syndromes. Secondary bleeding into an infarct can occur; ordinarily, this process does not increase neurologic deficits unless the blood extends into an area outside the initial boundaries of the infarction or causes a mass effect and increased intracranial pressure. The term *stroke in evolution* describes a clinical picture rather than a specific pathologic process.

Common Causes and Pathogenesis of Stroke

Atherosclerosis

Atherosclerosis (Chapter 70) is the most common disorder that leads to stroke. Atherosclerotic plaques are thought to cause stroke in three ways: (1) mural thrombosis forms at the site of an atherosclerotic lesion, and the clot obstructs the artery at that location; (2) ulceration or rupture of a plaque leads to formation of a clot and distal embolization; and (3) hemorrhage into a plaque obstructs the artery. The clinical manifestations of a stroke depend on the rate of occlusion. If occlusion occurs slowly, there may be time for collateral blood supply to develop, and a stroke is avoided. If the occlusion is abrupt, a stroke ensues, and the degree of damage depends on the extent of collateral supply that is available to the territory of the brain supplied by the occluded vessel. If collateral supply is marginal, just enough blood may pass through the stenotic region to maintain minimally adequate blood flow. In these circumstances, neurologic function may become critically dependent on changes in blood pressure, and small decreases can cause a stroke or recurrent TIAs.

More frequently, a platelet-fibrin thrombus forms on the roughened surface of an atherosclerotic plaque. The thrombus can break off and float distally in the blood stream, eventually becoming lodged in a distal, smaller branch; this process is termed *artery-to-artery embolization.* These embolic occlusions are more likely to be symptomatic because the more distal end vessels have no collateral supply. The amount of territory that is deprived of blood is smaller, however, and symptoms are usually less severe than with occlusion of the main stem of a vessel. The most common locations for an intravascular thrombus to form are the base of the aorta, the bifurcation of the common carotid artery, or the point at which the vertebral arteries originate from the subclavian arteries.

Emboli of Cardiac Origin

Emboli originating from the heart may lodge in any part of the body; however, because about 20% of the normal cardiac output goes to the brain, it is a common site of cardioembolism. Thrombus formation and release of emboli from the heart are promoted by arrhythmias and by structural abnormalities of the valves and chambers. The frequency of the various types of stroke produced by cardioembolism can only be estimated. Although some strokes are clearly embolic in origin, and others are unquestionably thrombotic, it is generally impossible to distinguish them pathologically. There is no diagnostic test to prove that a thrombus or embolus is of cardiac origin.

Mural Thrombi

Myocardial infarction may produce a region of dyskinetic myocardium that predisposes to the formation of mural thrombi (Chapter 73). Anterior wall myocardial infarction is associated with the highest frequency of thromboembolic stroke. Cardiomyopathies (Chapter 60), such as those caused by alcohol abuse or viral infections, also produce dyskinesia that promotes mural thrombi and can result in cerebral embolization, as can any cause of severe heart failure (Chapter 59). In some instances, a cardiac mural thrombus may release numerous pieces that produce a shower of emboli and cause several simultaneous strokes at various locations in the brain.

Valvular Heart Disease

Rheumatic heart disease (Chapter 298), which is now rare in industrialized countries, is associated with systemic emboli, especially in patients who have mitral stenosis (Chapter 75). Acute or subacute infectious endocarditis (Chapter 76) produces vegetations on heart valves, and these vegetations can embolize to the cerebral circulation. Endocarditis caused by staphylococci, fungi, or yeast is often extensive enough to occlude large intracranial arteries. Infective endocarditis is associated with other forms of cerebrovascular disease, including intracerebral hemorrhage, subarachnoid hemorrhage, and mycotic aneurysm (Chapter 415). Strokes can occur during the acute phases of the disease, and the combination of fever, a new murmur, and petechiae should prompt collection of blood for culture and consideration of empirical treatment with antibiotics. Anticoagulants may increase the risk for intracerebral hemorrhage in patients with bacterial endocarditis.

Nonbacterial endocarditis (Chapter 60), which is usually associated with various types of cancer, can also give rise to vegetations that produce cerebral embolization and cause focal strokes or diffuse encephalopathy, sometimes in the form of disseminated intravascular coagulopathy. Systemic lupus erythematosus (Chapter 274) is associated with atypical verrucous (Libman-Sacks) endocarditis in which friable vegetations form on the leaflets of any of the heart valves and can rarely produce cerebral embolization.

In patients with prosthetic heart valves, the incidence of stroke is 1 to 5% per year despite oral anticoagulation (Chapter 75). Mechanical valves have a higher risk than biologic valves. Many studies have suggested that anticoagulants reduce but do not completely eliminate cerebral embolization in these patients.

Arrhythmias

Atrial fibrillation, independent of the presence or absence of valvular disease, is a proven cause of embolic stroke and increases the relative risk, compared with age-matched controls, to about 5% per year (Chapter 64). Approximately 15% of all ischemic strokes are associated with nonvalvular atrial fibrillation. Most patients with atrial fibrillation never have a stroke, however. The strokes are often large and disabling, but minor strokes, silent strokes, and TIAs can occur. Most ischemic strokes in patients with atrial fibrillation are due to embolism from left atrial mural thrombi. The risk for atrial fibrillation–associated strokes is increased in patients who have chronic hypertension. The risk for embolic stroke is highest shortly after the development of atrial fibrillation, but embolism can also accompany cardioversion to normal sinus rhythm regardless of whether the conversion is spontaneous, induced by medication, or electrical.

Paradoxical Emboli

Embolic occlusion of intracranial vessels can be of venous origin. The embolic material gains access to the arterial circulation through various cardiac defects, such as a patent foramen ovale, atrial septal defect (Chapter 69), or arteriovenous malformation. When venous emboli enter the heart, a right-to-left shunt allows the emboli to enter the arterial circulation. A patent foramen ovale has been detected in 40% of patients with acute ischemic stroke of uncertain origin, and it is often assumed that paradoxical embolization is the cause of the stroke. Patients with an atrial septal aneurysm and a patent foramen ovale are at highest risk.

CLINICAL MANIFESTATIONS

The clinical manifestations are summarized in Table 414-1.

Internal Carotid Artery

The common carotid artery bifurcation, at the origin of the internal carotid artery (ICA), is the most frequent site of atherosclerotic lesions of the cerebral vasculature. Occlusion of the ICA is often clinically silent if the circle of Willis is complete. It is often impossible to distinguish ICA occlusion from similar damage to the middle cerebral artery (MCA) on clinical examination (see later). Because the ophthalmic artery originates from the ICA, however, TIAs of the ICA may be manifested as transient monocular blindness (also called *amaurosis fugax*). Severe stenosis of the ICA, particularly if bilateral, can cause hypoperfusion of the cerebral hemispheres and symptoms in border zones between the MCA and other major vascular territories (watershed areas), especially if superimposed on generalized hypoperfusion secondary to severe hypotension.

Anterior Cerebral Artery

Isolated occlusion of the anterior cerebral artery (ACA), which is relatively rare in comparison to strokes in other major branches of the circle of Willis, accounts for about 2% of all cerebral infarcts. The principal symptoms associated with occlusion of an ACA distal to the anterior communicating artery are upper motor neuron weakness and cortical sensory deficits (neglect) in the contralateral leg. Other manifestations of ACA occlusion can include urinary incontinence, generalized depression of psychomotor activity (abulia), and transcortical motor aphasia manifested as loss of verbal fluency with preserved ability to repeat. Bilateral occlusion may occur because the origins of the two ACAs are separated by only a short stretch of anterior communicating artery, and there are frequent anomalies in which both ACAs originate from a common source. Bilateral damage usually causes a patient to be mute, with severe mood disturbances and long-lasting incontinence from bilateral damage to the frontal lobes.

Middle Cerebral Artery

Strokes in the distribution of the MCA are the most common type of focal stroke, and such strokes cause approximately two thirds of all infarcts. Occlusion of the stem of the MCA often results in massive, devastating infarction of much of the hemisphere. Edema during the first 3 to 4 days may lead to

TABLE 414-1 CLINICAL MANIFESTATIONS OF ISCHEMIC STROKE

OCCLUDED BLOOD VESSEL	CLINICAL MANIFESTATIONS
ICA	Ipsilateral blindness (variable) MCA syndrome (see below)
MCA	Contralateral hemiparesis, sensory loss (arm, face worst) Expressive aphasia (dominant) or anosognosia and spatial disorientation (nondominant) Contralateral inferior quadrantanopsia
ACA	Contralateral hemiparesis, sensory loss (worst in leg)
PCA	Contralateral homonymous hemianopia or superior quadrantanopia Memory impairment
Basilar apex	Bilateral blindness Amnesia
Basilar artery	Contralateral hemiparesis, sensory loss Ipsilateral bulbar or cerebellar signs
Vertebral artery or PICA	Ipsilateral loss of facial sensation, ataxia, contralateral hemiparesis, sensory loss
Superior cerebellar artery	Gait ataxia, nausea, dizziness, headache progressing to ipsilateral hemiataxia, dysarthria, gaze paresis, contralateral hemiparesis, somnolence

ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PICA = posterior inferior cerebellar artery.

severely increased intracranial pressure and herniation. The classic picture of occlusion of the MCA stem is contralateral weakness and sensory loss in the face and arm (with relative sparing of the leg) and homonymous hemianopia on the side of the weakness; initially, there may be depressed consciousness and deviation of gaze toward the side of the lesion. There is little chance of substantial recovery. In right-handed people, occlusion of the left MCA produces global aphasia in which the patient can neither understand the speech of others nor produce meaningful speech. In the nondominant hemisphere, unilateral neglect, anosognosia (unawareness of the deficit), and spatial disorientation occur.

Occlusion of branches of the MCA produces partial syndromes. An embolus to the MCA frequently lodges in one of its two main divisions. Occlusion of the superior division can cause dense sensorimotor deficits in the contralateral face and arm without initial impairment of alertness. Later, some neurologic function may recover, and the aphasia may decrease. Strokes of the inferior division in the dominant hemisphere characteristically produce receptive aphasia of the Wernicke type (severe loss of speech comprehension with preserved spoken and written language). Damage to either hemisphere can result in contralateral loss of integrated sensation, such as perception of shapes (stereognosis). Occlusion of more distal branches causes less clinical damage.

Posterior Cerebral Artery

In about three fourths of people, both posterior cerebral arteries (PCAs) arise from the basilar artery; in most others, one PCA arises from the basilar artery and the other arises from the ICA. In a few individuals, both PCAs originate from the ICAs. As a consequence, the syndromes associated with occlusion of the PCA are highly variable. Strokes of the perforating branches most frequently cause complete contralateral hemianesthesia with loss of all sensation and complete hemianopia on that side. Macular (central) vision may be spared because of collateral blood supply from the MCA. Difficulty reading (dyslexia) and performing calculations (dyscalculia) may occur. Recovery is often good, but the initial numbness may be replaced by paresthesias or excruciating pain; this Dejerine-Roussy syndrome is caused by damage to the thalamus. Involvement of the subthalamic nucleus may produce hemiballismus, with wild flinging movements of the limbs on one side of the body. Distal branch occlusions of the PCA cause partial syndromes; occlusion of the terminal branch can produce a variety of incomplete visual field deficits, although the loss is characteristically congruous (superimposable) in both visual fields.

Vertebral and Basilar Arteries

Characteristic of occlusion of the blood supply to the brain stem are "crossed syndromes" (i.e., contralateral loss of strength and selected contralateral and ipsilateral sensory symptoms below the level of the lesion, in addition to ipsilateral motor and sensory deficits localized to the level of the lesion). Weber's syndrome is caused by a mesencephalic lesion that produces an ipsilateral third cranial nerve palsy resulting from damage to the oculomotor nerve as well as contralateral weakness.

The vertebral arteries are the principal blood supply for the medulla. The posterior inferior cerebellar artery is usually a branch of the vertebral artery. The consequences of occlusion of the posterior inferior cerebellar artery are variable, but lateral medullary infarction (Wallenberg's syndrome) is classically produced. In about 80% of cases, occlusion of the vertebral artery causes lateral medullary syndrome, which consists of severe vertigo, nausea, vomiting, nystagmus, ipsilateral ataxia (of the cerebellar type), and ipsilateral Horner's syndrome (ptosis, miosis, and decreased sweating). The syndrome also includes ipsilateral loss of facial pain and temperature sensation and contralateral loss of these sensory modalities in the trunk and limb. Partial syndromes are the rule; a complete lateral medullary syndrome is rare, so it is often misdiagnosed.

The basilar artery supplies most of the brain stem, and occlusion of this artery produces a variety of syndromes. Obstruction of the basilar artery trunk is often fatal because the main motor and sensory pathways between the cerebral hemispheres and the remainder of the body are compact and travel through the brain stem. The findings in occlusion of the basilar artery consist of a combination of bilateral sensory and motor long-tract signs, cerebellar dysfunction, and cranial nerve abnormalities: paralysis or weakness of all extremities and the bulbar muscles, impaired vision with various visual field defects, bilateral cerebellar ataxia, and a variety of sensory disturbances ranging from normal to total anesthesia. Coma may occur, or the locked-in syndrome may develop in which consciousness is preserved but the victims are unable to move anything voluntarily except their eyes or eyelids. It is possible to communicate with these patients and demonstrate normal mental status by codes involving eye movements.

Occlusion of the various branches of the basilar artery produces a large variety of syndromes. Because the pathways are so closely spaced in the brain stem, even small brain infarctions can cause substantial motor and sensory deficits. The characteristic findings are crossed syndromes with motor and sensory dissociation, unless the findings are bilateral. Distinguishing mild vertebrobasilar ischemia from the common causes of dizziness is occasionally difficult (Chapters 50 and 62), but ischemia is rarely a cause of isolated vertigo in the absence of other brain stem signs or symptoms.

DIAGNOSIS

The history gives initial clues about the site and severity of a stroke, and the physical examination helps refine a hypothesis on the location of the lesion. Based on this information, definitive laboratory testing can proceed efficiently.

History

As the name implies, stroke ordinarily starts at a clearly identifiable time. The most important aspect of the history, which must be elicited from a patient or accompanying observers if a stroke is suspected, is the time of onset of symptoms. If abnormalities began within the preceding 3 hours, the patient should be managed as an acute emergency, and thrombolytic therapy may be indicated. Patients may be confused, anxious, or aphasic, and they may not remember the duration of symptoms. It may be necessary to try to associate the onset of symptoms with events that the patient or accompanying persons can identify accurately. Did the patient wake up with symptoms? In this case the symptoms must be assumed, in terms of considering acute treatment, to have started at the time that the patient was last known to be in a premorbid state—usually at the time of going to sleep. Was the patient watching television, and if so, what program was it? Consultation with the program guide can be used to assign a time of onset. Was an ambulance called, and if so, what time was the patient first examined by paramedics? This information is usually available in the ambulance records.

TIAs may not be distinguishable from a stroke during the early phases, but TIAs usually resolve within the first hour or two. Rapid progression of deficits or the presence of headache occurs more often in patients with intracerebral hemorrhage (Chapter 415). Although intracerebral hemorrhage is responsible for only about 15% of strokes, hemorrhages generally produce more

severe symptoms that cannot be denied. By comparison, patients with minor strokes or predominantly sensory symptoms are often in a state of denial and do not seek medical care until long after vessel occlusion. Because ischemic strokes are nearly always painless, they do not awaken patients from sleep and are frequently discovered at the time of normal awakening in the morning. There is some diurnal variation in the onset of stroke, with a peak in the late morning.

Physical Examination

The neurologic examination (Chapter 403) is a cost-effective method for initiating a diagnostic evaluation, and it often helps localize the site of the lesion. The cardiovascular examination (Chapter 50) should focus on measurement of arterial blood pressure, including measurement in both arms to evaluate the possibility of aortic dissection (Chapter 78) or vascular abnormalities that result in reduced blood flow to the brain when the arms are exercised (subclavian steal). The greatest risk factor for stroke is preexisting hypertension. In many patients, transient hypertension develops in the immediate aftermath of a stroke, however, so it is important to determine whether a patient has had sustained hypertension (Chapter 67). Extremely elevated blood pressure at initial evaluation can lead to heart failure, which may have to be managed urgently. If hypertension is a transient manifestation of acute stroke, aggressive reduction may cause hypotension and enlarge the infarct. The pulse may reveal arrhythmias, such as atrial fibrillation, that can result in cerebral embolism. Cardiac murmurs may suggest valvular lesions (Chapter 75) that can cause cerebral embolism. Bruits of the carotid arteries can be produced by atherosclerotic disease of the arteries, and such disease is associated with embolic and thrombotic strokes. Evidence of peripheral vascular disease (Chapter 79) may be a reflection of generalized atherosclerosis.

Ophthalmoscopic visualization of retinal cholesterol or platelet-fibrin emboli suggests more proximal atherosclerotic disease. Examination of the retinal vessels may also reveal signs of chronic hypertension or diabetes (arteriovenous crossing defects or retinal hemorrhages; Chapter 431).

The neurologic examination usually suggests the location and size of the stroke. If the patient's mental status is depressed, bilateral cerebral lesions or a brain stem lesion is suggested. Multiple smaller strokes may lead to dementia. Speech is commonly affected, with various aphasic patterns suggesting the site of the lesion. Testing of strength, sensation, and deep tendon reflexes provides information about the patterns of the deficits and suggests the site of the vascular lesion. Plantar stimulation (Babinski's sign), which is a classic finding in patients with damage to the long tracts, indicates upper motor neuron damage caused by stroke. However, during the early phases of a large stroke, reflexes may be depressed rather than hyperactive.

Laboratory Examination

Hematologic Tests

A complete hemogram, including a platelet count, is essential to evaluate for polycythemia (Chapter 169), thrombocytosis, bacterial endocarditis (Chapter 76), and severe anemia. An erythrocyte sedimentation rate is also a useful screening test because it may be elevated in patients with hypercoagulable states (Chapter 179) and is markedly elevated in patients with giant cell arteritis (Chapter 279). A blood glucose level must be checked because hyperglycemia and hypoglycemia can produce focal and global neurologic deficits, sometimes mimicking stroke. Diabetes (Chapter 236) increases the risk for stroke, and stroke may be the initial symptom of diabetes. A prothrombin time and partial thromboplastin time should be obtained in patients who may have received anticoagulants before the onset of stroke to determine whether they have been taking their medications or the anticoagulation is excessive.

Although moderate hyperlipidemia is not a proven risk factor, extremely high lipid levels are strongly associated with stroke. Antiphospholipid antibodies are elevated in some patients with immune-related diseases. Measurement of protein C, protein S, antithrombin III, blood viscosity, and platelet function (Chapter 179) and tests for homocystinuria, collagen vascular diseases (Chapter 264), amyloidosis (Chapter 194), and syphilis (Chapter 327) should be performed in selected cases.

Cardiovascular Testing

Patients with acute myocardial infarction or a new or chronic atrial arrhythmia may have suffered an embolic stroke. A standard electrocardiogram and rhythm strip should be obtained at initial evaluation to determine whether acute myocardial ischemia or arrhythmia is present. Echocardiography is indicated urgently only in patients with a history of cardiac disease and an abnormal electrocardiogram; if no cause for the stroke is identified, however, particularly if the patient is relatively young, echocardiography is generally indicated.

Noninvasive Brain Imaging

Brain imaging (Chapter 403), which is essential to verify causes of focal neurologic dysfunction, can generally distinguish ischemic stroke from other diseases. The most important disorders to differentiate from acute ischemic stroke are intracerebral hemorrhage (Chapter 415), subarachnoid hemorrhage (Chapter 415), and brain tumors (Chapter 195).

CT is the standard initial imaging study (Fig. 414-1). Non–contrast-enhanced imaging usually detects intracerebral hemorrhage. Signals indicating tissue hypodensity, particularly in the region of the brain appropriate to the neurologic deficits, and loss of the distinction between gray and white matter are often observed 3 to 24 hours after the onset of stroke. These findings cannot predict the size of the infarction, however, and noncontrast CT findings may be normal for 3 to 24 hours after an ischemic stroke. The hypodensity typically becomes progressively more apparent over the first 3 to 24 hours and is usually readily detectable by 24 hours in patients with large infarcts. Small ischemic strokes in the brain stem can produce major neurologic dysfunction and may not be detected by CT. Contrast enhancement of CT scans seldom improves detection of acute stroke, but it may distinguish ischemic lesions from some types of neoplasms.

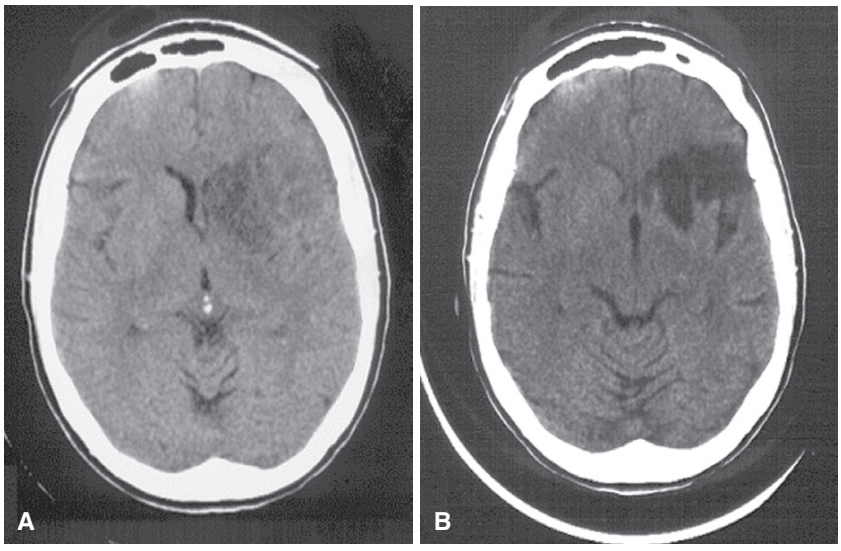


FIGURE 414-1. Computed tomographic imaging. A, A computed tomography (CT) scan of a patient with a left hemisphere infarction 6 to 24 hours after the onset of symptoms shows a hypodense area in the basal ganglia region and compression of the frontal horn of the lateral ventricle. **B,** A CT scan shows the chronic infarction 1 year later; atrophy and loss of tissue volume are visible. (Courtesy of Gregory W. Albers, Stanford University, Stanford, Calif.)

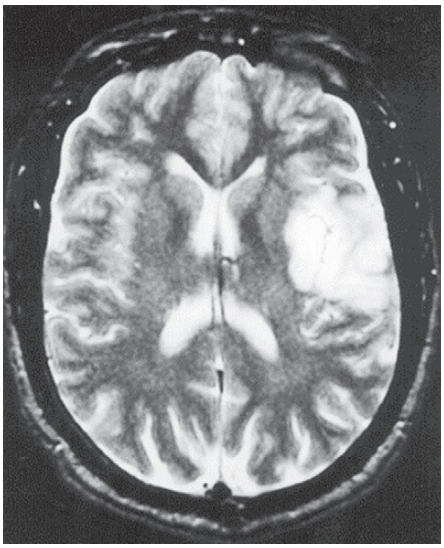


FIGURE 414-2. Magnetic resonance imaging showing early ischemic changes obtained 6 hours after the onset of right-sided weakness in a patient with an occluded left internal carotid artery. (Courtesy of Gregory W. Albers, Stanford University, Stanford, Calif.)

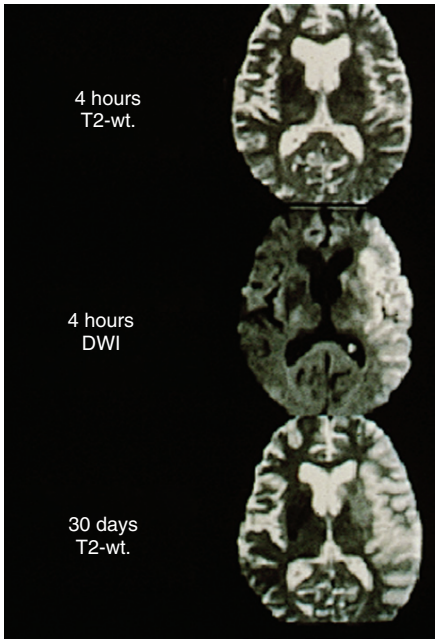


FIGURE 414-3. Magnetic resonance imaging (MRI) showing possible advantages of diffusion-weighted imaging (DWI) relative to conventional MRI at early times after vascular occlusion. *Top,* Conventional T2-weighted MRI 4 hours after symptom onset that appears normal. *Middle,* At the same time, a DWI scan shows abnormalities in the left hemisphere. *Bottom,* Repeat T2-weighted MRI 1 month later showed an infarction in the same location as the initial DWI scan. (Courtesy of Gregory W. Albers, Stanford University, Stanford, Calif.)

CT is currently the only imaging method useful for deciding whether to administer thrombolytic therapy. Detection of hemorrhage in areas of infarction is important because it precludes thrombolytic therapy. Small hemorrhages may be detected by CT scanning during the first few hours but may not have clinical importance. Hemorrhages become more evident with time and appear on repeat scans hours to weeks after infarction. Whether this apparent increase in the detection of hemorrhage is due to a progressive increase in the size of the initial hemorrhage or to alterations in the extravasated blood is not known.

MRI is more sensitive than CT for detecting early ischemia (Fig. 414-2). MRI sequences can identify tissue or blood flow abnormalities within minutes after the onset of ischemia (Fig. 414-3). These early indicators of tissue injury are qualitative and have not been shown to predict the ultimate volume of the lesion or whether the tissue damage is irreversible. MRI cannot be used in patients who have ferromagnetic materials within their bodies, is often impossible to use in critically ill patients, and renders the patient inaccessible for several minutes. No MRI sequences successfully distinguish ischemia from hemorrhage, especially during the early phases of injury, when decisions regarding whether thrombolysis should be administered are needed. CT remains the imaging procedure of choice for acute patient management.

Lumbar Puncture

Lumbar puncture is no longer performed routinely in the evaluation of a patient with stroke because CT detects intracerebral hemorrhage more reliably (Chapter 403). CT can also usually identify blood in the subarachnoid space, although lumbar puncture is more sensitive for this purpose and can give some indication about when the bleeding occurred (Chapter 415). After subarachnoid hemorrhage, erythrocytes hemolyze. As hemoglobin is metabolized, cerebrospinal fluid becomes xanthochromic. Lumbar puncture is required to determine whether a patient has neurosyphilis (Chapter 327), although screening blood testing should be conducted first. Lumbar puncture is also occasionally indicated if there is concern that a patient may have bacterial meningitis (Chapter 420).

Noninvasive Cerebrovascular Examination

Ultrasonography provides an estimate of luminal diameter and the direction and speed of blood flow. B-mode ultrasonography, which produces real-time images of the carotid vessels, and range-gated pulsed Doppler, which is guided visually by the B-mode image, can detect increased blood velocity through a stenotic lumen. The combination of the location of the Doppler frequency signal and the B-mode image provides a noninvasive method for analyzing the condition of the extracranial circulation. Limitations of the technique include (1) access to only the portion of the carotid circulation that lies between the clavicles and the mandible (in approximately 10% of patients, the carotid bifurcation lies above the angle of the jaw, thus making ultrasonography difficult or impossible); (2) absorption of sound waves by calcium within a mural plaque, a process that may "shadow" and obscure a plaque on a distal vessel wall; and (3) echolucency of acute thrombi, which can be indistinguishable from flowing blood. The direction and velocity of blood flow in the intracranial blood vessels originating from the circle of Willis can be examined with low-frequency pulsed transcranial Doppler. Although these methods are useful screening techniques with essentially no risk to the patient, the "gold standard" for defining the status of the cerebral vasculature remains cerebral angiography. Moreover, ultrasound technique is critically dependent on the training and skill of the technician; there is considerable variation among different laboratories, and the clinician must confirm new or suspicious findings with repeat examinations or other tests.

CT and magnetic resonance (MR) angiography can visualize the larger cerebral vessels and detect abnormalities such as stenosis, aneurysms, or arteriovenous malformations. These methods lack sensitivity for small lesions, however, and the degree of stenosis tends to be exaggerated.

Cerebral Angiography

Cerebral angiography is reserved for patients who are suspected to have a surgically correctable lesion. Arterial vessels are displayed initially, and delayed images can outline the venous system. Patients commonly receive anticoagulants during the procedure. The images give high-quality resolution of the vessels but do not provide quantitative information about blood flow. This method is the only one that has been proved useful for selecting patients who can benefit from carotid endarterectomy.

Angiography, particularly in patients with abnormal vasculature, can itself cause stroke and result in permanent neurologic deficits or death. The rate of injury varies in different surveys but is about 0.5% in good facilities. Angiography requires exposure to ionizing radiation, may be associated with adverse reactions to the contrast material, and involves a fluid load that poses a risk to patients with severe cardiac disease.

Other Techniques

Single-photon emission computed tomography provides only qualitative blood flow rates. Positron emission tomography quantitatively measures blood flow or brain metabolism. CT and MRI methods for measurement of cerebral blood flow and metabolism are in development. None of these

techniques has yet been shown to be useful for the management of stroke patients (Chapter 403).

Differential Diagnosis

The characteristic feature of ischemic stroke is the abrupt, painless onset of a neurologic deficit. Blood supply is lost in the distribution of a terminal vessel, and loss of function begins within seconds. The brain does not have pain receptors in its parenchyma, so the symptoms are painless unless the dura mater, which does have pain fibers, is stretched or irritated. One type of stroke that can evolve slowly is subdural hematoma (Chapter 415), which may be distinguishable from ischemic stroke because a hematoma produces deficits more slowly. Focal symptoms and signs of tumors (Chapter 195) of various types typically evolve over a period of weeks or longer, except in uncommon cases in which a tumor erodes a vessel and causes bleeding or crushes it and causes infarction. TIAs cannot initially be distinguished from strokes, but they generally resolve within the first 1 or 2 hours.

Other neurologic disorders can be manifested as an abrupt onset of neurologic abnormalities. Migraine (Chapter 405) with or without aura may simulate stroke or TIA because of its associated hemiparesis or other focal deficits. Migraine is primarily an exquisitely painful, throbbing, unilateral headache that sometimes has an aura (symptoms preceding the headache) of scintillating scotomas (flashing lights). Complicated migraine (migraine accompanied by focal deficits) can rarely evolve into a true ischemic stroke, probably because of the decreased blood flow that often accompanies migraine.

Seizures (Chapter 410) can be confused with TIAs. Many seizures produce tonic (sustained) or clonic (rapid) motor activity or positive sensory phenomena. Strokes and TIAs produce weakness and sensory loss without involuntary motor activity. Seizures can sometimes be associated with these negative symptoms, particularly in the postictal state after (unobserved) seizures. The patient generally returns to the premorbid state after a seizure, however. Serial observations usually permit the differentiation of stroke from seizure, but early differentiation may be difficult and require laboratory testing, particularly an electroencephalogram. In a few patients with stroke, especially with emboli, a seizure occurs at the onset of the stroke.

Hyperglycemia and hypoglycemia can cause focal neurologic deficits. Most patients have a history of diabetes, and the glucose abnormality is substantial at the time of focal neurologic deficits.

Hemorrhagic stroke (Chapter 415) cannot generally be definitively distinguished from ischemic stroke on the basis of the history or clinical examination. Primary hemorrhages are often severe at onset and may result in headache and rapidly evolving deficits. Ischemic strokes are normally painless and characterized by a fixed deficit or a stuttering onset followed by rapid waxing and waning fluctuations. Headaches can occur in conjunction with many ischemic strokes, however, and the only way to distinguish infarct from hemorrhage definitively is with a CT scan.

Brief global cerebral anoxia causes syncope without any permanent sequelae. Prolonged diffuse ischemia, by contrast, can have devastating consequences. The most common causes are cardiac asystole or other forms of overwhelming cardiopulmonary failure. Aortic dissection (Chapter 78), global hypoxia, or carbon monoxide poisoning (Chapter 94) can cause a similar picture. Clinically, these disorders result in unconsciousness. If ischemia persists for more than 4 to 5 minutes, patients often remain in a coma, sometimes evolving into the vegetative state, in which brain stem functions are preserved but the patient has no higher cortical function (Chapter 411). If patients do not regain consciousness within 2 or 3 days, the prognosis for return of independent function is poor. Prompt and aggressive effort to restore cardiovascular circulation is most important. Clinical trials have shown that induced hypothermia within minutes to hours improves outcome in adults who remain comatose after initial resuscitation from out-of-hospital ventricular fibrillation cardiac arrest.

In young patients, hypoxia caused by near-drowning in cold water may result in resistance to prolonged hypoxic-ischemic damage. Therapeutic hypothermia has not yet been proved useful in adults with stroke.

TREATMENT

Acute Stroke

Thrombolytic therapy is the only safe and effective method for acute management of ischemic stroke of typical cause (i.e., atherosclerotic and embolic stroke). Meta-analyses provide support for the efficacy and safety of thrombolysis if patients are treated within 4.5 hours after the onset of symptoms, with about a one third increase in the likelihood of a favorable neurologic outcome, directly attributable to the drug, despite the minimal risk for hemorrhage. Obstacles to thrombolytic treatment include the need to redesign and implement acute stroke care systems, delay of patients in reaching medical facilities, and insufficient expertise in the use of thrombolysis by many physicians. Telemedical approaches, whereby physicians can communicate through audio, video, and digital imaging with consultants at referral institutions, can improve the evidence-based use of acute thrombolytic therapy.

The recommended therapy with intravenous tissue plasminogen activator (t-PA) requires adherence to relatively stringent eligibility criteria (Table 414-2 and Fig. 414-4). Therapy must be started within 4.5 hours after the onset of stroke. Before initiating therapy, a non–contrast-enhanced CT scan should be obtained to exclude patients with intracranial hemorrhage. Blood pressure limits are a maximum of 185 mm Hg systolic or 110 mm Hg diastolic. If blood pressure exceeds these limits, it should be lowered with an antihypertensive drug such as labetalol before initiating t-PA. In addition, patients who have had major surgery or serious trauma within the preceding 2 weeks or evidence of gastrointestinal bleeding should not be treated. The recommended dose of intravenous t-PA is 0.9 mg/kg to a maximum of 90 mg, administered as a 10% initial bolus with the remainder given over a 60-minute period.

Treatment should begin as soon as possible, and even patients with mild strokes or rapidly resolving deficits probably merit treatment. Patients with severe strokes, as evidenced by major clinical deficits or early signs of a large infarct by CT scan, do not fare well regardless of whether they are treated. Treatment 3 to 6 hours after the onset of ischemic stroke is not currently recommended, although one study of intra-arterial prourokinase given 3 to 6 hours after the onset of an ischemic stroke showed benefit from such therapy. Streptokinase is not of benefit. Intra-arterial t-PA has been used in patients who are not candidates for intravenous t-PA, but there are no controlled studies of this form of treatment.

Acute anticoagulation with various forms of heparin or warfarin is of no benefit in patients with ischemic stroke. Patients with stroke in evolution, in which deficits increase over the first day after the onset of the stroke, commonly receive anticoagulants, but there is no strong evidence that such therapy is effective. Vital signs and neurologic status should be monitored. After the acute stroke has stabilized and begun to improve, hypertension must be treated.

Blood pressure is often transiently elevated in the initial hours after a stroke and should not be rapidly lowered except as a prelude to t-PA therapy (see earlier). Many stroke patients have markedly elevated blood pressures, even in the absence of a history of hypertension. Until multiple ongoing trials are completed, a reasonable acute blood pressure goal is less than 180 mm Hg systolic in patients who have an intracerebral hemorrhage or are eligible for thrombolysis (<220 mm Hg otherwise), then a goal of 160/100 mm Hg after 24 hours.

If a patient has suffered an acute myocardial infarction, the preferred therapy is primary angioplasty (Chapter 74). It is uncertain what dose of t-PA should be administered if a patient simultaneously has a stroke and myocardial infarction. If a patient is a candidate for coronary artery bypass graft surgery and is found to have surgically correctable carotid stenosis, the more urgent procedure should generally be performed first.

There is an increased risk for pulmonary embolism and deep vein thrombosis in patients with ischemic stroke, particularly those with neurologic deficits that produce immobility. In these patients, prophylactic low-dose subcutaneous heparin or low-molecular-weight heparin (Chapter 37) is recommended unless there are other contraindications to anticoagulation. The use of graduated compression stockings does not significantly reduce deep vein thrombosis after stroke but results in adverse skin effects.

UNUSUAL CAUSES OF STROKE

Atrial Myxoma

Atrial myxomas (Chapter 60) are the most common type of primary cardiac tumor and are found in about 0.05% of autopsies of young adults with ischemic strokes or TIAs. Nonspecific constitutional symptoms are frequent, and less than half of myxomas produce emboli. When these tumors do produce emboli, the danger period usually lasts days to weeks. Metastasis can rarely cause cerebral aneurysms. Other primary and metastatic cardiac tumors can embolize neoplastic tissue or thrombus.

Vasculitis

Vasculitis (Chapters 274, 278, and 279) can produce focal or multifocal cerebral ischemia by means of inflammation and necrosis of extracranial or intracranial blood vessels. Segmental inflammation of cerebral blood vessels is associated with cerebral ischemia acutely at the site of involvement.

Vasculitis of the central nervous system (CNS) is often manifested as cognitive disturbances, headache, and seizures. Because the vascular damage is commonly diffuse, these nonfocal neurologic abnormalities occur more

TABLE 414-2 TISSUE PLASMINOGEN ACTIVATOR THERAPY FOR ACUTE ISCHEMIC STROKE

Clinical manifestation—focal neurologic deficits
Patient selection
Therapy must be started within 3 hr of the onset of acute ischemic stroke symptoms
A baseline CT scan must be obtained before initiation of therapy
Contraindications
Evidence of intracranial hemorrhage on pretreatment evaluation
Suspicion of subarachnoid hemorrhage
Recent intracranial surgery, serious head trauma, or previous stroke
History of intracranial hemorrhage
Uncontrolled hypertension at the time of treatment—≥185 mm Hg systolic or >110 diastolic—that cannot be reduced with acute antihypertensive therapy
Seizure at stroke onset
Active internal bleeding
Intracranial neoplasm, AVM, or aneurysm
Known bleeding diathesis, including but not limited to
Oral anticoagulation with a prothrombin time >15 sec
Heparin administration within the preceding 48 hr and an elevated activated partial thromboplastin time at initial evaluation
Platelet count <100,000/mm^3
Warnings
Patients with a severe neurologic deficit (NIH Stroke Scale >22) at initial evaluation have an increased risk for ICH
Patients with major early infarct signs on CT (edema or mass effect) are probably >3 hr since vessel occlusion
Dosing information for acute ischemic stroke
0.9 mg/kg to a maximal dose of ≤90 mg
10% of the total dose administered as an intravenous bolus over a 1-min period
90% of the remainder infused continuously over a 60-min period
Follow-up
Monitor vital signs and neurologic status
Maintain blood pressure at ≤185/≤110 mm Hg
No anticoagulant or antiplatelet therapy for 24 hr

AVM = arteriovenous malformation; CT = computed tomography; ICH = intracranial hemorrhage; NIH = National Institutes of Health.
Modified from package insert for Activase, Genentech, Inc., South San Francisco, Calif.

frequently with vasculitis than with focal ischemic disorders. The diagnosis is often difficult to make because the signs and symptoms are frequently nonspecific. The angiographic appearance of a beadlike segmental narrowing of cerebral blood vessels, when present, is virtually diagnostic, but cerebral angiograms are often normal in histologically proven cases. Definitive diagnosis requires the demonstration of characteristic inflammatory histopathology in leptomeningeal or cortical biopsy specimens. Because of the segmental and highly focal nature of the inflammatory process, the histopathology may go undetected at biopsy despite a positive angiogram.

Primary CNS vasculitis, Behçet's disease (Chapter 278), Takayasu's arteritis (Chapters 78 and 278), and temporal arteritis (Chapter 279) are notable for their infrequent involvement of the peripheral nervous system. By contrast, hypersensitivity and systemic necrotizing vasculitides frequently produce polyneuropathies. Primary CNS arteritis (Chapter 278), giant cell arteritis (Chapter 279), and vasculitis associated with certain CNS infections may be manifested initially or solely as neurologic abnormalities.

Primary arteritis of the CNS causes headache and other encephalopathy-like symptoms in young or middle-aged individuals. The course is usually insidiously progressive but may wax and wane for periods of several months. A few of these patients initially have a strokelike episode.

Giant cell arteritis (Chapter 279) can affect any medium or large artery in the body. When it is present in the cerebral vasculature, it is called *temporal arteritis* and is characterized by panarteritis, including intimal proliferation, destruction of the internal elastic lamina, and thickening of the media. Luminal obstruction is caused by edema, thickening of the intima, and thrombosis. A prominent inflammatory infiltrate consisting of mononuclear cells, giant cells, and eosinophils with granuloma formation is present with active disease. Giant cell arteritis is the most common angiitis causing ischemic stroke. Temporal arteritis predominantly affects patients older than 55 years. Symptoms include fever, malaise, weight loss, and headache. In many patients, constitutional symptoms consistent with polymyalgia rheumatica may coexist, including jaw, neck, and facial pain and morning stiffness. Pain over the temporal arteries and an erythrocyte sedimentation rate greater than 50 mm/hour are frequently present. Biopsy of the superficial temporal artery provides a definitive diagnosis; because of the segmental nature of the vasculitis, however, serial sections must be examined or the characteristic histology may be missed. The diagnosis is important to establish because early initiation of corticosteroid therapy (e.g., prednisone, 60 mg/day) may decrease the risk for acute ischemic blindness or stroke (Chapter 279). This treatment can be started shortly before performing the biopsy.

Takayasu's arteritis, also called *pulseless disease* (Chapters 78 and 278), is a chronic, idiopathic inflammatory disorder, primarily of young women. It affects mainly the aortic arch, the large brachiocephalic arteries, and the abdominal aorta. Mononuclear infiltrates and fibrous proliferation produce progressive narrowing of the lumen of these vessels and thus reduced flow into the upper extremities and cerebral ischemia. Although initially diagnosed in Japanese families, it has been recognized in Western countries.

Fibromuscular dysplasia is a segmental vasculopathy of unknown etiology (Chapters 78 and 127). Its frequency in large angiographic series is less than 1%. Bilateral extracranial involvement of the ICA is common, but abnormalities of the intracranial carotid or vertebrobasilar artery are rare. Dysplasia of the arterial wall may involve the intima, media, or adventitia. This disorder, which may also affect the renal arteries and is associated with hypertension, can lead to aneurysm formation and cervicocephalic arterial dissection. The diagnosis is made by cerebral angiography. Little information on treatment is available; angioplasty and stenting to open the narrowed lumen are unproven experimental procedures.

Other types of vasculitis are unusual causes of stroke. Such diseases include Wegener's granulomatosis (Chapter 278); sarcoidosis (Chapter 95); bacterial, fungal, and viral infections; meningovascular syphilis (Chapter 327); and lymphomatoid angioendotheliomatosis.

Hemoglobinopathies

In sickle cell anemia (Chapter 166), irreversible sickling results in increased blood viscosity, microvascular sludging, and brain infarction. Sickle cell disease also causes hyperplasia of fibrous tissue and muscle cells of the vascular intima, thereby leading to stenosis and occlusion of some medium to large cerebral arteries.

Estimates of the incidence of stroke vary but are generally reported to be 8 to 17% in patients with hemoglobin SS and about 2% in individuals with hemoglobin SA. The mean age at first stroke is about 8 years in people with hemoglobin SS. Ischemic stroke occurs more frequently in children. In adults, hemorrhagic strokes are more common.

Hyperviscosity Syndrome

Cerebral blood flow decreases with increasing blood viscosity. Blood viscosity increases with increasing levels of red and white blood cells, platelets, and plasma proteins. A hyperviscosity syndrome can occur when any of these blood components is markedly increased and produce focal or multifocal neurologic dysfunction, including headache, encephalopathy, and seizures. Common causes of hyperviscosity include polycythemia vera (Chapter 169) and paraproteinemias (Chapter 193) secondary to macroglobulinemia or multiple myeloma.

Coagulation Disorders

Hereditary

Four circulating proteins that inhibit coagulation are protein C, protein S, antithrombin III, and factor V (Chapters 81 and 179). Deficiencies of these proteins rarely cause arterial strokes but more frequently cause venous thrombosis. Deficiencies of proteins C and S are dominantly inherited. Homozygotes have serious, frequently fatal clotting abnormalities at birth, whereas heterozygotes may show no signs of hypercoagulability. Because of incomplete penetrance, the occurrence of thrombosis and stroke in adults is extremely rare; testing for these abnormalities should be undertaken only in unusual cases. Antithrombin III is vitamin K independent and synthesized in the liver. Deficiency should be suspected in young patients with a history of recurrent deep vein thrombosis or pulmonary embolism, especially if there is a similar family history. Inheritance is autosomal dominant with incomplete penetrance. Arterial stroke is rare.

Acquired

Cancer and pregnancy, including the postpartum period, are associated with hypercoagulable states that predispose to arterial and venous thrombosis (Chapters 81, 179, and 187). Although a variety of clotting abnormalities may be present, no tests have been devised to detect patients at risk for stroke. No treatments have been proved useful for strokes associated with these conditions.

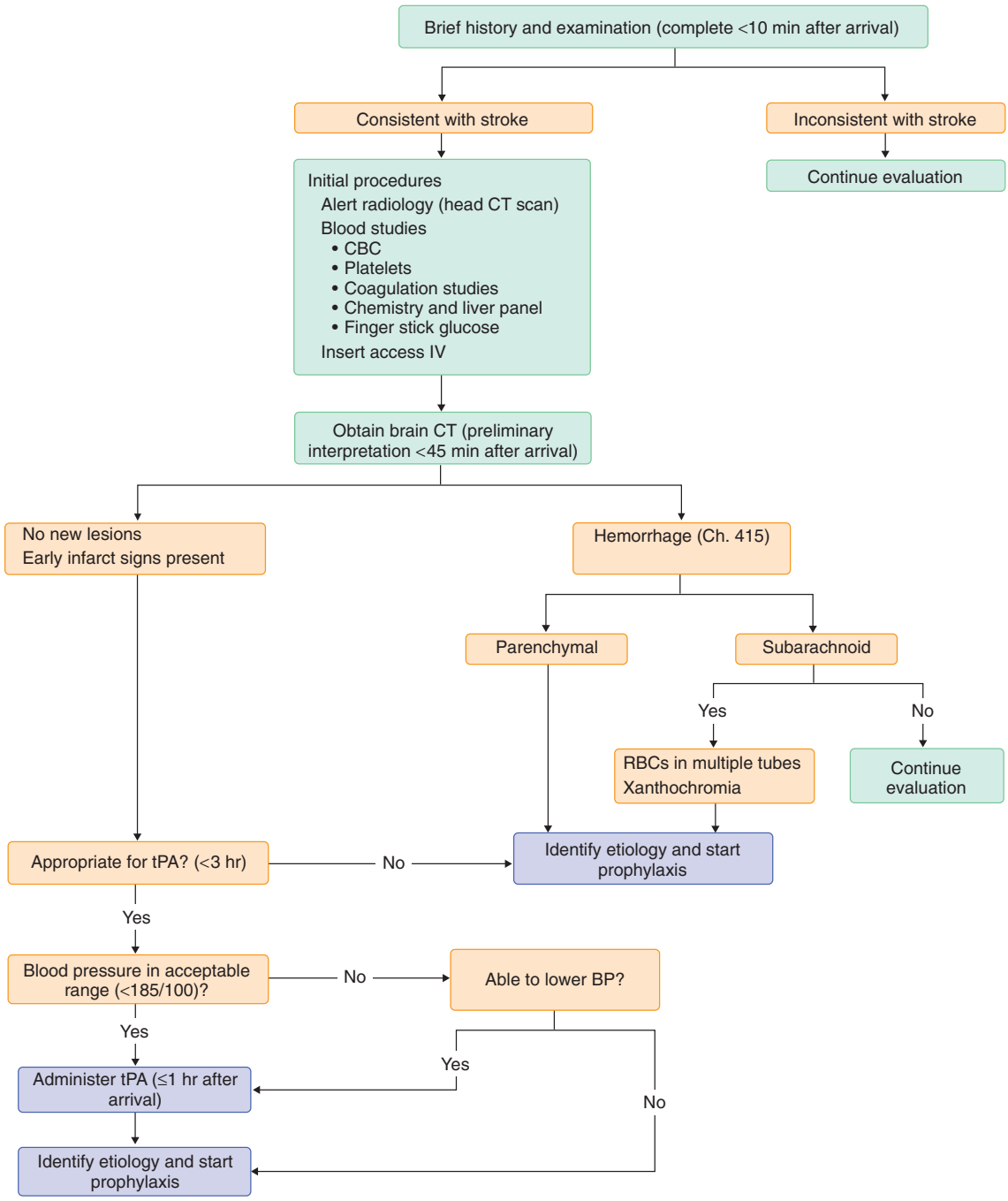


FIGURE 414-4. Algorithm for the emergency evaluation of a patient with suspected stroke. BP = blood pressure; CBC = complete blood count; CT = computed tomography; RBCs = red blood cells; tPA = tissue plasminogen activator.

Antiphospholipid Antibodies

The antiphospholipid antibody syndrome is associated with cerebral arterial and venous infarction, particularly in young adults (Chapter 179). There is no clear relationship between the levels of these antibodies and the risk for stroke. Other laboratory abnormalities include a prolonged activated partial thromboplastin time, biologic false-positive Venereal Disease Research Laboratory results, thrombocytopenia, and a positive antinuclear antibody test. There is an association with atypical migraine, TIA, and ischemic encephalopathy. The reason for the relationship between the antibodies and cerebral thrombosis is unknown.

Drug-Related Causes of Stroke

Numerous legal and illicit drugs have been associated with stroke (Chapter 33). Even the process of drug administration may cause a stroke. Intravenous drug abuse may lead to septicemia and diseases that cause strokes, such as bacterial endocarditis and mycotic aneurysms. Particles of adulterants can be trapped by pulmonary arterioles and cause local arteritis and later arteriovenous shunts that are thought to allow the microemboli to reach the brain. Paradoxical embolization is also possible through structural cardiac defects or arteriovenous malformations.

Some of the drugs that are associated with stroke are potent vasoconstrictors and may initiate cerebral vasospasm. In other instances, cerebral vasculitis is associated with either immune responses to the primary drug or hypersensitivity to contaminating adulterants.

Over-the-counter common cold remedies and nasal decongestants containing sympathomimetic amines, such as ephedrine, phenylpropanolamine, and fenoxazoline, have been associated with ischemic stroke, although hemorrhages are more common (Chapter 415). These drugs are often used in

high doses as appetite suppressants, and case reports suggest that the high doses are especially likely to be related to stroke, often after the first use of these products. Herbs taken as dietary supplements may also include sympathomimetics (e.g., ephedra, also known as *ma huang*) that have been associated with stroke (Chapter 38).

Cervical Artery Dissection

Spontaneous dissection of the cervical or cerebral arteries is produced by subintimal dissection of blood with subsequent longitudinal extension of the intramural hematoma between its layers for various distances. Hemorrhage into the intima can cause luminal stenosis and obstruction, whereas hemorrhage into the media or adventitia produces a pseudoaneurysm that can rupture. Most dissections are spontaneous, but this process is also associated with trauma, including whiplash and other neck-stretching injuries, and chiropractic cervical manipulation. Some cases are associated with fibromuscular dysplasia and others with a variety of inherited conditions, including Ehlers-Danlos and Marfan syndromes (Chapter 268) and tuberous sclerosis (Chapter 426). Recognition of dissection is sometimes difficult, and the physician must probe carefully for recent injuries to the neck. Cerebral angiography can occasionally show a double lumen, although a tapered lumen leading to an obstruction is more common. MRI with attention to vessel cross section may show a crescent-shaped hyperintense mass adjacent to a flow void. Some patients with this condition have been treated by thrombolysis or anticoagulation and surgical repair, but no therapy has been proved to be useful in randomized trials.

Homocystinuria

Homocystinuria (Chapter 216) is associated with a variety of disorders, including dislocated ocular lenses, bone deformities, mental retardation, and accelerated atherosclerosis of large and medium-sized arteries. Strokes commonly occur before 20 years of age. Detection of homocystine in urine is the diagnostic test of choice. Individuals with modest increases in serum homocystine levels may also have an increased risk for stroke. Treatment with a diet low in methionine and supplements of cysteine and pyridoxine (vitamin B_6) can decrease the plasma level of methionine. Folate administration may also be helpful because it is necessary for methylation of homocystine. Vitamin therapy has not been proved to reduce the risk for stroke in patients with homocystinuria, however.

Fat Embolism

Fat embolism (Chapter 98) is mostly a complication of long bone trauma (Chapter 112), intramedullary manipulation during orthopedic procedures, contusions of soft tissues, and severe trauma to large fat deposits. Strokes typically occur several days after the trauma. Clinical features of cerebral embolization depend on the sites within the brain that are affected. Diffuse embolization can produce encephalopathy or seizures, but more discrete lesions can cause focal neurologic deficits. The condition is probably underdiagnosed clinically and at autopsy. Peripheral features that suggest the diagnosis include petechiae and fat emboli visible on ophthalmoscopic examination. Laboratory abnormalities include hypoxemia, anemia, lipuria, and disorders of blood coagulation. The chest radiograph commonly shows bilateral fluffy infiltrates.

Air Embolism

Air embolism can occur with a variety of surgical procedures, particularly cardiac surgery, and as a complication of neurosurgical procedures performed with the patient in the sitting position. Trauma can produce pneumothorax, and air may enter the pulmonary vein and subsequently lodge in the brain. Extended underwater dives and too rapid an ascent can cause the air in the blood to come out of solution and form bubbles that can be pumped into the cerebral circulation (caisson disease). Arterial gas embolism can cause disturbances in cortical function, including seizures and focal deficits. Segmental areas of pallor may be observed on the tongue, marbling of the skin may be seen, and air emboli can be detected on funduscopic examination. When caused by rapid decompression, barotrauma is treated in a decompression chamber.

Moyamoya

Moyamoya disease is a chronic, noninflammatory occlusive vasculopathy of unknown etiology. It is a rare condition that is most common among the Japanese. It has a bimodal age distribution, with peaks in the first and fourth decades. Diagnostic criteria include stenosis or occlusion involving the bifurcation of the ICA and proximal portions of the ACA and MCA, the presence of unusual netlike ("puff of smoke") collateral arteries arising from the circle of Willis, and bilateral occurrence. In adults, the clinical manifestation is usually hemorrhages. Moyamoya is diagnosed by cerebral angiography. No treatment has been proved effective.

Cerebral Venous Sinus Thrombosis

Thrombosis of a cerebral venous sinus may be manifested as headache, focal neurologic deficits, seizures, altered mental status, and papilledema. With obstruction of the superior sagittal sinus, veins draining into the sinus from the superior and medial surfaces of both cerebral convexities are commonly obstructed; in its early stages, the condition can result in bilateral weakness and sensory changes in the legs. The presence of bilateral leg weakness should alert the clinician to the possibility of sinus thrombosis. Seizures occur more often with venous than with arterial occlusion. The most dangerous form of venous disease arises when the superior sagittal sinus is occluded, but obstruction of a transverse sinus or one of the major veins over the cerebral convexity can also produce major damage. These venous occlusions occur most commonly in association with coagulopathies, often in the puerperal period, or in patients with disseminated cancer. The transverse sinus can be occluded as a consequence of inner ear infections, a condition called *otitic hydrocephalus.*

The differential diagnosis of venous obstruction can include an arterial stroke, but the findings more often suggest a diffuse process, such as herpes simplex encephalitis or meningitis. The diagnosis depends on the recognition of impaired venous flow, which can be suspected on routine CT or MRI and confirmed by CT or MR angiography; conventional angiography is rarely needed. Unfractionated dose-adjusted heparin (see Table 81-4 in Chapter 81) and perhaps low-molecular-weight heparin may be safe and effective for cerebral venous sinus thrombosis during the acute phase, even in the presence of hemorrhagic infarction caused by the sinus thrombosis. Oral warfarin anticoagulation is generally continued for 3 to 6 months with the usual target international normalized ratio of 2.0 to 3.0.

Rare Genetic Causes

More than 50 genetic disorders have stroke as at least one of their features, but the prevalence of these abnormalities is low, so strokes produced by monogenetic anomalies are relatively rare. Cerebral autosomal dominant arteriopathy with small subcortical infarcts and leukoencephalopathy (CADASIL) is characterized by recurrent strokes resulting in multiple deep infarcts and dementia, without the usual risk factors for stroke. It has an autosomal dominant pattern of inheritance. The mean age at onset is approximately 40 years, and dementia ensues within 10 to 15 years. Migraine with aura often precedes the strokes by several years. The responsible gene on chromosome 19 results in mutations of the Notch3 receptor protein. As is true of all these genetic causes of stroke, treatment is symptomatic. Antenatal diagnosis is possible in these disorders.

Fabry's disease (angiokeratoma corporis diffusum) (Chapter 215) is an X-linked disease that causes a reduction in α-galactosidase A enzyme activity. Patients have diseases of the skin, eyes, and kidneys as well as frequent neurologic complications that result from either vascular occlusion or, infrequently, intracerebral hemorrhage related to the accumulation of glycolipids in small and medium-sized arteries. The gene encoding this enzyme is located at Xq22. Enzyme replacement therapy is of benefit (Chapter 215).

Neurofibromatosis (Chapter 426) is associated with strokes as a result of occlusion of the internal carotid arteries or the proximal part of the anterior cerebral circulation. Histologically, arterial lesions consist of hyperplasia of the intimal layer with fragmentation and reduplication of the elastic layer. Cerebral aneurysms can also occur. The diagnosis of type I neurofibromatosis is usually based on clinical findings. *DNA-based testing* of the *NF1* gene is available clinically but is infrequently needed for diagnosis.

Marfan syndrome (Chapter 268), which is an autosomal dominant disorder of the fibrillin gene on chromosome 15, affects the skeletal, ocular, cardiovascular, and central nervous systems. Expression is highly variable, and only one system may be involved. Involvement of large arteries, such as the aorta and carotid arteries, is common and may cause death. The most life-threatening problem is dissection of these arteries. Pathologically, the disease results from defective fibrillin, which is an important component of connective tissue.

PREVENTION AND TREATMENT OF STROKE AND TRANSIENT ISCHEMIC ATTACK

Rx

Primary Prevention

Risk factors for stroke fall into two general categories, nonmodifiable and modifiable (Table 414-3). Within the modifiable group are risk factors that are well documented and others that are not. Blood pressure control (Chapter 67) is the most important primary prevention strategy. It is especially important in patients with diabetes, in whom tight control of hypertension with angiotensin-converting enzyme inhibitors substantially reduces the incidence of stroke. Statins are recommended in patients who meet the criteria for treating hyperlipidemia (Chapter 213), in whom they reduce the risk of stroke proportionately to the reductions in the LDL cholesterol levels.[1] Statins also reduce the risk for stroke in patients with an elevated C-reactive protein level even when the LDL level is less than 130 mg/dL.[2] Smoking cessation (Chapter 31) is routinely recommended, but there are no prospective randomized trials to prove that cessation of smoking reduces the risk for stroke. Anticoagulation markedly reduces the risk for stroke in patients with atrial fibrillation (Chapter 64), and blood transfusion is the usual treatment to prevent strokes in patients with sickle cell disease (Chapter 166).

Prophylactic Carotid Interventions

In asymptomatic patients, ipsilateral carotid endarterectomy benefits patients who have a 60% or greater reduction in diameter of the artery without ulceration, provided that the perioperative complication rate is less than 3%,[3] a rate that requires a skilled surgeon. Carotid artery angioplasty and stent placement are not as efficacious as operative endarterectomy, mainly because of their higher risk for stroke.[4]

Secondary Prevention in Patients with Previous Stroke or Transient Ischemic Attack

All the risk factor reductions that are recommended for primary prevention are also recommended in patients who have suffered a previous stroke or TIA and have no contraindication. In addition, specific medical and surgical therapies should be considered.

Medications

Aspirin and other antiplatelet agents reduce the odds of nonfatal stroke by 31% when used in patients with known vascular disease (Chapter 37). All patients who have sustained a stroke and have no contraindication should receive an antiplatelet agent to reduce the risk for recurrent stroke. The optimal dose of aspirin has not yet been established, and doses of 50 to 1300 mg/day have been used. Clopidogrel, 75 mg/day, instead of or in addition to aspirin appears to be no better than aspirin alone[5,6] but is substantially more expensive. The addition of dipyridamole to aspirin can benefit high-risk patients with prior cerebral ischemia.[7,8] Warfarin anticoagulation is not superior to antiplatelet agents in preventing recurrent strokes, except in patients with atrial fibrillation or another cardiac source of emboli, because of its risks for cerebral hemorrhage.[9,10] In patients with previous cerebrovascular disease or high-risk conditions, aggressive cholesterol reduction with 40 mg of simvastatin or 80 mg of atorvastatin reduces the rate of stroke by 25% or more.[11]

Surgery

Carotid endarterectomy reduces the cumulative risk for any ipsilateral stroke at 2 years from 26 to 9% in patients with a 70 to 99% symptomatic (i.e., previous TIA or nondisabling stroke) internal carotid stenosis and from 22 to 16% at 5 years in patients with a 50 to 70% symptomatic stenosis. Patients with less than a 50% symptomatic stenosis do better with medical management alone. In patients with advanced occlusive disease of the carotid arterial system, extracranial-intracranial bypass is no better than medical therapy.[12]

Devices

Carotid artery stents can restore patency to stenotic arteries with an efficacy and safety comparable to that of open endarterectomy in experienced centers. Intra-arterial clots can also be extracted under radiologic guidance with a corkscrew-like device inserted into the common or internal carotid artery for occlusion of the anterior circulation or into the subclavian artery for occlusion of the posterior circulation and then advanced to remove clot located in medium or large intracranial vessels (ICA, MCA, vertebral artery, basilar artery, PCA, or ACA). Using proximal balloon occlusion to arrest flow, the corkscrew device can grab and hold the clot as it is extracted from the patient's artery. Currently, however, outcomes appear to be better with endarterectomy than with stenting, suggesting that stenting should be reserved for selected situations.[13,14]

TABLE 414-3 WELL-DOCUMENTED MODIFIABLE RISK FACTORS FOR STROKE

FACTOR	PREVALENCE (%)	RELATIVE RISK	RISK REDUCTION WITH TREATMENT
Hypertension (by age group)			38%
50 yr	20	4	
60 yr	30	3	
70 yr	40	2	
80 yr	55	1.4	
90 yr	60	1	
Smoking	25	1.8	50% within 1 yr, baseline after 5 yr
Diabetes	20	1.8-6	Reduction of stroke risk in hypertensive diabetics with blood pressure control No demonstrated benefit in stroke reduction with tight glycemic control
Asymptomatic carotid stenosis	2-8	2	50%
Hyperlipidemia			20-30% with statins in patients with known coronary disease
Adults <35 yr	8-9	1.8	
Men >55 yr	25	2.6	
Women >65 yr	40		
Atrial fibrillation (nonvalvular)			68% warfarin 21% aspirin
50-59 yr	0.5	4	
60-69 yr	1.8	2.6	
70-79 yr	4.8	3.3	
80-89 yr	8.8	4.5	

Modified from Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke. *Stroke.* 2001;32:280-299.

PROGNOSIS AND REHABILITATION

Patients who receive care in specialized, acute stroke units are less likely to die, more likely to go home, and more likely to be independent 3 months later. In most clinical trials, about 15% of patients with ischemic stroke die within the first 3 months. Immediate causes of death include herniation because of brain swelling or neurologic dysfunction directly related to the stroke. Deaths that occur days after stroke and are not directly related to neurologic dysfunction are commonly produced by pulmonary embolism or pneumonia. Most large population studies report that about 20% of patients who survive a stroke require long-term institutionalization and that 33 to 50% of the others are left with substantial disability. Stroke is the most common cause of adult disability in the United States. Most functional recovery takes place during the first month, but some continued slow improvement is possible for 1 year. The most common long-term cause of death in patients with stroke is myocardial infarction.

Grade A

1. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:549-556.
2. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;359:1317-1329.
3. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet.* 2010;375:1695-1703.
4. Schwamm LH, Holloway RG, Amarenco P, et al. A review of the evidence for the use of telemedicine within stroke systems of care: a scientific statement from the American Heart Association/American Stroke Association. *Stroke.* 2009;40:2616-2634.
5. Dennis M, Sandercock PA, Reid J, et al, for the CLOTS Trials Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet.* 2009;373:1958-1965.
6. De Caterina R, Scarano M, Marfisi R, et al. Cholesterol-lowering interventions and stroke: insights from a meta-analysis of randomized controlled trials. *J Am Coll Cardiol.* 2010;55:198-211.
7. Everett BM, Glynn RJ, MacFadyen JG, et al. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein. Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Circulation.* 2010;121:143-150.

8. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491-1502.
9. Murad MH, Shahrour A, Shah ND, et al. A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs stenting. *J Vasc Surg*. 2011;53:792-797.
10. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706-1717.
11. The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367:1665-1673.
12. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005;352:1305-1316.
13. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549-559.
14. Fluri F, Engelter S, Lyrer P. Extracranial-intracranial arterial bypass surgery for occlusive carotid artery disease. *Cochrane Database Syst Rev*. 2010;2:CD005953.
15. International Carotid Stenting Study investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375:985-997.

SUGGESTED READINGS

Gorelick PB, Ruland S. Cerebral vascular disease. *Dis Mon*. 2010;56:39-100. *Detailed review*.

Ifejika-Jones NL, Harun N, Mohammed-Rajput NA, et al. Thrombolysis with intravenous tissue plasminogen activator predicts a favorable discharge disposition in patients with acute ischemic stroke. *Stroke*. 2011;42:700-704. *Patients who receive intravenous recombinant tissue plasminogen activator are more likely to be discharged directly home*.

O'Kelly CJ, Butcher KS, Marchak BE, et al. Carotid revascularization: an update. *Can J Neurol Sci*. 2010;37:320-335. *Review of indications, methods, and timing of interventions*.

Xian Y, Holloway RG, Chan PS, et al. Association between stroke center hospitalization for acute ischemic stroke and mortality. *JAMA*. 2011;305:373-380. *Admission to a designated stroke center is associated with modestly lower mortality and more frequent use of thrombolytic therapy*.

415

HEMORRHAGIC CEREBROVASCULAR DISEASE

JUSTIN A. ZIVIN

Approximately 15% of all strokes are due to intracranial hemorrhage. Hemorrhagic stroke can be diffuse (i.e., bleeding into the subarachnoid or intraventricular spaces) or focal (i.e., intraparenchymal hemorrhage). About two thirds of intracranial bleeding cases are predominantly subarachnoid hemorrhages, whereas about one third are intracerebral hemorrhages. Subarachnoid hemorrhage is usually caused by rupture of vessels on or near the surface of the brain or ventricles (e.g., aneurysms, vascular malformations), with bleeding mainly into the cerebrospinal fluid (CSF) spaces. Intracerebral hemorrhage is most frequently caused by the rupture of arteries that are within the brain substance (e.g., hypertensive hemorrhage, vascular malformations) but do not extend to the CSF spaces. Both types of hemorrhagic stroke have high mortality rates, depending on subtype and location. Prevention is the mainstay of management because there are no sufficiently efficacious therapies for hemorrhage-induced cerebral injury.

SUBARACHNOID HEMORRHAGE

EPIDEMIOLOGY

In the United States, about 30,000 new cases of subarachnoid hemorrhage occur each year and predominantly involve young adults. Both genders are equally affected, and the rate may be twice as high in African Americans as in whites. Rupture of aneurysms is by far the most common cause of nontraumatic subarachnoid hemorrhage. Advances in diagnostic imaging have improved the detection of intracranial aneurysms, but most cases are not discovered until after rupture.

Risk factors include cigarette smoking, binge drinking, illicit drugs, phenylpropanolamine, and other sympathomimetic agents. Although hypertension is well established as a risk factor for ischemic stroke, the relationship of nonmalignant hypertension to subarachnoid hemorrhage is less well documented; the decline in hypertension in the general population has not been accompanied by a decrease in the incidence rate of subarachnoid hemorrhage.

PATHOBIOLOGY

The principal causes of subarachnoid hemorrhage are aneurysms and arteriovenous malformations (AVMs), but trauma can also cause subarachnoid bleeding (Chapter 406). Rare causes of subarachnoid hemorrhage include vasculitis, central nervous system neoplasms (Chapter 195), and hematologic disorders such as hemophilia, disseminated intravascular coagulopathy, and thrombocytopenic purpura.

CLINICAL MANIFESTATIONS

The classic symptom of a subarachnoid hemorrhage is a very rapidly developing, severe headache, typically called the "worst headache of my life," that is sometimes accompanied by a stiff neck. Aneurysms may generate prodromal signs and symptoms as they gradually expand or cause sentinel (warning) leaks that produce focal or generalized head pain. Such sentinel headaches are frequently severe, and they may be accompanied by nausea or vomiting and may cause meningeal irritation.

Arterial blood pressure is often elevated, and body temperature usually increases, particularly during the first few days after bleeding as subarachnoid blood products produce chemical meningitis. Transient alterations in mental status occur in nearly half the patients, particularly if intracranial pressure exceeds cerebral mean arterial pressure. Patients can remain in coma for several days, depending on the location of the aneurysm and the amount of bleeding.

Acute subarachnoid hemorrhage causes meningeal irritation; nuchal rigidity and photophobia can require several hours to develop. Ophthalmoscopic observation reveals well-circumscribed, bright red, preretinal hemorrhages, known as subhyaloid hemorrhages and thought to be a result of increased intracranial pressure, raised retinal venous pressure, and dissection of blood along the optic nerve sheath. Focal neurologic dysfunction is not usually a prominent feature unless an aneurysm compresses surrounding brain structures, a jet of blood dissects directly into a clinically eloquent brain region, or vasospasm subsequently develops.

DIAGNOSIS

Laboratory Findings

A complete blood cell count, including platelets, should be obtained, and clotting times should be determined to assess whether the patient has an infection or clotting abnormalities. Blood should also be sent for electrolyte analysis to serve as a baseline for detecting later complications.

Imaging

The patient should then be sent immediately for emergency computed tomography (CT). A scan performed within 24 hours of onset generally reveals an area of high signal attenuation consistent with hemorrhage; if blood is present in the subarachnoid space, it is seen within the basal cisterns in more than 90% of patients. By 48 hours after onset, the sensitivity of CT declines to about 75%. Conventional magnetic resonance imaging (MRI) sequences (T1- or T2-weighted scans) are less sensitive than CT scans.

The location of subarachnoid hemorrhage by CT suggests the source of bleeding. High signal attenuation in the basal cisterns, sylvian fissure, or interhemispheric fissure often indicates rupture of a saccular aneurysm, whereas higher concentrations of blood over the convexities or within the superficial parenchyma of the brain are more consistent with rupture of an AVM or a mycotic aneurysm. A large amount of blood in the subarachnoid space increases the likelihood of subsequent vasospasm. A contrast-enhanced CT scan may aid in the identification of an AVM and some large aneurysms.

An electrocardiogram should be performed to detect peaked or inverted T waves and increased U waves. These abnormalities and subsequent arrhythmias have been attributed to multifocal myocardial necrosis caused by elevated levels of circulating catecholamines.

If the CT findings are normal but the index of suspicion remains high for subarachnoid hemorrhage, a lumbar puncture is usually diagnostic. A traumatic lumbar puncture (i.e., penetration of the needle into a small blood vessel of the venous plexus on the anterior wall of the spinal canal) produces a declining number of red blood cells in subsequent tubes, whereas subarachnoid hemorrhage produces a relatively constant number of red blood cells in each tube. In the presence of bloody fluid, one of the CSF samples should be centrifuged immediately and the supernate examined for the presence of hematin or xanthochromia by visual inspection. Red blood cells in CSF begin to lyse within a few hours, and the centrifuged supernate then appears pink. Later (about 10 hours), as the hemoglobin is converted to bilirubin, the fluid

becomes slightly yellow. Opening CSF pressure is generally elevated and may remain so for many days. CSF samples obtained within the first day may show a white blood cell count consistent with the normal circulating white cell–to–red cell ratio (about 1:1000). Chemical meningitis is produced by the presence of blood or breakdown products within the subarachnoid space, and CSF samples contain increased numbers of polymorphonuclear and mononuclear cells relative to red blood cells. The CSF glucose concentration is usually normal shortly after the onset of bleeding, but as chemical meningitis develops, the glucose level may decline, rarely to less than 40 mg/dL. After a subarachnoid hemorrhage, the protein content of CSF is generally elevated, consistent with contamination by blood (the usual ratio is 1 mg/dL of protein for every 1000 red blood cells).

Cerebral angiography remains the definitive study to identify the source of subarachnoid hemorrhage. When the diagnosis of aneurysmal subarachnoid hemorrhage seems highly probable, the timing and need for a cerebral angiogram should be determined by surgical considerations. If doubt exists, angiography should be performed with minimal delay. Because many patients have multiple cerebral aneurysms, the carotid and vertebral artery systems should be examined angiographically. The initial cerebral angiogram fails to detect the source of bleeding in about 20% of patients; such patients are thought to have a fairly good prognosis, with only a 1 to 2% annual risk for recurrent hemorrhage. Failure to detect the bleeding source can be due to obliteration of the aneurysm because of clot or may be due to the small size of the ruptured aneurysm. A superficial venous angioma, a spinal cord aneurysm, or a spinal AVM also will not be seen on a cerebral angiogram. The presence of back pain or neurologic signs localized to the spinal cord at onset should prompt a search for a spinal source of hemorrhage. If the initial angiogram is negative and no other clues to the bleeding site can be found, repeat cerebral angiography is usually performed within a few weeks; MRI or CT with and without contrast may also be helpful.

TREATMENT

Treatment of Complications

If a patient does not die immediately after a subarachnoid hemorrhage, a number of neurologic complications can occur. Some result from blood in the subarachnoid space, and other concerns include rebleeding from the same aneurysm, cerebral vasospasm and its ischemic consequences, hydrocephalus caused by blockage of CSF outflow pathways, and seizures. Non-neurologic complications include cardiac and electrolyte abnormalities.

Rebleeding

If an aneurysm is not repaired promptly, it can rupture again. A new headache or neurologic worsening suggests repeat rupture, which can be diagnosed only if a repeat CT scan or lumbar puncture shows the presence of new blood in the subarachnoid space. Approximately 30% of patients with aneurysmal subarachnoid hemorrhage rebleed during the first month, and the incidence is highest during the first 2 weeks after the initial episode. Patients with unrepaired aneurysms who survive their initial bleeding for more than 1 month have a 2 to 3% annual risk for rebleeding. Infusion of factor VII can reduce the growth of the hemorrhage but does not improve outcomes.■

Vasospasm

A common cause of death and disability in patients with aneurysmal subarachnoid hemorrhage is cerebral vasospasm. The vessels at the base of the brain become narrowed, thereby reducing blood flow; if the vasospasm is severe, it can produce infarction of the brain distal to the site of the spasm. The vessels that go into spasm are often different from the artery that was responsible for the initial bleeding. Vasospasm has been reported in up to 75% of patients after subarachnoid hemorrhage, and delayed neurologic deficits develop in as many as 30% of patients with vasospasm. The onset of vasospasm is typically between days 3 and 14 after bleeding, but this complication can develop as late as 3 weeks after subarachnoid hemorrhage. The arteries of the circle of Willis and their major branches are the usual initial site of spasm, with more distal arteries becoming involved later. The amount and location of blood detected within the basal cisterns on CT correlate with the incidence and location of vasospasm. The pathogenesis of cerebral vasospasm is unknown.

Cerebral angiography, which is the best established method to diagnose vasospasm, shows narrowing of the dye column. However, other methods such as transcranial Doppler ultrasonography and magnetic resonance angiography are increasingly being used. Transcranial Doppler has high specificity, but its sensitivity is not as good as that of angiography.

Hydrocephalus

Acute hydrocephalus occurs in up to two thirds of patients within 3 days after subarachnoid hemorrhage. Hydrocephalus is caused by obstruction of CSF outflow pathways at the level of the fourth ventricle and the pacchionian granulations lining the venous sinuses. Increasing age, a history of hypertension, intraventricular hemorrhage, focal neurologic findings, a decreased level of consciousness, and hyponatremia are associated with risk for the development of hydrocephalus. Chronic ventricular enlargement occurs in as many as 60% of patients within 1 month after subarachnoid hemorrhage and is often asymptomatic. Several forms of treatment have been advocated for the management of hydrocephalus, including repeated lumbar puncture and shunt placement, but their value has not been proved.

Seizures

Seizures may occur shortly after subarachnoid hemorrhage in 15 to 90% of patients. Seizures are thought to be caused by cortical damage from bleeding into the neocortex or from ischemic necrosis related to vasospasm. The development of persistent epilepsy is unusual. Prophylactic anticonvulsant therapy has not been useful.

Non-neurologic Complications

Cardiac complications occur as a consequence of subarachnoid hemorrhage. In the acute phases of subarachnoid hemorrhage, electrocardiographic patterns can mimic acute myocardial infarction (Chapter 73). A pattern of deep inverted T waves across the pericardium is classic. Appropriate biomarker assays and repeat electrocardiograms are needed to document true myocardial damage.

Hyponatremia (Chapter 118) is the most common electrolyte abnormality after subarachnoid hemorrhage. Sodium loss, which is typically mild, may occur in up to 25% of patients. The natriuresis has been attributed to inappropriate levels of antidiuretic hormone (Chapter 232), but this hypothesis has not been proved. Hyponatremia can itself result in a decreased level of consciousness and seizures, but it is often impossible to distinguish the effects of hyponatremia from the other possible causes of these neurologic abnormalities.

SPECIFIC CAUSES AND THEIR TREATMENT AND PROGNOSIS

Saccular Aneurysms

DEFINITION AND EPIDEMIOLOGY

Saccular or "berry" aneurysms, which account for 80 to 90% of all intracranial aneurysms, are thin-walled outpouchings that protrude from the arteries of the circle of Willis or its major branches; 85% are located at branching points (Fig. 415-1). Because of the local weakness and degeneration of the media, the intima bulges outward and is covered only by the adventitia. A saccular aneurysm may be an incidental finding on a scan or may be detected at autopsy in patients who die of other diseases; in symptomatic cases, however, the sack gradually enlarges and ultimately ruptures.

Saccular aneurysms are rarely detected in children, and the incidence of subarachnoid hemorrhage increases with age; therefore, it seems clear that congenital wall defects develop into aneurysms only after some time. Congenital defects in the muscle and elastic tissue of the arterial media are observed at autopsy in up to 80% of normal vessels of the circle of Willis. It is postulated that these defects gradually degenerate over time as they are exposed to pulsatile arterial blood pressure. Multiple aneurysms are found in about 15% of people with at least one aneurysm. Because the incidence of aneurysmal subarachnoid hemorrhage is approximately 1 in 10,000, it is evident that most saccular aneurysms do not rupture.

PATHOBIOLOGY

Approximately 10 to 20% of patients with known aneurysms have a family history. Diseases that are associated with intracranial saccular aneurysms include polycystic kidney disease (Chapter 129), Marfan and Ehlers-Danlos syndromes (Chapter 268), fibromuscular dysplasia (Chapter 78), pseudoxanthoma elasticum (Chapter 268), systemic lupus erythematosus (Chapter 274), and sickle cell anemia (Chapter 166). Screening of other family members is often recommended when two or more members of a family have aneurysms.

TREATMENT

Primary Prevention of Bleeding

Because the natural history of aneurysms may be highly variable and the risk-to-benefit ratio for the various invasive techniques is unknown, expectant waiting may sometimes be the best option. However, an aneurysm may rupture without warning, and the uncertainty is unacceptable to some

patients and physicians. Medical therapies may delay the time of rupture but cannot repair the lesion.

Treatment of Aneurysms that Have Bled

Medical Treatment

Medical management of a ruptured aneurysm aims to reduce the risk for rebleeding and cerebral vasospasm and prevent other medical complications before and after surgical intervention. The only form of medical therapy that has been useful in treating subarachnoid hemorrhage patients is the voltage-regulated calcium-channel antagonist nimodipine. Although it does not reduce the frequency of vasospasm, nimodipine (60 mg orally every 4 hours for 21 days) lowers the incidence of cerebral infarction by about one third.

General support consisting of bed rest, analgesics for headache, and gentle sedation as needed is provided to quiet the patient. Stool softeners can minimize straining. Hypertension should be treated appropriately but not aggressively (Chapter 67) because elevated blood pressure may represent a normal compensatory mechanism, particularly in a chronically hypertensive patient, and excessive reduction may cause extension of the infarct. There is no conclusive evidence that modification of blood pressure in patients with acute subarachnoid hemorrhage is of benefit. Antifibrinolytic drugs, including tranexamic acid and ε-aminocaproic acid, may reduce rebleeding, but any such benefit is outweighed by an increased incidence of infarction.

Interventional Therapies

The objectives of interventional procedures are to exclude the aneurysm from the circulation or relieve pressure on adjacent brain tissue caused by expansion of the sack. The optimal timing of these therapies is uncertain, but many surgeons recommend treatment as soon as possible after the subarachnoid hemorrhage.

An electrical current applied to a detachable coil threaded into an aneurysm by means of percutaneous angiography causes the surrounding blood to clot. The coil is detached and left in place, and the catheter is then removed. This approach is more effective than surgical clipping for achieving disability-free survival in patients who have had ruptured aneurysms.■ With very large aneurysms, for which use of a coil is not possible, wrapping the sack with various types of material to prevent it from rupturing or growing is sometimes performed. Indirect procedures include various methods of occluding the feeding artery; if there is sufficient collateral supply, the risk for infarction may be less than that of spontaneous rupture of the aneurysm with subsequent extensive subarachnoid hemorrhage.

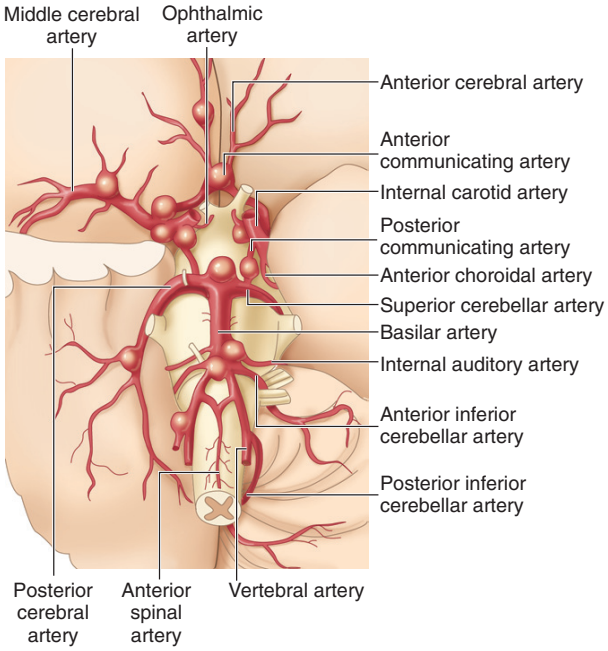


FIGURE 415-1. Saccular aneurysms. Saccular or berry aneurysms typically develop at the bifurcations of arteries on the undersurface of the brain.

PROGNOSIS

Mortality and morbidity rates differ among studies. About 12% of subarachnoid hemorrhage victims die before reaching medical attention. By 30 days, approximately 50% die, but 30-day survivors generally survive for at least a year. An equally high mortality rate accompanies each episode of rebleeding. Approximately 25% of survivors have persistent neurologic deficits.

Fusiform Aneurysms

Fusiform aneurysms are so named because they are elongated dilations (i.e., ectasia) of large arteries associated with atherosclerosis. These aneurysms typically develop in the basilar artery but also may affect the internal, middle, and anterior cerebral arteries of individuals with widespread arteriosclerosis and hypertension. These aneurysms may progressively dilate and become tortuous, thereby producing neurologic dysfunction, most frequently by compressing surrounding structures. Thrombi may form in them and embolize distally to cause ischemic strokes. Typically, ectatic aneurysms of the basilar artery compress cranial nerves and cause facial pain (V), hemifacial spasm (VII), and hearing loss with vertigo (VIII). Fusiform aneurysms may mimic pituitary and suprasellar mass lesions or cerebellopontine angle tumors. Fusiform aneurysms rarely rupture; if they do, they are difficult to treat surgically because their shape and stiff walls generally preclude easy surgical clipping, and total occlusion is usually required.

Mycotic Aneurysms

Infected emboli, usually originating on an infected heart valve (Chapter 76), may lodge in a distal branch of a cerebral artery and cause small areas of infarction or microabscesses. In arteries that do not rupture immediately, focal arteritis and mycotic aneurysms, also known as septic aneurysms, may develop. Mycotic aneurysms are frequently multiple and can be found distally in the cerebral arteries. Rates of rupture of these aneurysms may be as high as 10%. Such lesions may be detected by noninvasive imaging studies, but the definitive test is contrast-enhanced angiography, for which the indications are controversial. Aside from treatment of the underlying infection, other treatments are not established.

Vascular Malformations

EPIDEMIOLOGY

About 1% of all strokes and 10% of intracerebral hemorrhages are caused by vascular malformations. The prevalence of AVM is approximately 0.5%, and the annual incidence of hemorrhage is between 1 and 3 cases per 100,000 people. Familial cases occur but are rare.

PATHOBIOLOGY

Conventional classifications of cerebrovascular malformations are based on the histologic appearance of the vessels and the intervening neural parenchyma. The most frequent type of vascular malformation is an AVM, which has a core of dysplastic vessels (i.e., nidus), feeding arteries, and draining veins. In the nidus, arteries connect directly to veins without intervening capillaries to produce a low-resistance, high-flow shunt that ultimately dilates feeding arteries and thickens the walls of the draining veins. The classic arteriographic appearance includes an early draining vein. Ordinarily, there is no intervening neural tissue in the nidus. The nidus is the usual site of hemorrhage in an AVM.

The next most common lesions are cavernous malformations (i.e., cavernous angiomas or hemangiomas), which are composed of small-caliber sinusoidal vascular channels that are commonly thrombosed. The low flow rate through these vessels makes them difficult to detect by angiography, and they are unlikely to hemorrhage; these malformations also do not contain neural tissue. Cavernous AVMs are often associated with venous malformations, which are composed of small veins separated by normal parenchyma. Smaller venous channels drain into a dilated venous trunk that ultimately drains into a large vein and sinus in the brain. The classic angiographic appearance is a caput medusae in the late venous phase. These anomalies are readily detected by CT, but they rarely hemorrhage.

A cerebral varix is a single dilated vein that seldom causes clinical symptoms. Telangiectasis, also called capillary malformation, is a cluster of enlarged capillaries surrounded by normal parenchyma. These lesions are too small to be detected by conventional imaging methods and are usually noted as petechiae that are found incidentally at autopsy; these benign lesions rarely hemorrhage.

CLINICAL MANIFESTATIONS

Although increasing numbers of probably asymptomatic vascular malformations are being diagnosed by brain imaging as part of the evaluation of nonspecific headaches, about 50% of AVMs are manifested as intracranial

hemorrhage, a lower proportion initially present as seizures, and the remainder cause progressive neurologic disability as the first symptom. Hemorrhage, which is the most feared complication of an AVM, has an associated mortality rate of 10 to 15%. The mortality and morbidity rates associated with AVMs are somewhat less than for aneurysms. The initial hemorrhage tends to occur during the second through fourth decades, and hypertension before the hemorrhage is uncommon. The risk for acute rebleeding averages approximately 6 to 7%. In the next 5 years, the rate is about 2% per year, and it is 1 to 2% per year thereafter. If this rebleeding rate is maintained for life, a young individual who has a hemorrhagic AVM faces a 50 to 60% chance of an incapacitating or fatal subsequent hemorrhage during a normal lifespan.

AVMs can bleed into the subarachnoid space, the brain parenchyma, or the ventricular system. Focal neurologic abnormalities depend on the severity of the bleeding and the location of brain parenchyma that has been affected. The frequency of cerebral vasospasm after hemorrhage from an AVM is less than that for aneurysmal bleeding.

Approximately 30% of patients who have an AVM are initially evaluated for seizures, which often have a focal onset. Focal neurologic deficits independent of seizures can develop, possibly caused by vascular thrombosis and perhaps by shunting of blood through arteriovenous fistulas away from normal brain tissue.

DIAGNOSIS

If a hemorrhage has occurred, unenhanced CT scanning may show evidence of bleeding in an unusual location for primary intracerebral hemorrhage or a ruptured aneurysm. Contrast-enhanced CT scans may demonstrate marked enhancement of the feeding arteries and draining veins. MRI with signal void on T1- or T2-weighted images can also establish the diagnosis. Angiography remains the definitive test to identify the AVM and delineate its size, gross morphology, feeding arteries, and draining veins. Because AVMs are occasionally multiple and may be associated with saccular aneurysms, four-vessel angiography is indicated even if an AVM is found by unilateral carotid injection. Extracranial or contralateral arteries occasionally supply intracranial AVMs and should be considered in the angiographic evaluation.

TREATMENT

Rx

There is uncertainty regarding the prognosis of unruptured AVMs as a result of their various locations, sizes, and morphology. Because the safety and efficacy of the various procedures for treating AVMs have not been established, there are no guiding therapeutic principles.

Conservative treatment is often recommended for unruptured AVMs manifested as seizures or headache, especially in patients older than 55 to 60 years. This approach emphasizes control of hypertension, avoidance of anticoagulants, and use of anticonvulsants to control seizures.

If an AVM has ruptured and the patient has recovered from the initial hemorrhage, the two goals of interventional therapy are to remove the AVM completely and to avoid deterioration of neurologic dysfunction. Removal can be curative, but it is important to eliminate residual abnormal vessels, which may produce hemorrhages, especially if reduction of outflow increases perfusion pressure within the remaining anomalous vasculature. However, it is particularly dangerous to perform these procedures in critical neurologic areas, such as in or near the speech centers.

Therapeutic options include surgical resection of the AVM, embolization of the feeding arteries, and radiation-induced thrombosis. In some cases, combinations of these treatments are used. Selective embolization of the lesion through the transfemoral angiographic approach is commonly the initial procedure, with the goal of reducing blood flow through the AVM. Embolization may be performed in stages to reduce the size of the lesion sequentially, but endovascular treatment seldom obliterates an AVM. A risk for embolization is that embolic material may escape from the AVM and occlude normal vessels.

Stereotactic radiosurgery can eliminate an AVM but is satisfactory only for small lesions. The therapeutic effect of this technique is delayed because the abnormal vessels shrink gradually after the procedure.

Direct surgical intervention involves the use of microsurgical techniques. If the AVM is large, the procedures are often performed in stages to reduce blood flow in an adjacent region and make subsequent surgery easier. Surgery is considered successful if the postoperative angiogram shows no residual AVM. However, long-term occlusion rates are unknown, and recanalization with recurrent hemorrhage is possible.

TABLE 415-1 CAUSES, MEANS OF DIAGNOSIS, AND CHARACTERISTICS OF INTRACEREBRAL HEMORRHAGES

CAUSES	PRIMARY MEANS OF DIAGNOSIS	CHARACTERISTICS
Hypertension	Clinical history	Rupture of small arterioles related to degenerative changes induced by uncontrolled hypertension
Amyloid angiopathy	Clinical history	Rupture of small and medium-sized arteries with deposition of β-amyloid protein; manifested as lobar hemorrhages in people older than 70 years
Arteriovenous malformation	MRI or angiogram	Rupture of abnormal small vessels connecting arteries and veins
Intracranial aneurysm	MRI or angiogram	Rupture of a saccular dilation from a medium-sized artery; usually associated with subarachnoid hemorrhage
Cavernous angioma	MRI or angiogram	Rupture of abnormal capillary-like vessels with intermingled connective tissue
Venous angioma	MRI or angiogram	Rupture of an abnormal dilation of venules
Venous sinus thrombosis	MRI or angiogram	Result of hemorrhagic venous infarction
Intracranial neoplasm	MRI or angiogram	Result of necrosis and bleeding within hypervascular neoplasms
Coagulopathy	Clinical history	Most commonly associated with the use of anticoagulants or thrombolytics
Vasculitis	Serologic and cerebrospinal fluid markers, brain biopsy	Rupture of small or medium-sized arteries with inflammation and degeneration
Cocaine or alcohol abuse	Clinical history	Underlying vascular abnormalities may be present
Hemorrhagic transformation	CT	Hemorrhage in the region of cerebral infarction as a result of ischemic damage to the blood-brain barrier

CT = computed tomography; MRI = magnetic resonance imaging.
Modified from Qureshi AI, Tuhrim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. *N Engl J Med.* 2001;344:1450-1460.

PRIMARY INTRACEREBRAL HEMORRHAGE

DEFINITION

Primary nontraumatic intracerebral hemorrhage (i.e., hemorrhage that does not result from ischemic injury) occurs predominantly as a consequence of chronic, poorly controlled hypertension (Chapter 67). Less frequently, a ruptured vascular malformation or amyloid angiopathy is responsible. Intracerebral hemorrhage can also be caused by a bleeding diathesis and certain drugs of abuse (Table 415-1).

EPIDEMIOLOGY

In the United States, primary intracerebral hemorrhage is responsible for 10 to 15% of strokes and about 80% of all intracranial hemorrhages. The average annual incidence in the United States is approximately 50,000. Intracerebral hemorrhage has the highest mortality rate of all subtypes of stroke, and almost 60% of affected patients die within the first year. The risk for primary intracerebral hemorrhage in blacks is about 40% higher than in whites. Worldwide, the incidence of intracerebral hemorrhage ranges from 10 to 40 per 1 million people, with the rate in Japan being at the top end of this range. Age-adjusted rates for men are about 50% higher than those for women. As with ischemic stroke, the incidence appears to be declining in the industrialized world, concurrent with the decline in hypertension.

PATHOBIOLOGY

Primary intracerebral hemorrhage typically consists of a large, confluent area of blood that clots (Fig. 415-2). Most bleeding occurs at or near bifurcations

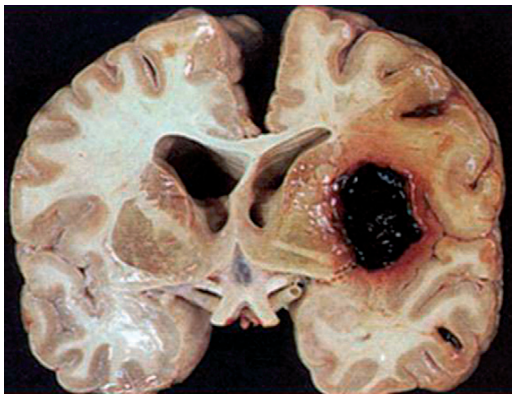


FIGURE 415-2. Pathology specimen showing a large basal ganglia parenchymal hemorrhage in the left hemisphere. (Courtesy of Gregory W. Albers, Stanford University, Stanford, Calif.)

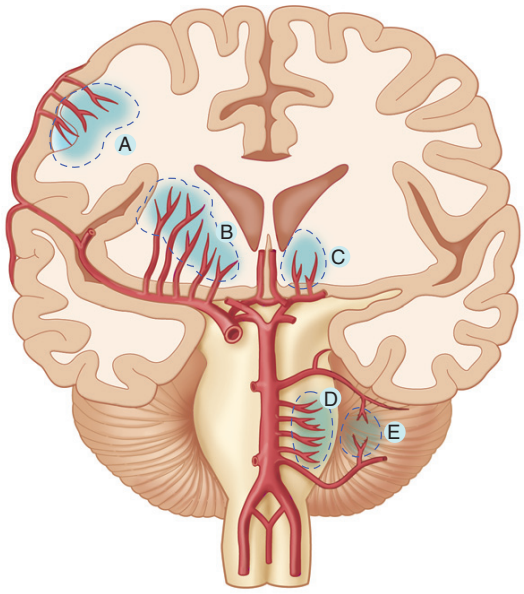


FIGURE 415-3. Typical sites and sources of intracerebral hemorrhage. Intracerebral hemorrhages most commonly involve the cerebral lobes and originate from penetrating cortical branches of the anterior, middle, or posterior cerebral arteries (A); the basal ganglia and originate from ascending lenticulostriate branches of the middle cerebral artery (B); the thalamus and originate from ascending thalamogeniculate branches of the posterior cerebral artery (C); the pons and originate from paramedian branches of the basilar artery (D); and the cerebellum and originate from penetrating branches of the posterior inferior, anterior inferior, or superior cerebellar arteries (E). (From Qureshi AI, Tuhrim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. *N Engl J Med.* 2001;344:1450-1460.)

of arteries with prominent degeneration of the media and smooth muscle. Several weeks later, the blood is slowly removed by phagocytosis, and after several months, only a small, collapsed cavity lined by hemosiderin-containing macrophages may remain. Rupture into the ventricles with bleeding into the subarachnoid space commonly occurs with large hemorrhages. Edematous parenchyma rapidly develops around the clot. Although hemorrhage may destroy brain tissue locally, histologic examination suggests that displacement of normal brain tissue and dissection of blood along fiber tracts account for much of the pathology. Viable and salvageable neural tissue may exist in the vicinity of the hematoma.

The most important risk factor for intracerebral hemorrhage is hypertension, particularly in people who are younger than 55 years, smokers, and poorly compliant with antihypertensive medications. Excessive chronic alcohol consumption also increases the risk for intracerebral hemorrhage. A less well established risk factor is a low serum cholesterol concentration (<160 mg/dL).

Hypertension is associated with hemorrhage in various locations throughout the brain, especially in the external capsule–putamen, internal capsule–thalamus, central pons, and cerebellum (Fig. 415-3). A smaller number of hemorrhages occur in the subcortical white matter, especially in the frontal, temporal, and occipital lobes.

Evidence, especially from serial CT scans, shows that hematomas expand for many hours after the onset of bleeding in many patients. Bleeding may cease when the lesion grows to a size sufficient to produce increased tissue pressure with consequent tamponade.

Amyloid (congophilic) angiopathy is a pathologic diagnosis that is more frequently made in people older than 55 years. This condition, which is unrelated to generalized amyloidosis and is occasionally hereditary, commonly produces multiple, small hemorrhages. It often appears in the brains of patients with Alzheimer's disease (Chapter 409) and has been associated with nonhypertensive hemorrhage in unusual lobar locations in the cerebral hemispheres. Amyloid deposits, chemically similar to those in Alzheimer's plaques, are seen in the media and adventitia of small and medium-sized arteries.

Anticoagulation, thrombolysis, and various hematologic abnormalities (Chapters 175 to178) are associated with intracerebral hemorrhages. Warfarin anticoagulation to conventional intensities (i.e., international normalized ratio of 2.0 to 3.0) has been associated with a risk for intracranial hemorrhage of approximately 1% per year in many stroke-prone patients (Chapter 37). This rate is about 7 to 10 times greater than the risk in similar patients who have not undergone anticoagulation. On average, when such hemorrhages occur, the fatality rate is about 60%. Predictors are advanced age, previous ischemic stroke, hypertension, and the intensity of anticoagulation.

The most feared complication of thrombolytic therapy for acute myocardial infarction (Chapter 73) or ischemic stroke (Chapter 414) is intracerebral hemorrhage. When tissue plasminogen activator (t-PA) is administered within 3 hours after the onset of stroke symptoms, the intracerebral hemorrhage rate is 6.5%, compared with 0.5% in placebo patients; 50% of the patients who sustain these hemorrhages die. However, the overall benefit of t-PA therapy in appropriate patients persists because the increased risk for hemorrhage is more than counterbalanced by the improvement in ischemic strokes (Chapter 414).

Cerebral hemorrhages also occur in patients with leukemia (Chapter 189), polycythemia vera (Chapter 169), thrombocytopenia (Chapter 175), hemophilia (Chapter 177) and other clotting abnormalities, infectious and noninfectious vasculitis, intracranial neoplasms, and venous thrombosis. In addition, intracerebral hemorrhage can occur in patients who abuse various sympathomimetic agents and cocaine (Chapter 33).

CLINICAL MANIFESTATIONS

Neck stiffness, seizures, diastolic blood pressure higher than 110 mm Hg, vomiting, and headache increase the likelihood of a hemorrhagic stroke rather than an ischemic stroke. Otherwise, however, the neurologic abnormalities caused by intracerebral hemorrhage do not differ from those caused by ischemic strokes (Chapter 414) because destruction of neural tissue is the basis of the neurologic dysfunction caused by both entities. The signs and symptoms are related to the location of the lesion. Because the site of intracerebral hemorrhage often differs from that of ischemic strokes, characteristic patterns of neurologic loss may be more frequently associated with intracerebral hemorrhage than with ischemic strokes (Table 415-2). Hemorrhages may grow as the bleeding continues, whereas ischemic lesions usually do not change in size after vascular occlusion; as a result, hemorrhages characteristically cause progressively increasing loss of neurologic function until a plateau is reached, whereas ischemic strokes may fluctuate or remain static after the early phases of the stroke. Subsequent deterioration in the level of consciousness after an intracerebral hemorrhage occurs in about one fourth of patients who are initially alert.

Intracranial hemorrhages in each of the four typical locations produce characteristic findings. Patients with massive *putaminal hemorrhages* become lethargic or comatose within minutes to hours after onset and concurrently experience contralateral weakness (including the face) with contralateral hemianopia and gaze paresis (i.e., eyes deviated toward the side of the hemorrhage). *Cerebellar hemorrhages* initially spare the brain stem, and consciousness is generally preserved in the early stages. Occipital headache may be the first symptom. The usual findings are unsteady gait, ataxia, nausea, and vomiting, which is often severe and repetitive. A variety of eye movement abnormalities may be present. Weakness is not prominent at onset, but with progression and brain stem compression, focal or bilateral weakness and coma develop, often rapidly. Further deterioration can result from herniation of cerebellar tissue downward through the foramen magnum or upward across the tentorium; hydrocephalus may be caused by obstruction of CSF flow. With continued bleeding or tissue swelling, severe brain stem damage ensues and causes rapid demise of the patient. Less frequent are *thalamic*

TABLE 415-2 CLINICAL FEATURES OF COMMON HYPERTENSIVE HEMORRHAGES

	Site of Hemorrhage			
CLINICAL FEATURES	**PUTAMINAL**	**THALAMIC**	**PONTINE**	**CEREBELLAR**
Unconsciousness	Later	Later	Early	Late
Hemiparesis	Yes	Yes	Quadriparesis	Late
Sensory change	Yes	Yes	Yes	Late
Hemianopia	Yes	Yes	No	No
Pupils				
Size	Normal	Small	Small	Normal
Reaction	Yes	Yes or no	Yes or no	Yes
Gaze paresis side	Contralateral, sometimes ipsilateral	Contralateral	Ipsilateral	Ipsilateral
Response to calorics	Yes	Yes	No	Yes or no
Downward eye deviation	Yes	No	No	
Ocular bobbing	No	No	Sometimes	Sometimes
Gait loss	No	No	Yes	Yes
Vomiting	Occasional	Occasional	Often	Severe

hemorrhages, which cause patients to lose consciousness relatively rapidly; those who survive often experience contralateral hemiparesis, sensory deficits, and homonymous hemianopia. *Pontine hemorrhage* was once thought to produce coma invariably, but modern imaging detects smaller hemorrhages that are not fatal. Patients with severe pontine hemorrhages become comatose, usually with very small but detectable reactive pupils. Oculovestibular responses are often lost early, vomiting can occur at onset, and these patients generally have quadriplegia and bilateral extensor posturing. Patients may be "locked-in" (Chapter 411).

Lobar hemorrhages, which are more characteristic of amyloid angiopathy than hypertension, usually originate at the junctions between gray and white matter in the cerebral hemispheres. Such hemorrhages account for about one third of intracerebral hemorrhages and are approximately as common as putaminal hemorrhages. The clinical manifestation depends on the location of the hemorrhage. Most patients are elderly because amyloid angiopathy and hypertension are relatively frequent in this age group. Nonspecific symptoms, including headache, nausea, and vomiting, probably occur with about the same frequency but with less intensity than with deep, hypertensive hemorrhages. Coma and seizures are uncommon, possibly because most of these hemorrhages are comparatively small and located in subcortical white matter.

DIAGNOSIS

Intracerebral hemorrhage often cannot be distinguished from other types of stroke based on clinical findings alone. The test of choice for making the diagnosis is a non–contrast-enhanced CT scan (Fig. 415-4) that shows areas of hemorrhage as zones of increased density, which may or may not have associated regions of decreased density indicating infarction. Primary parenchymal hemorrhages typically display homogeneous areas of increased density and a mass effect (i.e., shift of normal tissue from its usual location), whereas hemorrhagic infarctions are characterized by areas of increased density (i.e., blood) interspersed with areas of decreased density (i.e., infarction).

MRI findings depend on the precise imaging sequence and the age of the hemorrhage. The sensitivity and specificity of MRI for the diagnosis of hemorrhage, particularly in the presence of infarction, are unknown. MRI is able to detect small lesions, particularly in the posterior fossa, better than CT, but how much of the lesion is hemorrhage or hypoperfusion is uncertain. Cerebral angiography is not needed for the acute evaluation of hemorrhages, but it is commonly used later to identify a suspected aneurysm or AVM that may be considered for intervention.

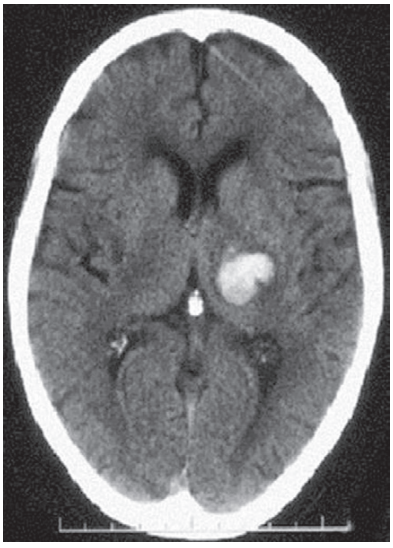


FIGURE 415-4. Intracerebral hemorrhage. A computed tomographic scan shows a parenchymal hemorrhage involving the left thalamus and posterior internal capsule. (Courtesy of Gregory W. Albers, Stanford University, Stanford, CA.)

TREATMENT

Rx

General Measures

The usual medical management of acute parenchymal hemorrhage has been supportive, with initial care directed at maintenance of the airway, oxygenation, nutrition, and prevention and treatment of secondary complications. Optimal blood pressure treatment is uncertain, although the general guidelines for excessive hypertension and reduction of cerebral perfusion apply as for ischemic strokes (Chapter 414). There is no accepted protocol for the management of increased intracranial pressure; osmotherapy, hyperventilation, and neuromuscular paralysis rarely are beneficial. Fluid management should maintain euvolemia; fluid restriction or volume expansion is not of proven value. Seizures are particularly harmful in critically ill patients and are treated despite lack of data from randomized trials. Maintenance of normal body temperature is theoretically desirable because fever may accelerate tissue destruction.

Medical Therapy

Intravenous administration of recombinant factor VIIa within 4 hours after onset reduces the volume of hemorrhage and surrounding cerebral edema, as measured by CT, but does not improve clinical outcomes.■ Larger trials of this promising therapy are in progress. Small clinical trials of corticosteroids, glycerol, and hemodilution have not demonstrated benefit, and corticosteroids may increase the risk for infectious complications.

Surgical Therapy

The goal of surgical treatment of intracerebral hemorrhage is to remove as much blood clot as possible as quickly as possible. Ideally, surgery should remove the underlying cause, such as an AVM, and prevent hydrocephalus. Early surgical intervention to evacuate intracerebral hematomas within 24 hours is no better than medical therapy.■ However, patients who have cerebellar hemorrhages and are deteriorating because of brain stem compression and hydrocephalus caused by ventricular obstruction are still recommended by some for removal of the clot or amputation of part of the cerebellum, although no proof exists to support this approach.

PROGNOSIS

In recent series, the 30-day case-fatality rate averaged 30 to 50%. Most early deaths result from the direct neurologic consequences of the hemorrhage; the severity of bleeding (e.g., size, extension into ventricles) and level of neurologic function are the best predictors of poor outcomes. Supratentorial hemorrhages smaller than 30 mL rarely lead to death unless they are located in the thalamus. The long-term prognosis for various degrees of recovery is similar or better than that of cerebral infarctions of comparable severity. The risk for recurrent intracerebral hemorrhage has not been well studied, but the risk for at least one rebleeding episode may be as high as 25% over the next several years. The risk for intracerebral hemorrhage can be reduced by appropriate treatment. Control of mild to moderate hypertension decreases the risk for hemorrhagic stroke by one third to one half (Chapter 67).

HYPERTENSIVE ENCEPHALOPATHY

DEFINITION

Hypertensive encephalopathy is usually defined as malignant hypertension associated with central nervous system abnormalities (Chapter 67). Malignant hypertension is commonly defined as sustained, elevated arterial blood pressure, with diastolic levels of 130 mm Hg or greater and systolic pressure in excess of 200 mm Hg. Abnormal funduscopic findings include papilledema, retinal linear hemorrhages, or extravascular cotton-wool exudates. Hypertensive encephalopathy is classically characterized by rapidly evolving severe hypertension associated with headache, nausea, vomiting, visual disturbances, seizures, confusion, stupor, and ultimately coma. Focal neurologic signs are common.

PATHOBIOLOGY

The pathogenesis of hypertensive encephalopathy remains unclear. Pathologic findings include purpura in the brain, retinal hemorrhages, papilledema, and fibrinoid arteriolar lesions of the glomeruli. Diffuse fibrinoid necrosis and thrombotic occlusion of arterioles cause microinfarctions and petechial hemorrhages, and these changes lead to distal ischemia. Ring hemorrhage around a thrombosed precapillary is the characteristic microscopic lesion of hypertensive encephalopathy. Multiple, compacted petechiae can resemble a hematoma.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Hypertensive encephalopathy is associated with hypertension of any cause and can occur in patients of any age. Severe headache is the most frequent manifestation. Nausea, vomiting, impaired vision, and dizziness are common. Confusion, stupor, and coma with generalized seizures may develop. Retinal changes characteristic of severe hypertension are common and often include hemorrhages or papilledema, but arteriolar narrowing may be the only abnormality. Because there are no pathognomonic findings in this disorder, it is a diagnosis of exclusion.

Uremic encephalopathy also occurs in patients with renal failure (Chapter 132). Uremia can cause altered mental status and seizures, and differentiation from hypertensive encephalopathy may be difficult. However, uremia is usually accompanied by metabolic acidosis or water intoxication, which may differentiate it from hypertensive encephalopathy, and correction of the uremia by dialysis may help clarify the picture.

Other complications of hypertension to be considered in the differential diagnosis of hypertensive encephalopathy include hemorrhagic and ischemic strokes. Focal neurologic signs predominate in these other conditions, whereas mental status changes are characteristic of hypertensive encephalopathy. Increased intracranial pressure from obstructive hydrocephalus (Chapter 195), brain tumor (Chapter 195), or subdural hematoma (Chapter 406) can elevate blood pressure and slow the pulse, but encephalopathy and markedly elevated blood pressure are absent.

TREATMENT

Rx

Therapy should be initiated immediately, but the rate of decrease in blood pressure should be controlled to avoid hypotension (Chapter 67). Seizures can usually be stopped with intravenous diazepam (10 mg); in eclamptic patients (Chapter 247), fosphenytoin (15 to 20 mg phenytoin equivalent per kilogram intravenously) or magnesium sulfate (4 g intramuscularly every 4 hours as needed) are often used, particularly because they may not depress the respiratory drive of the fetus as much as some other drugs. Prompt delivery of the fetus may be quite helpful.

Grade A

1. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358:2127-2137.
2. Molyneux AJ, Kerr RS, Birks J, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol*. 2009;8:427-433.
3. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STITCH): a randomised trial. *Lancet*. 2005;365:387-397.

SUGGESTED READINGS

Runchey S, McGee S. Does this patient have a hemorrhagic stroke? Clinical findings distinguishing hemorrhagic stroke from ischemic stroke. *JAMA*. 2010;303:2280-2286. *Neck stiffness, seizures, diastolic blood pressure >110 mm Hg, vomiting, and headache increase the likelihood of a hemorrhagic stroke rather than an ischemic stroke, but neuroimaging is required for reliable diagnosis.*

Smith SD, Eskey CJ. Hemorrhagic stroke. *Radiol Clin North Am*. 2011;49:27-45. *Review of imaging options.*

416 PARKINSONISM

ANTHONY E. LANG

Parkinsonism is a clinical syndrome that consists of four cardinal signs: tremor, rigidity, akinesia, and postural disturbances (TRAP). Parkinson's disease is a common cause of the TRAP syndrome, but there are numerous other causes (Table 416-1).

PARKINSON'S DISEASE

EPIDEMIOLOGY

Parkinson's disease, which is the second most common neurodegenerative disorder after Alzheimer's disease, occurs in approximately 1 in 1000 in the general population and in 1% of persons older than 65 years. Men are affected slightly more often than women (3:2).

PATHOBIOLOGY

The cause of Parkinson's disease is believed to be a variable combination of poorly understood genetic and environmental factors. Both autosomal dominant and recessive genes can cause classic Parkinson's disease. The protein α-synuclein, which is the chief constituent of the hallmark cytoplasmic inclusion, the Lewy body (Chapter 409), is critical in the pathogenesis of Parkinson's disease. Abnormal aggregation of the protein, either from mutations in the α-synuclein gene or as a result of excessive production of the normal protein because of gene duplications or triplications, is associated with varying disease phenotypes. Other defined genetic abnormalities may be associated with classic later-onset Parkinson's disease, including *LRRK2*, which is currently the most common cause of autosomal dominantly inherited Parkinson's disease, or with early-onset parkinsonism, typically found in the autosomal recessive forms associated with *parkin*, *DJ-1*, and *PINK1*. Other genes in which mutations may increase the risk for development of Parkinson's disease include the glucocerebrosidase gene (*GBA*).

Although monogenetic forms of Parkinson's disease are uncommon, knowing that parkin is an E-3 ubiquitin protein ligase has implicated the ubiquitin proteasome system in the pathogenesis of Parkinson's disease. Proteasome inhibitors, which may be present in the environment, are being

studied for their potential to cause parkinsonism in animals. Such findings support the "environmental hypothesis" of sporadic Parkinson's disease, similar to the discovery that the selective neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is oxidized to the active toxin MPP^+, which is a selective inhibitor of complex I of the mitochondrial electron transport chain. This knowledge, combined with recognition of the importance of dopamine (see later), has implicated oxidative stress in the pathogenesis of Parkinson's disease. Other proposed pathogenetic factors include mitochondrial dysfunction, protein misfolding or aggregation, excitotoxicity, and inflammation.

Pathology

Many of the features of Parkinson's disease are due to loss of dopamine in the neostriatum (especially the putamen) secondary to loss of pigmented dopaminergic neurons in the substantia nigra pars compacta (SNc) of the midbrain. Approximately 60% of these dopaminergic neurons will have degenerated before clinical features of the disease develop.

In addition to the prominent degenerative changes in the SNc (cell loss, gliosis, abnormal deposition of aggregated α-synuclein as Lewy bodies and Lewy neurites), pathologic changes are also evident in other brain stem nuclei, in cortical regions, and in peripheral autonomic neurons. Indeed, it has been suggested that Parkinson's disease may begin in the lower brain stem and the olfactory system, where it causes early loss of the sense of smell and only later involves the substantia nigra. Independent of the order of involvement, it is likely that the widespread extranigral neurodegenerative changes account for the many symptoms that do not respond to dopamine replacement and that become increasingly problematic as the disease progresses.

CLINICAL MANIFESTATIONS

Typically, the symptoms begin in one limb. This asymmetry often persists into later stages of the disease.

Motor Symptoms

Tremor

The classic "resting tremor" of Parkinson's disease has characteristic clinical features. The tremor has a frequency of 4 to 6 cycles per second, typically with a "pill-rolling" character when it involves the hand. It is generally present with the limb in complete repose and typically subsides when the limb moves and takes up a new position, although the tremor may reemerge ("reemergent tremor") within a short time after maintaining the new position (Video 416-1). Because resting tremor diminishes or subsides with action, it may not be disabling but can be embarrassing and may be associated with aching or fatigue of the affected limb. Resting tremor is usually accentuated by stress (e.g., by asking the patient to perform mental calculations). It is also characteristically present in the upper limbs while walking. A higher-frequency (e.g., 7 to 10 Hz) postural and kinetic tremor is also common in patients with various causes of parkinsonism.

Rigidity

Rigidity is a form of increased muscle tone appreciated best on slow passive movements. It may be characterized as "cogwheel" when a tremor is superimposed or as "lead pipe" when it is not. Rigidity is "activated" or accentuated on examination by asking the patient to move the limb opposite the one being tested. Patients may complain of stiffness, but the rigidity is not usually disabling.

Akinesia

Akinesia or bradykinesia comprises a variety of disturbances in movement, including slowness, reduced amplitude, fatiguing, and interruptions in ongoing movement. This disabling aspect of parkinsonism interferes with all voluntary activities and accounts for many of the well-known features of parkinsonism: lack of facial expression with reduced blinking (hypomimia or masked facies—the "reptilian stare"), soft monotonous speech (hypophonia), impaired swallowing resulting in drooling (sialorrhea), small handwriting (micrographia), reduced arm swing while walking, shortened stride and shuffling gait, difficulty arising from a low chair, and problems turning over in bed. Arrest in ongoing movement ("motor block") can interfere with a variety of activities, but it is best appreciated as freezing of gait (Video 416-2). Bradykinesia is evident on inspection and elicited by testing rapid repetitive and alternating movements: finger tapping, opening and the closing the fist, pronating and supinating the wrist, and toe and heel tapping.

TABLE 416-1 DIFFERENTIAL DIAGNOSIS OF PARKINSONISM

PARKINSON'S DISEASE
Sporadic
Genetic
Autosomal dominant (e.g., α-synuclein gene mutations, duplications, triplications; *LRRK2* mutations)
Autosomal recessive (e.g., *parkin, DJ-1, PINK-1*)
SECONDARY PARKINSONISM
Neurodegenerative diseases (sporadic or genetic)
Progressive supranuclear palsy* (Videos 416-3 through 416-6)
Multiple system atrophy* (Videos 416-7 through 416-9)
Corticobasal degeneration* (Videos 416-10 and 416-11)
Dementia with Lewy bodies*
Alzheimer's disease*
ALS-parkinsonism-dementia complex of Guam
Huntington's disease
Rapid-onset dystonia-parkinsonism
Pallidopyramidal degeneration (including PARK9 and PARK15)
Neuroacanthocytosis
Spinocerebellar ataxias (e.g., SCA-3, SCA-2)
Wilson's disease
Pantothenate kinase–associated neurodegeneration (Hallervorden-Spatz syndrome)
Neuroferritinopathy
Calcification of the basal ganglia (Fahr's disease)
Dopa-responsive dystonia (not a degenerative disorder)
Drugs*
Neuroleptics, metoclopramide, prochlorperazine, tetrabenazine, reserpine, cinnarizine, flunarizine, α-methyldopa, lithium
Toxic
MPTP, manganese (including illicit use of ephedrone), carbon monoxide, mercury
Infectious
Encephalitis lethargica
Other encephalitis, including HIV associated
Subacute sclerosing panencephalitis
Creutzfeldt-Jakob disease
Vascular*
Atherosclerosis
Amyloid angiopathy
Neoplastic
Brain tumor
Other mass lesions
Normal-pressure hydrocephalus*
Head trauma
Multiple sclerosis

*See Table 416-4 for additional details.
ALS = amyotrophic lateral sclerosis; HIV = human immunodeficiency virus; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.
Adapted from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

Postural Disturbances

Postural disturbances include a flexed posture in the limbs and trunk (stooped, simian posture), as well as postural instability resulting in imbalance and falls. Patients may complain of being unable to stop themselves from going forward (propulsion) or backward (retropulsion). Clinical assessment of postural instability includes the "pull test," in which the examiner abruptly pulls the patient off balance while being ready to catch the patient in the event of a fall.

Other Symptoms

In addition to the motor features of parkinsonism, a variety of non–motor-related features are extremely common and include pain and other sensory disturbances; dysautonomic complaints, such as urinary urgency and frequency; orthostatic faintness; constipation; male erectile dysfunction; sleep abnormalities, including rapid eye movement behavioral disorder (Chapter 412); anxiety; fatigue; depression; and cognitive disturbances, including dementia. As the disease progresses, more resistant features develop, including "axial" motor disturbances (speech and swallowing abnormalities, freezing, and postural instability), as well as neurobehavioral and cognitive dysfunction.

TABLE 416-2 PROBLEMS IN LATE-STAGE PARKINSON'S DISEASE

PROBLEM	SYMPTOMS
LATER TREATMENT-RESISTANT SYMPTOMS	
Motor	Dysarthria Dysphagia Freezing of gait (on-period freezing) Postural instability with falls
Non–motor related*	Dysautonomia, weight loss Sensory symptoms, including pain (some may be responsive to levodopa) Changes in mood or behavior (depression, anxiety), sleep disturbances (excessive daytime sleepiness often caused by or aggravated by dopaminergic medication) Rapid eye movement sleep behavior disorder (may develop before parkinsonism) Fatigue Cognitive dysfunction and dementia
RELATED TO TREATMENT AND DISEASE	
Motor fluctuations	Wearing off of drug effect (predictable end-of-dose deterioration, morning akinesia), increased latency to benefit ("delayed-on"), dose failures ("no-on") On-off phenomenon, more rapid and unpredictable fluctuations Concomitant fluctuations of non–motor-related symptoms that may be as disabling as motor symptoms (or more so)
Dyskinesias (abnormal involuntary movements)	Peak-dose dyskinesias: chorea, athetosis, and less often, more prolonged dystonia, typically worse on the initially affected side (Video 416-12) Diphasic dyskinesia ("beginning-of-dose" and "end-of-dose" dyskinesias): mixtures of choreoathetosis, ballism, dystonia, alternating movements (especially in the legs) Off-period dystonia: most often involving the legs and feet (including morning foot dystonia)
Psychiatric disturbances	Vivid dreams and nightmares Visual hallucinations with a clear sensorium Hallucinations with confusion Mania, hypersexuality, problem gambling, dopaminergic drug addiction Paranoid psychosis

Adapted from Lang AE, Lozano AM. Parkinson's disease—second of two parts. *N Engl J Med.* 1998;339:1130-1143.

TABLE 416-3 CLINICAL CLUES TO AN ALTERNATIVE (NON-PARKINSON'S DISEASE) CAUSE OF PARKINSONIAN SIGNS AND SYMPTOMS

Extraocular movements—e.g., nystagmus, limitation of vertical gaze, especially with slowing of downward saccadic eye movements (see Video 416-4)
Early and prominent dysarthria/dysphagia
Prominent or early abnormal neck postures: flexion or extension (see Video 416-8)
Ataxia—limb, gait (impaired tandem gait)
Lower body distribution with relative sparing of upper limb function
Early postural instability/falls/freezing (see Video 416-3)
Dysautonomia (early/prominent), prominent hypotensive response to dopaminergic medication
Pyramidal tract signs—very brisk reflexes, clonus, extensor plantar responses
Peripheral nerve dysfunction—loss of reflexes, distal sensory loss, weakness
Apraxia/cortical sensory changes
Early severe dementia
Poor response to levodopa

Complications

In addition to the manifestations of the disease itself, complications of drug therapy include motor- and non–motor-related fluctuations and psychiatric or behavioral disturbances. Thus, in the later stages of the disease, the clinical picture often fluctuates from hour to hour and even from minute to minute; accordingly, patients exhibit a mixtures of the classic features of parkinsonism, which may improve considerably in response to medication, symptoms that persist despite the peak benefit of medication, and symptoms that occur as a complication of dopaminergic medication (Table 416-2).

DIAGNOSIS

Testing for monogenetic forms of Parkinson's disease (e.g., parkin) is becoming available, but guidelines for its use have not yet been developed. Given the classic clinical manifestations, the diagnostic evaluation focuses largely on ways to exclude other causes of parkinsonism (Table 416-3). Young-onset patients should have Wilson's disease excluded by determination of 24-hour urine copper and serum ceruloplasmin and by slit lamp examination (Chapter 218). Findings on magnetic resonance imaging are generally normal in Parkinson's disease, but it is indicated to exclude other diagnoses (Table 416-4). Positron emission tomography, which can assess the presynaptic and postsynaptic sides of the nigrostriatal dopamine system, is useful for research, but the most common ligand, [^{18}F]fluorodopa, does not reliably distinguish Parkinson's disease from many other neurodegenerative diseases that mimic it. The same limitations apply to evaluation of the dopamine transporter by single-photon emission computed tomography. The finding of increased echogenicity in the SNc of the midbrain on transcranial ultrasound may be more specific in diagnosing Parkinson's disease, but the data are not conclusive.

For evidence-based recommendations on investigation of parkinsonism, see the article by Suchowersky and colleagues in Additional Suggested Readings.

TREATMENT Rx

Treatment of Parkinson's disease is directed at slowing its progression ("neuroprotective" or "disease-modifying" treatments); improving symptoms, typically by restoring dopaminergic tone medically or by correcting basal ganglia neurophysiology surgically ("symptomatic"); or attempting to restore or regenerate the damaged neurons ("neurorestorative" or "neuroregenerative" therapy).

Medical Treatment

To date, no medical treatment (Table 425-5) has been proved to modify the progressive course of Parkinson's disease. The selective monoamine oxidase B (MAO-B) inhibitors selegiline and rasagiline■ may exert disease-modifying effects, and the potential effects of agents such as coenzyme Q_{10}, creatine, the calcium-channel blocker isradipine, the pro-urate agent inosine, and the dopamine agonist pramipexole are currently under study.

Early treatment in a patient with little or no disability may entail only education, psychological support, encouragement to remain active and become involved in an exercise program, and ongoing follow-up. There is some evidence that early treatment, even when patients are only mildly symptomatic, may preserve quality of life. A treatment philosophy that still requires evidence-based support involves the early initiation of symptomatic therapy to bolster the brain's compensatory mechanisms that have begun to fail as the physical symptoms of parkinsonism become manifested.

When symptoms begin to interfere with function, mildly effective drugs such as an MAO-B inhibitor, amantadine, and anticholinergics (the latter predominantly for tremor in younger patients) may provide adequate benefit (see Table 425-5). When symptoms are more pronounced or inadequately controlled with these approaches, dopaminergic therapy should be introduced. In patients younger than 65 years who are cognitively intact and lack other major medical problems, initial therapy with a dopamine agonist may delay the development of motor complications.■ However, these drugs result in more excessive sleepiness, leg edema, "impulse control disorders" (such as pathologic gambling, hypersexuality, binge eating, and shopping), and hallucinations than levodopa does. If a full dose of a dopamine agonist does not provide adequate clinical benefit or has intolerable side effects, levodopa should be initiated. In older patients, in those with cognitive dysfunction (more prone to hallucinations with dopamine agonists), and in circumstances that require more rapid improvement of pronounced disability, levodopa should be the initial drug used.

Alleviating Symptoms

Levodopa is the most effective treatment of Parkinson's disease, but it is associated with a variety of side effects (see Table 416-2). For the first year or

TABLE 416-4 DISEASES THAT MUST BE DISTINGUISHED FROM PARKINSON'S DISEASE

DIAGNOSIS	IMPORTANT DISTINGUISHING CLINICAL FEATURES	RESPONSE TO LEVODOPA/COMMENTS (INCLUDING IMAGING)
Multiple system atrophy (MSA) (includes striatonigral degeneration, sporadic olivopontocerebellar atrophy, and Shy-Drager syndrome)	Early dysautonomia (including orthostatic hypotension and sexual impotence) and bladder dysfunction (with autonomic and nonautonomic components) Cerebellar dysfunction	Good response initially evident in 20% and sustained partial response in ≈15% Dyskinesias or motor fluctuations possible; cranial dystonia may be prominent (see Video 416-7) Patient is wheelchair bound despite response to levodopa (early loss of postural reflexes, with or without ataxia)
MSA-P = a predominant parkinsonian manifestation	Pyramidal tract signs Stimulus-sensitive myoclonus of the hands and face	MRI (including diffusion-weighted imaging and gradient-echo sequences) often shows diagnostic changes in the striatum in MSA-P and "hot cross bun sign" in the pons and hyperintensity in middle cerebellar peduncles in MSA-C
MSA-C = a predominant cerebellar manifestation (mixed features are common)	Extreme forward neck flexion (anterocollis) Mottled, cold hands Inspiratory stridor (see Video 416-9) Prominent dysarthria	
Progressive supranuclear palsy	Supranuclear vertical ophthalmoplegia (see Video 416-4) Other oculomotor and eyelid disturbances (see Video 416-6) Axial rigidity greater than limb rigidity Early falls, speech and swallowing disturbances Nuchal extension Cognitive or behavioral changes Possibly a higher incidence of hypertension than in Parkinson's disease and other neurodegenerative causes of parkinsonism	Good response rarely evident; benefit only for classic parkinsonian features such as limb rigidity, bradykinesia, and rare examples of tremor at rest MRI often demonstrates profound midbrain atrophy ("hummingbird sign" on a midline sagittal view)
Corticobasal (cortical-basal ganglionic) degeneration	Apraxia, cortical sensory loss, alien-limb phenomenon (see Video 416-10) Pronounced asymmetrical rigidity Limb dystonia Stimulus-sensitive myoclonus (see Video 416-11) Aphasia (progressive nonfluent aphasia) Cognitive dysfunction (frontotemporal dementia)	Usually negligible MRI may show pronounced asymmetrical cortical atrophy
Vascular parkinsonism	"Lower-half" parkinsonism with gait disturbances predominating, often with minimal or much milder upper body involvement Additional neurologic deficits (e.g., pyramidal tract signs, pseudobulbar palsy)	Usually poor but some respond well Imaging demonstrates multiple infarcts involving the basal ganglia and subcortical white matter
Dementia with Lewy bodies	Early dementia (cognitive profile somewhat different from that of Alzheimer's disease) Spontaneous hallucinations, fluctuating cognitive status, falls, orthostatic hypotension, RBD Pronounced sensitivity to the extrapyramidal side effects of neuroleptic drugs Parkinsonism may be similar to typical Parkinson's disease, although rigidity may be more prominent than bradykinesia or tremor	Motor features may respond well; psychiatric side effects of dopaminergic drugs are typically dose limiting
Alzheimer's disease	Early dementia (memory loss, apraxia, aphasia) Tremor uncommon Spontaneous hallucinations less common than in dementia with Lewy bodies	Poor
Normal-pressure hydrocephalus	"Lower-half" parkinsonism ("gait apraxia") Urinary complaints (frequency, urgency, incontinence) Cognitive disturbances	Generally poor Imaging demonstrates ventriculomegaly out of proportion to cortical atrophy
Drug-induced parkinsonism	All the classic features of parkinsonism (tremor may be less common than in Parkinson's disease) Usually symmetrical signs and symptoms Other drug-induced movement disorders (e.g., tardive dyskinesia with neuroleptics)	Usually poor because of ongoing dopamine receptor blockade; may aggravate movements of tardive dyskinesia

MRI = magnetic resonance imaging; RBD = rapid eye movement sleep behavior disorder.
Adapted from Lang AE, Lozano AM. Parkinson's disease—first of two parts. *N Engl J Med.* 1998;339:1044-1053.

more the benefit of levodopa lasts throughout the day with little symptomatic variability. However, in time the duration of benefit declines, with worsening of symptoms the first thing in the morning (morning akinesia) and for a variable time before scheduled daytime doses (wearing-off/end-of-dose akinesia). Within 2 to 5 years of initiating treatment, up to 50% of patients may also experience involuntary movements (chorea, athetosis, dystonia), most often at the peak action of the medication. These complications, which are generally more prominent and occur earlier in patients with an onset of disease at a younger age, reflect the short half-life of levodopa combined with the underlying progressive loss of presynaptic dopamine neurons and result in nonphysiologic "pulsatile" stimulation of striatal dopamine receptors, which then induces "neuroplastic" changes in postsynaptic striatal neurons. Initially, these complications rarely cause major disability.

Although initiating therapy with a dopamine agonist rather than levodopa may be associated with a delay in the onset of these motor problems, the clinical benefit is generally less than with levodopa, and all patients eventually require the addition of levodopa to control symptoms. No data support delaying treatment with levodopa, and some data suggest that levodopa could have a neuroprotective effect. Even as Parkinson's disease progresses, most of the classic features continue to respond after 20 or more years of treatment.

TABLE 416-5 DRUGS FOR PARKINSON'S DISEASE

CLASS	DRUG	USUAL STARTING DOSE	USUAL FINAL DOSAGE	IMPORTANT ADVERSE EFFECTS	COMMENTS	INDICATIONS
Anticholinergic	Many (e.g., benztropine, trihexyphenidyl)	Benztropine or trihexyphenidyl, 1-2 mg 2-3 times per day	Varied	Peripheral effects, e.g., dry mouth, blurred vision, constipation, difficulty with urination Central effects, e.g., confusion, memory problems, hallucinations	Relatively contraindicated in the elderly and contraindicated in patients with cognitive disturbances	Early treatment of tremor
Miscellaneous	Amantadine	100 mg once per day	100 mg 2 or 3 times per day	Confusion, visual hallucinations; livedo reticularis, swelling of the ankles; dose reduction or drug withdrawal necessary in patients with renal failure	Previously considered a dopaminergic drug, now thought to act primarily through NMDA antagonist effects	Early treatment; later for dyskinesias
	Memantine	5 mg once daily	10 mg twice daily	Confusion, fatigue, dizziness, headache	NMDA antagonist	Possibly effective for cognitive dysfunction in PDD
Dopamine precursor	Levodopa given with peripheral dopa decarboxylase inhibitor (DDCI) (carbidopa [in 4:1 and 10:1 ratios] or benserazide [4:1]*)	50 (levodopa)/12.5 (DDCI) mg (4:1 preparation) 3 times per day (with meals to reduce nausea and vomiting)	Varied; begin with 3-times-daily schedule (controlled-release levodopa-carbidopa may be given twice daily at first); late in the disease patients may require multiple doses per day (sometimes > 2 g/day). Initially give with meals to reduce GI upset; later avoid meals to improve absorption and reliability of response	Peripheral and central dopaminergic side effects Peripheral: nausea, vomiting, and orthostatic hypotension Central: motor fluctuations, dyskinesias, psychiatric disturbances	Peripheral side effects often controlled by additional carbidopa or the peripheral dopamine receptor blocker domperidone* Controlled-release formulations often less bioavailable with less reliable absorption (more "dose failures" later on)	Formulations: immediate release—for early and later treatment Controlled-release (with carbidopa [4:1] or benserazide [4:1]*)—for predictable motor fluctuations (wearing off) and nighttime akinesia Stalevo (with carbidopa and entacapone)—for wearing off Parcopa (orally disintegrating tablets for faster absorption)—for patients with problematic long latency to benefit with individual doses Duodopa* (used with a pump for duodenal infusions)—for problematic motor fluctuations
Dopamine agonists Ergot derived	Bromocriptine	1.25 mg 3 times per day with meals	30-40 mg/day	Peripheral and central dopaminergic side effects; pedal edema, excessive daytime sleepiness Pleuropulmonary reaction, retroperitoneal fibrosis, erythromelalgia Impulse control disorders probably equally common with all dopamine agonists	Peripheral side effects often well controlled with domperidone* Rare pulmonary, retroperitoneal, and skin effects possibly caused by ergot derivation (drug withdrawal usually required)	Early and adjunctive therapy
	Pergolide	0.05 mg once per day × 2 days, increasing slowly thereafter	3-5 mg/day	As for bromocriptine; cardiac valvulopathy	As for bromocriptine	Not the first agonist because it causes restrictive cardiac valve disease
	Cabergoline*	0.5-1 mg once per day	2-6 mg/day	As for pergolide	As for pergolide Long half-life allows once-daily dosage	As for pergolide, although advantage of a long half-life may outweigh this concern
	Lisuride*	0.1-0.2 mg 1-3 times per day	2-5 mg/day	As for bromocriptine	As for bromocriptine	Uncertain whether cardiac valve abnormalities occur Parenteral formulations allow chronic infusion (pump) therapy

Non–ergot derived	Ropinirole	0.25 mg 3 times per day	Up to 24 mg/day in 3 divided doses Once daily extended/prolonged-release formulation available	Peripheral and central dopaminergic side effects similar to those of ergot-derived dopamine agonists, with the probable exceptions of pleuropulmonary reaction, retroperitoneal fibrosis, erythromelalgia, and cardiac valvulopathy	Effective as first-line and adjunctive therapy; dopamine D_3 agonist effects may contribute to efficacy	De novo therapy shown to be associated with less motor complications than with levodopa Implications of less progressive loss of dopamine terminal function on imaging uncertain
	Pramipexole	0.125 mg 3 times per day	Up to 4.5 mg/day in 3 divided doses Once daily extended/prolonged-release formulation available	As for ropinirole	As for ropinirole, possibly greater "D_3-preferring" effects—may account for antidepressant effect	As for ropinirole
	Rotigotine*	4.5 mg/day (10 cm^2)	Transdermal patch (4.5-27.0 mg/day; 10-60 cm^2)	As for ropinirole Additional adverse effects related to skin patch application (dermatitis)	May be effective for both first-line and adjunctive therapy	Limited availability because of problems with patch formulation
	Apomorphine	3-5 mg SC injection	Parenteral agent given as needed or as continuous infusion	Peripheral and central dopaminergic side effects Local skin reactions, including nodule formation	Concomitant antiemetic (e.g., domperidone,* trimethobenzamide) needed	Late-stage problematic motor fluctuations Long-term use of infusions may reduce dyskinesias, as well as motor fluctuations
Monoamine oxidase B inhibitors	Selegiline	5 mg once per day	5 mg 2 times per day	Dopaminergic effects of other drugs possibly accentuated, insomnia, confusion	Last dose given at midday to avoid insomnia	Early mild disease Some controversial evidence suggesting disease-modifying effects Predictable motor fluctuations (wearing off)
	Zydis selegiline	1.25 mg once per day	1.25 or 2.5 mg/day (wafer formulation)	As for selegiline	As for selegiline Absorbed from the buccal mucosa, thereby avoiding first-pass hepatic metabolism and methamphetamine metabolite of selegiline	As for selegiline
	Rasagiline	1 mg once per day	1-2 mg once per day	As for selegiline		Possible disease-modifying effects As for selegiline
Catechol *O*-methyltransferase (COMT) inhibitors	Tolcapone	100 mg 3 times per day	100 or 200 mg 3 times per day (at 6-hr intervals)	Effects of levodopa accentuated Diarrhea in approximately 5% of patients Hepatotoxicity	Dose of levodopa may have to be reduced by as much as 25%; diarrhea (sometimes explosive) typically forces discontinuation Ongoing monitoring of liver function tests required (second-line COMT inhibitor)	Motor fluctuations, especially wearing off (probably more effective than entacapone)
	Entacapone	200 mg with each dose of levodopa	200 mg 4-10 times per day (given with doses of levodopa)	Effects of levodopa accentuated	As for tolcapone; diarrhea possibly less frequent Liver function monitoring unnecessary	As for tolcapone Available in a combination tablet with levodopa/carbidopa (Stalevo)

TABLE 416-5 DRUGS FOR PARKINSON'S DISEASE—cont'd

CLASS	DRUG	USUAL STARTING DOSE	USUAL FINAL DOSAGE	IMPORTANT ADVERSE EFFECTS	COMMENTS	INDICATIONS
Atypical neuroleptics	Clozapine	12.5 mg hs	Wide range (6.25-150 mg/day), usually <75 mg/day	Agranulocytosis, sedation, hypotension, sialorrhea	Very low risk of worsening parkinsonism; agranulocytosis rare (<1%) and reversible if discovered early (requires regular monitoring of complete blood count)	Drug-induced psychosis Other "off-label" indications include drug-resistant tremor and possibly levodopa-induced dyskinesias Drug-induced psychosis
	Quetiapine	12.5-25 mg hs	25-150 mg/day	Sedation May worsen parkinsonism	Probably less effective than clozapine	
Acetylcholinesterase inhibitors	Donepezil	5 mg once per day	5-10 mg/day	Peripheral cholinergic side effects: nausea, vomiting, diarrhea Increased tremor, worsening of other Parkinson's features		Dementia Possibly effective for psychotic symptoms
	Rivastigmine	1.5 mg twice per day	3-12 mg/day	As for donepezil	Patch formulation available for transdermal administration—tolerability may be improved over oral formulation	As for donepezil

*Unavailable in the United States.
GI = gastrointestinal; NMDA = *N*-methyl-D-aspartate, PDD = Parkinson's disease dementia.
For evidence-based treatment recommendations, see Suchowersky O, Gronseth G, Perlmutter J, et al. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;66:976-982; Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;66:983-995; and Miyasaki JM, Shannon K, Voon V, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;66:996-1002.

It is not clear that delaying motor complications in the first 5 years of treatment by the initial use of a dopamine agonist improves long-term outcome or quality of life; indeed, clinical status, including the incidence of motor complications, may be no different after 10 years of treatment in those initiating therapy with a dopamine agonist and those starting with levodopa.

There is no clear advantage to starting a controlled-release rather than an immediate-release preparation of levodopa or combining levodopa with a catechol *O*-methyltransferase [COMT] inhibitor. The motor fluctuations that develop during levodopa therapy are managed by a number of approaches (see Table 416-5), including increasing the frequency of the dose, using a controlled-release preparation, prolonging the action by blocking metabolism (MAO-B or COMT inhibition), or adding a dopamine agonist. For example, adding rasagiline or entacapone to levodopa provides significant incremental benefits. Dyskinesias improve when doses of dopaminergic medications are reduced, but the parkinsonism often increases to an intolerable level. Amantadine may improve the dyskinesias without worsening the parkinsonism.

Medical management of Parkinson's disease often includes a variety of other agents, for example, drugs directed at the treatment of orthostatic hypotension, depression (Chapter 404), anxiety (Chapter 404), urinary frequency and urgency (Chapters 25 and 125), and male erectile dysfunction (Chapter 242). Management of late-stage Parkinson's disease requires skill in polypharmacy and an understanding of the complicated benefit-risk ratios of the many drugs needed.

Surgical Treatment

Surgical therapy, which involves deep brain stimulation of the subthalamic nucleus, improves the symptoms of Parkinson's disease and permits lower doses of antiparkinson medications to be used, whereas deep brain stimulation of the internal segment of the globus pallidus may provide a less consistent and durable response. Nevertheless, a randomized trial comparing these two approaches found no differences in outcome at 24 months. Bilateral deep brain stimulation of the subthalamic nucleus or globus pallidus is more effective (71%) than medical therapy (32%); it also improves self-reported quality of life despite the adverse events associated with the procedure. Thalamic deep brain stimulation is of limited utility because it is effective only for tremor. The best predictor of a good response to deep brain stimulation of the subthalamic nucleus is the patient's ongoing clinical response to levodopa. Apart from tremor, which may be resistant to the highest tolerable dose of levodopa, symptoms that are resistant to the peak effect of levodopa (e.g., dysarthria, postural instability with falls) also fail to respond to deep brain stimulation. The typical good candidate for deep brain stimulation of the subthalamic nucleus is an otherwise healthy, relatively young, cognitively intact, and psychiatrically stable patient who still responds well to levodopa but is suffering from disabling motor fluctuations and dyskinesias.

Double-blind randomized trials of transplantation of fetal substantia nigra into the striatum have not only failed to show significant efficacy but have also been associated with the side effect of transplant-induced off-medication dyskinesias. Postmortem assessments in a small number of patients surviving for more than 10 years following fetal transplants have shown Lewy bodies in the transplanted dopamine neurons, thus suggesting that the pathology can be "transmitted" to neurons placed in the diseased host. Double-blind randomized trials of bilateral intraputamenal infusion of glial-derived neurotrophic factor and gene therapy with AAV-neurturin failed to confirm the benefits found in unblinded studies.

PROGNOSIS

Parkinson's disease progresses inexorably over a period of many years; the speed and course of progression vary considerably from patient to patient. Some patients maintain an excellent response to treatment and seem to change very little over prolonged follow-up, but most note increasing disability, with the development of many symptoms that are poorly responsive to medications. Factors such as poor postural stability, falls, dysarthria, dysphagia, dysautonomia, excessive daytime sleepiness, and dementia contribute to the disability and increased mortality.

FUTURE DIRECTIONS

Gene therapies directed at either modifying neurotransmitter function or inducing neuroregeneration and other cell-based therapies are under development. Future treatments must also address the widespread, multisystemic nature of the disease, especially symptoms that are unrelated to nigrostriatal dopamine deficiency and that fail to respond to current therapies.

OTHER CAUSES OF PARKINSONISM

The numerous causes of parkinsonism (see Table 416-1) are sometimes termed "akinetic-rigid syndrome," "Parkinson's syndrome," "atypical parkinsonism," or even "Parkinson-plus syndrome" to emphasize that these patients commonly demonstrate additional clinical features indicative of the more widespread and particularly more severe pathologic involvement of areas beyond the dopaminergic SNc. These other parkinsonism conditions are generally associated with "postsynaptic" changes that result in a poor or unsustained response to levodopa, and this unresponsiveness serves as one of the most important of several clues that the parkinsonism features are caused by conditions other than Parkinson's disease (see Table 416-4) (i.e., "parkinsonism minus" a levodopa response; see Table 416-3).

Grade A

1. Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed start trial of rasagiline in Parkinson's disease. *N Engl J Med*. 2009;361:1268-1278.
2. Parkinson Study Group CALM Cohort Investigators. Long-term effect of initiating pramipexole vs levodopa in early Parkinson disease. *Arch Neurol*. 2009;66:563-570.
3. Fahn S, Shoulson I, Kieburtz K, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med*. 2004;351:2498-2508.
4. Katzenschlager R, Head J, Schrag A, et al. Parkinson's Disease Research Group of the United Kingdom. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. *Neurology*. 2008;71:474-480.
5. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006;355:896-908.
6. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep brain stimulation for Parkinson's disease. *N Engl J Med*. 2010;362:2077-2091.
7. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*. 2009;301:63-73.

SUGGESTED READINGS

Benabid AL, Chabardes S, Mitrofanis J, et al. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol*. 2009;8:67-81. *An excellent review*.

Brooks DJ. Imaging approaches to Parkinson disease. *J Nucl Med*. 2010;51:596-609. *Overview of positron emission tomography and single-photon emission computed tomography*.

International Parkinson Disease Genomics Consortium. Imputation of sequence variants for indentification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet*. 2011;377:641-649. *Eleven loci were associated with risk for Parkinson's disease*.

Lang AE. When and how should treatment be started in Parkinson disease? *Neurology*. 2009;72:S39-S43. *A practical overview*.

Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet*. 2009;13:2055-2066. *Review*.

417 OTHER MOVEMENT DISORDERS

ANTHONY E. LANG

DEFINITION

Movement disorders are first divided into hypokinetic and hyperkinetic categories. *Hypokinetic disorders,* which are characterized by akinesia, bradykinesia, and rigidity, are parkinsonian syndromes and are discussed elsewhere (Chapter 416). The common *hyperkinetic movement* disorders (Table 417-1) are defined by their specific clinical phenomena.

CLINICAL MANIFESTATIONS AND DIAGNOSTIC APPROACH

The traditional approach to a neurologic symptom is first to address localization within the nervous system (i.e., "Where is the lesion?"), followed by an evaluation of the origin ("What is the lesion?"). The neurologic examination is critical in determining the localization of the lesion, and generally the history, including the nature of onset and the progression of the symptoms, determines the most likely diagnosis. However, when a movement disorder is the predominant problem, the approach is somewhat different. The pathophysiology of most movement disorders is complex and often poorly understood. Many of these disorders are the result of dysfunction of different

TABLE 417-1 HYPERKINETIC MOVEMENT DISORDERS

Tremor
Chorea
Ballism
Dystonia
Athetosis
Tics
Myoclonus
Startle
Stereotypies
Miscellaneous

circuits in the brain, and it is often impossible to ascertain a specific anatomic localization. Instead, an accurate appreciation of the clinical phenomena is the first important step in evaluating these patients. The clinician must observe and examine the patient to define the type of movement disorder that best describes the clinical picture. This accurate characterization then allows the generation of a differential diagnosis for the specific movement disorder. The age and nature of onset, the distribution, the progression of symptoms, a family history of similar or related symptoms, and the presence of systemic signs then help to determine the most likely explanation for that movement disorder.

TREMOR

Tremor, which is a rhythmic, sinusoidal movement of a body part, is caused by regular, either synchronous or alternating, contractions of reciprocally innervated muscles. Tremors are classified based on whether they occur at rest (weight fully supported against gravity) or in action. Resting tremors are typically seen in Parkinson's disease and other parkinsonism syndromes (see Table 416-1 in Chapter 416). Action tremors are further divided into postural, kinetic, or intention tremors. A *postural tremor* is seen with the maintenance of a posture against gravity (e.g., when the arms are outstretched in front of the body). A *kinetic tremor* is seen with a voluntary movement of the limb (e.g., a tremor in an upper limb when performing the finger-to-nose test). An *intention tremor* increases in amplitude on approaching a target.

CLINICAL MANIFESTATIONS

Most action tremors (Table 417-2) combine postural and kinetic components. All tremors worsen with stress, including performing an affected activity in public. Initially, a tremor may be evident only when one attempts fine, dextrous tasks such as threading a needle, soldering, or using a screwdriver. More severe tremors interfere with activities such as handwriting, fastening buttons, shaving, eating soup with a spoon, or drinking from a cup. Patients often adapt or use compensatory measures, such as switching an activity to a less affected hand (e.g., shaving with the nondominant hand), using two hands to drink, drinking only from an incompletely filled glass or cup, or completely avoiding more challenging feeding activities in public. Severe action and intention tremors can cause handwriting to become completely illegible and can result in dependence on others for care.

Head tremors, which may be side to side, up and down, or mixed, are rarely disabling but are often a source of embarrassment. Tremor of the larynx, which causes the voice to quaver, is best appreciated by asking the patient to sustain a note. Action tremor of the lower limbs is assessed by having the patient hold the foot up to a target (e.g., the examiner's hand) and then perform a heel-knee-shin test.

Most upper limb action tremors affect many activities to a similar extent. Less commonly, tremors can affect a single task in isolation (*task-specific tremors*), the most common being a primary writing tremor. *Orthostatic tremor* is apparent in the legs and in antigravity muscles only when the patient is standing in one spot and subsides during walking or leaning against a wall; these patients commonly complain of a tremendous sense of insecurity while standing and a fear of falling. Electrophysiologic assessment demonstrates a very characteristic high-frequency tremor (14 to 16 Hz).

Enhanced Physiologic Tremor

A 7- to 12-Hz tremor is found in everyone on electrophysiologic recording. This physiologic tremor is enhanced and may become symptomatic in a variety of circumstances, including fatigue, anxiety, and excitement. This same tremor may be accentuated by drugs and systemic processes.

TABLE 417-2 DIFFERENTIAL DIAGNOSIS OF TREMOR AND RHYTHMIC MOVEMENT DISORDERS

ENHANCED PHYSIOLOGIC TREMOR
Metabolic disorders
Hyperthyroidism
Hyperparathyroidism
Hypoglycemia
Pheochromocytoma
Drugs
Caffeine
Theophylline
Amphetamines
Lithium
Valproic acid
Antidepressants
Amiodarone
β-Agonists
Others
Withdrawal of drugs
Benzodiazepines
Alcohol
Others
Fever, sepsis
Anxiety, stress, fatigue
PRIMARY OR IDIOPATHIC TREMOR
Essential tremor
Task-specific tremor
Orthostatic tremor
Idiopathic palatal tremor
TREMOR ASSOCIATED WITH CENTRAL NERVOUS SYSTEM DISEASES
Tremor with parkinsonian syndromes
Idiopathic Parkinson's disease
Multiple system atrophy
Progressive supranuclear palsy
Corticobasal degeneration
Neuroleptic-induced parkinsonism
Wilson's disease
Multiple sclerosis
Fragile X premutation-tremor/ataxia syndrome
Stroke
Arteriovenous malformation
Tumor
Head trauma
Midbrain tremor (Holmes' tremor)
TREMOR ASSOCIATED WITH PERIPHERAL NEUROPATHIES
PSYCHOGENIC TREMOR
OTHER RHYTHMIC MOVEMENT DISORDERS
Rhythmic movements in dystonia ("dystonic tremor")
Rhythmic myoclonus (including "myoclonic tremor")
Asterixis
Clonus
Epilepsia partialis continua
Hereditary chin quivering
Spasmus nutans
Head bobbing with hydrocephalus
Nystagmus

Adapted from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders.* Malden, Mass: Blackwell; 2005:3-19.

Essential Tremor

Essential tremor affects up to 5% of the general population after the age of 60 years. Essential tremor is often inherited in an autosomal dominant fashion, with the phenotype showing genetic heterogeneity from at least three different genes, most recently *LINGO1*, as well as environmental influences. Recent pathology studies have demonstrated microscopic abnormalities of cerebellar Purkinje cells. The age of onset may be as early as the first or second decade of life, but senile tremor may be delayed until the mid-60s. Patients first become aware of a mild postural and action tremor in the hands, which is indistinguishable from an enhanced physiologic tremor and may result in little functional impairment for many years until it gradually interferes with

activities. Older patients with large-amplitude, lower-frequency tremors can have a resting component that is often misdiagnosed as Parkinson's disease (see Table 416-1 in Chapter 416). (Video 417-1).

TREATMENT

Rx

Treatment of essential tremor does not influence the course of the illness and therefore is justified only when the tremor interferes with function. At least 50% of patients note improvement or complete amelioration of tremor following the ingestion of a small amount of ethanol.

First-line drug treatment includes trials of a noncardioselective β-adrenergic blocker (e.g., propranolol, ≤320 mg/day) or primidone (starting in a low dose of 25 to 62.5 mg at night and increasing to 500 to 750 mg/day). Other drugs that have been shown to be effective in double-blind crossover trials include gabapentin (1200 to 1800 mg/day), topiramate (≤400 mg/day), and alprazolam (0.125 to 3 mg/day), but many patients remain resistant to all drugs. If disability is substantial, thalamic deep brain stimulation or thalamotomy can be of major benefit, but a few patients suffer permanent neurologic sequelae owing to intracranial hemorrhage or other postoperative complications.

CHOREA

Chorea (Table 417-3) consists of irregular, random, brief, flowing movements that often flit from one body part to another in an unpredictable and purposeless sequence. Patients may incorporate choreiform movements into a voluntary movement to mask them. The severity varies from the appearance of being slightly fidgety or restless, to striking, continuous movements involving the whole body. Many patients with chorea seem unaware of their movements, whereas others can be very troubled and disabled.

Huntington's Disease

DEFINITION AND EPIDEMIOLOGY

Huntington's disease is a fully penetrant autosomal dominant neurodegenerative disorder caused by an expanded trinucleotide (CAG) repeat in the gene for the protein *huntingtin*. The prevalence is approximately 10 per 100,000.

PATHOBIOLOGY

Huntington's disease is characterized neuropathologically by neuronal loss accompanied by intraneuronal inclusions and gliosis, especially in the caudate nucleus and putamen (the striatum) and the cerebral cortex. Understanding how these changes result from the expanded polyglutamine tract in the mutated huntingtin protein is the goal of current research.

CLINICAL MANIFESTATIONS

Symptoms typically begin between the ages of 30 and 55 years, but 5 to 10% of patients have an onset before the age of 20 years (juvenile Huntington's disease), and a few patients begin to have symptoms quite late in life. Symptoms include a combination of a movement disorder, psychiatric disturbances, and cognitive dysfunction. Early on, the movement disorder is predominantly chorea, but parkinsonism and dystonia develop later (Video 417-2). Some patients, especially those with juvenile onset, have a more rapidly progressive akinetic-rigid and dystonic form (the Westphal variant). Psychiatric manifestations, which are universal but widely variable, include personality changes, impulsiveness, aggressive behavior, depression, and paranoid psychosis. These psychiatric symptoms may precede the motor manifestations, and psychotropic drug therapy may be incorrectly blamed for the subsequent development of the movement disorder. Cognitive changes result in progressive "subcortical dementia" with disturbed attention, concentration, judgment, and problem-solving that differs from the typical "cortical dementia" of Alzheimer's disease. Oculomotor dysfunction, most often manifested by difficulties with refixating the gaze and a resulting tendency to use blinks and head thrusts, is another common feature.

DIAGNOSIS

The diagnosis is confirmed by genetic testing. Normal alleles of the *IT15* gene have fewer than 30 CAG repeats, whereas 40 or more repeats invariably result in clinical illness. An earlier age of onset correlates with larger numbers of CAG repeats.

TABLE 417-3 DIFFERENTIAL DIAGNOSIS OF CHOREA

GENETIC DISORDERS
Benign hereditary chorea
Huntington's disease
Huntington-like conditions
Neuroferritinopathy
Neuroacanthocytosis including McLeod's syndrome
Dentatorubropallidoluysian atrophy
Wilson's disease
Neurodegeneration with Brain Iron Accumulation 1 (NBIA 1) (previously Hallervorden Spatz disease)
Spinocerebellar ataxias
Ataxia-telangiectasia
Ataxia-oculomotor apraxia type 1
Tuberous sclerosis
INFECTIONS/PARAINFECTIOUS CAUSES
Sydenham's chorea
Acquired immunodeficiency syndrome (including complications)
Encephalitis and postencephalitic disorders
Creutzfeldt-Jakob disease
DRUGS
Levodopa
Dopaminergic agonists used for Parkinson's disease
Amphetamines
Anticholinergics
Anticonvulsants (especially phenytoin)
Neuroleptics
Tricyclic antidepressants
Selective serotonin reuptake inhibitors (occasionally)
Oral contraceptives (typically in patients with a prior history of Sydenham's chorea)
Antihistaminics
ENDOCRINOLOGIC/METABOLIC CONDITIONS
Hyperthyroidism
Hypoparathyroidism
Chorea gravidarum
Acquired hepatolenticular degeneration
IMMUNOLOGIC DISORDERS
Systemic lupus erythematosus
Antiphospholipid syndrome
Henoch-Schönlein purpura
VASCULAR DISORDERS
Stroke
Hemorrhage
Arteriovenous malformation
Polycythemia rubra vera
OTHER CONDITIONS
Cerebral palsy
Kernicterus
Head trauma
Cardiopulmonary bypass with hypothermia
Neoplastic and paraneoplastic syndromes
Paroxysmal dyskinesias

Adapted from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

TREATMENT AND PROGNOSIS

Rx

Current care for patients with Huntington's disease involves a multidisciplinary team of clinical geneticists, neurologists, psychiatrists, psychologists, social workers, occupational and physical therapists, speech therapists, nutritionists, and nurses. Genetic counseling for patients and family members is critical. Chorea may be extremely responsive to drugs that reduce central dopamine activity, especially tetrabenazine, starting at 12.5 mg two or three times daily and gradually increasing to up to 200 mg per day. Other potential agents include haloperidol (3 to 30 mg/day), pimozide (0.5 to 10 mg/day), fluphenazine (0.5 to 20 mg/day), and reserpine (0.75 to 5 mg/day). These agents should be reserved for patients with disabling chorea because they may be associated with increased parkinsonism, postural instability, depression, sedation, and other adverse effects. Unfortunately, physical function may not improve significantly even when the chorea is controlled. Psychiatric symptoms (e.g., anxiety, psychosis, depression) can be managed effectively with the same strategies as in other psychiatric diseases (Chapter 404). The disease progresses to institutionalization and death over the course of approximately 15 years.

TABLE 417-4 DIFFERENTIAL DIAGNOSIS OF BALLISM

Focal lesions in basal ganglia
Vascular: stroke (including infarction and hemorrhage), cavernous angioma, postsurgical complications
Neoplastic: metastases; primary central nervous system tumors
Infections: cryptococcosis; toxoplasmosis; tuberculoma
Inflammatory: multiple sclerosis
Iatrogenic: subthalamotomy; thalamotomy
Immunologic: systemic lupus erythematosus; scleroderma; Behçet's disease
Nonketotic hyperglycemia (high intensity lesions in striatum on T1 MRI)
Hypoglycemia
Sydenham's chorea
Head injury
Drugs
Anticonvulsants
Oral contraceptives
Levodopa

Adapted from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

Other Choreas

Most of the non-neurodegenerative causes of chorea (see Table 417-3) can be excluded by a careful history (including a detailed drug history) and a focused set of investigations, including, in appropriate circumstances, wet preparation of peripheral blood for acanthocytes, immunologic studies (including anticardiolipin antibodies), endocrine assessment (hyperthyroidism, pregnancy), and neuroimaging. *Sydenham's chorea,* which is a late component of rheumatic fever (Chapter 298), is presumably the result of immunologic cross-reactivity between the causative group A β-hemolytic streptococcus and the basal ganglia. This disorder is infrequently seen in North America but is more common in developing countries. Sydenham's chorea usually affects children and young adults, and it is more common in girls before puberty. Adults with a past history of Sydenham's chorea in childhood may develop chorea during pregnancy or in response to taking oral contraceptive agents or estrogen preparations. Drugs that can cause chorea should be withdrawn if possible.

Ballism

Ballism, which is considered an extreme form of chorea, involves large-amplitude, random, often violent flinging movements of the proximal limbs (Table 417-4). It is most often a consequence of an acute cerebral insult, such as a stroke, and it usually involves one side of the body, particularly the arm, hence the term *hemiballism* (Video 417-3). When a causative lesion can be demonstrated, it typically involves the region of the subthalamic nucleus or the striatum. When the condition is caused by a stroke, movements usually subside spontaneously over days to weeks, although they may persist indefinitely in some patients. Treatment often requires the use of medication that antagonizes the effects of dopamine in the brain, including dopamine receptor blockers (neuroleptics such as haloperidol, 3 to 30 mg/day) or dopamine depleters (e.g., tetrabenazine, 50 to 200 mg/day). Functional neurosurgery (e.g., pallidotomy, deep brain stimulation) can be considered in patients with refractory, persistent symptoms.

DYSTONIA

DEFINITION AND PATHOBIOLOGY

In *dystonia,* sustained muscle contractions result in twisting and repetitive movements and abnormal postures. Dystonia can be classified according to its origin (Table 417-5). *Primary dystonia* includes syndromes in which the only phenotypic expressions are dystonia and tremor. These diseases can be hereditary or sporadic. *Dystonia-plus* is characterized by a combination of dystonia with other neurologic signs resulting from a known or presumed genetic defect without an underlying progressive neurodegenerative process; *dopa-responsive dystonia* and *myoclonus dystonia* are examples of such diseases. *Secondary dystonias* are the result of acquired injury to the central nervous system. *Heredodegenerative dystonias* include a large number of genetic as well as idiopathic neurodegenerative diseases.

CLINICAL MANIFESTATIONS

Common forms of dystonia include eyelid closure (blepharospasm), jaw opening or closing (oromandibular dystonia), pulling or turning of the neck in any one or combination of directions (cervical dystonia: rotatory torticollis, laterocollis, retrocollis, anterocollis), hyperadduction and less often excessive abduction of the vocal cords (laryngeal dystonia or spasmodic dysphonia), abnormal posturing and tightness of the hand while writing or using the hand for other tasks (writer's cramp, manual dystonia), abnormal posturing of the trunk or pelvis (axial dystonia), or abnormal posturing of the lower limb, including plantar flexion and inversion of the foot (Videos 417-4 through 417-7). The movements are often slow and sustained, although they may also be rapid (*dystonic spasms*). Slower, sinuous writhing dystonic movements, particularly present in the distal limbs, are referred to as *athetosis*. Dystonia is often made worse by activity (*action dystonia*), and a unique aspect of dystonia is that only selected acts may be affected, with complete sparing of all other activities in the same limb *(task-specific dystonia,* including *writer's cramp* and *musician's cramp)* (Video 417-8). In some patients, dystonia remains isolated and action specific over many years, whereas in others, it progresses to involve adjacent muscles (*overflow dystonia*) and may eventually be present at rest, in which case joint contractures may result. Another common feature of dystonia is its transient improvement with the use of a sensory trick (*geste antagoniste*), such as lightly touching the chin to relieve severe cervical dystonia or the lid to relieve disabling blepharospasm (Video 417-9). Patients with dystonia, independent of cause, often have additional postural and action tremors, phenotypically similar to essential tremor. Some patients also demonstrate more irregular, coarse, lower-frequency rhythmic movements called *dystonic tremor*.

Dystonia is often classified according to the site of involvement: focal, only one body part (e.g., blepharospasm, cervical dystonia, writer's cramp); segmental, two or more contiguous body parts; multifocal, two or more noncontiguous body parts; generalized, legs and other body areas; and hemidystonia, unilateral (generally a causative focal brain lesion is found most often involving the putamen).

DIAGNOSIS AND PROGNOSIS

For diagnostic and prognostic purposes, dystonia also may be distinguished by age of onset as childhood-onset, adolescent-onset, or adult-onset dystonia. The younger the age of onset, the more likely that a cause can be defined. Conversely, isolated dystonia beginning in adult life is most often an idiopathic disorder; further investigations are typically unrewarding and are usually not indicated. Likewise, independent of the cause, dystonia beginning in childhood commonly progresses to segmental or generalized involvement, whereas adult-onset dystonia usually remains focal or segmental.

Specific Dystonias

PRIMARY (IDIOPATHIC) DYSTONIAS

Primary dystonia accounts for up to 90% of patients with a pure dystonic syndrome. To date, no consistent neuropathologic changes have been found in the small numbers of brains affected by primary dystonia that have been studied.

When symptoms begin in *childhood,* a definable genetic cause is often identified, the most common being DYT1 resulting from the autosomal dominant inheritance of a GAG deletion in the *torsin A* gene (*Oppenheim's dystonia*). This disorder is more common in persons of Ashkenazi Jewish descent. The dystonia often begins in the first decade of life and can progress to severe disability, although the spectrum of disease, even within the same family, can be quite varied, and penetrance is relatively low (~40%) (Video 417-10). Genetic testing is available but is recommended only when the age of onset in the patient or another affected family member is less than 26 years. Increasing numbers of other genetic forms of primary dystonia, most recently *THAP1* for DYT6, are being defined, but genetic testing is not yet available for most of them.

ADULT-ONSET IDIOPATHIC DYSTONIA

Adult-onset idiopathic dystonia is the most common type of dystonia seen in general neurologic practice. The dystonia typically begins in the face, neck, or arm and may remain focal and nonprogressive or spread only to contiguous muscles after many years. The cause of this disorder is not known, although a positive family history may be noted if multiple family members can be examined.

DYSTONIA-PLUS

Dopa-responsive dystonia, which usually results in dystonia beginning in the first decade of life, most often in the lower limbs, sometimes can be mistaken for hereditary spastic paraplegia or cerebral palsy. Most patients with

TABLE 417-5 CLASSIFICATION AND CAUSES OF DYSTONIA

PRIMARY DYSTONIAS (PRIMARY TORSION DYSTONIA)
Familial (several genetic causes and types)
Sporadic, usually adult onset, focal, or segmental
DYSTONIA-PLUS
Dystonia with parkinsonism
Dopa-responsive dystonia
Dopamine agonist–responsive dystonia (e.g., aromatic acid decarboxylase deficiency)
Myoclonus dystonia
SECONDARY DYSTONIAS
Perinatal cerebral injury
Athetoid cerebral palsy
Delayed-onset dystonia
Pachygyria
Kernicterus
Encephalitis
Reye's syndrome
Subacute sclerosing leukoencephalopathy
Wasp sting
Creutzfeldt-Jakob disease
Human immunodeficiency virus infection
Head trauma
Thalamotomy
Brain stem lesion
Primary antiphospholipid syndrome
Stroke
Arteriovenous malformation
Hypoxia
Brain tumor
Multiple sclerosis
Central pontine myelinolysis
Cervical cord injury
Peripheral injury
Drugs
Toxins
Hypoparathyroidism
Psychogenic conditions

HEREDODEGENERATIVE DYSTONIAS
X-linked
Lubag disease
Deafness-dystonia-optic atrophy (Mohr-Tranebjaerg) syndrome
Pelizaeus-Merzbacher disease
Lesch-Nyhan syndrome
Autosomal dominant
Rapid-onset dystonia-parkinsonism
Juvenile parkinsonism (e.g., from mutations in the parkin gene)
Huntington's disease
Machado-Joseph disease (SCA3) and other SCAs
Dentatorubropallidoluysian atrophy
Autosomal recessive
Wilson's disease
Niemann-Pick disease type C
GM1 gangliosidosis
GM2 gangliosidosis
Metachromatic leukodystrophy
Homocystinuria
Glutaric acidemia
Triose-phosphate isomerase deficiency
Hartnup's disease
Ataxia-telangiectasia
Neurodegeneration with Brain Iron Accumulation (NBIA 1) (previously Hallervorden Spatz disease)
Juvenile neuronal ceroid lipofuscinosis
Neuroacanthocytosis
Intranuclear hyaline inclusion disease
Hereditary spastic paraplegia with dystonia
Probably autosomal recessive
Familial basal ganglia calcifications (also dominantly inherited)
Progressive pallidal degeneration
Rett's syndrome
Mitochondrial
Leigh's disease
Leber's disease
Other mitochondrial cytopathies
Sporadic, with parkinsonism
Parkinson's disease
Progressive supranuclear palsy
Multiple system atrophy
Corticobasal degeneration

Adapted from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

dopa-responsive dystonia have a mutation in the *GCH1* gene, which results in reduced production of dopamine. Approximately 75% of patients have notable worsening of dystonia as the day progresses (*diurnal variation*). Exercise often aggravates the dystonia. Patients commonly demonstrate some degree of bradykinesia (especially in the legs) and postural instability. Rare adult-onset disease may result in a pure parkinsonian phenotype. Dopa-responsive dystonia should be considered in all children with dystonia. Symptoms are exquisitely sensitive to low doses of levodopa (typically as little as 50 mg/day of levodopa), and this treatment allows patients to live a normal life without the usual complications seen in Parkinson's disease (Chapter 416).

Myoclonus dystonia, which usually begins within the first decade of life, combines dystonia with separate multifocal myoclonic jerks. Myoclonus dystonia is genetically heterogeneous; the most common definable cause is a mutation in the *e-sarcoglycan* gene. The dystonia in these patients most often involves the neck or upper limbs, is mild, and is often overlooked. The disorder can also include psychopathology, such as obsessive-compulsive behavior. A characteristic feature of this disorder is the marked ameliorative effect of ethanol on both the myoclonus and the dystonia, a feature that sometimes results in alcohol abuse.

OTHER DYSTONIAS

Dystonia may be a symptom of many diseases. The nature and extent of the investigations undertaken depend on such factors as age of onset, clues provided on the history, and additional neurologic or systemic features on examination. *Wilson's disease* (Chapter 218) is an important consideration in the diagnosis of dystonia beginning in children and young adults.

Some patients with dystonia, chorea, or a mixture of the two ("choreoathetosis") have intermittent symptoms (*paroxysmal dyskinesias*) and may be normal between episodes. The duration of symptoms can be as brief as a few seconds to a few minutes or persist for several hours. Symptoms triggered by sudden movement, which are termed *kinesigenic*, are typically brief; prolonged episodes are commonly triggered by exercise, stress, fatigue, caffeine, or alcohol. These paroxysmal dyskinesias may be genetically determined, idiopathic, the manifestation of another disorder (e.g., head injury, brain tumor, or stroke), or even psychologically based.

TREATMENT

Ideally, treatment is directed at the underlying cause, such as dopa-responsive dystonia, which is treated with levodopa (usually up to 300 mg per day) or Wilson's disease (Chapter 218). Unfortunately, cause-specific treatment usually is not possible, so a variety of symptomatic treatments may be tried, often unsuccessfully, in an attempt to reduce disability.

Focal injections of botulinum toxin are now usually the first choice for treatment of focal and segmental dystonias. This approach can improve the condition of patients with cranial (blepharospasm, oromandibular dystonia) and cervical dystonia. Patients with task-specific limb dystonias (e.g., writer's cramp) often benefit less because weakness of the treated muscles, which is the most common side effect of this therapy, can impair other important upper limb functions.

Young patients in particular can tolerate and benefit from high doses of anticholinergic drugs such as trihexyphenidyl (6 to 40 mg/day, but sometimes as much as 100 mg/day). Muscle relaxants, including benzodiazepines (diazepam, 5 to as much as 100 mg/day) and baclofen (40 to 120 mg/day), may provide some benefit. Dopamine-depleting (e.g., tetrabenazine, 50 to 200 mg/

day) and dopamine-blocking (e.g., haloperidol, 3 to 30 mg/day) agents are occasionally helpful (more often effective in tardive dystonia than in other types). Neurosurgical treatments, particularly deep brain stimulation of the internal segment of the globus pallidus, can be considered in medically refractory, disabling dystonia, especially in patients with idiopathic dystonia (e.g., DYT1, adult-onset cervical dystonia).

TICS

EPIDEMIOLOGY AND PATHOBIOLOGY

Tics are repetitive, stereotyped movements (motor tics) or vocalizations (vocal tics). Transient tics are extremely common in childhood, and simple tics may begin in childhood and persist throughout adult life. Most tics (Table 417-6) are primary or idiopathic and have no identifiable cause. Secondary tics are caused by a defined underlying brain disease or environmental factor.

CLINICAL MANIFESTATIONS

Tics vary in terms of complexity, from abrupt, brief, meaningless movements or sounds (*simple motor tics* such as eye blinking, nose wrinkling, or head jerking; *simple vocal-phonic tics* such as sniffing, throat clearing, or grunting) to more sustained, more deliberate, almost meaningful gestures or utterances (*complex motor tics* such as touching, hand shaking, and jumping; *complex vocal tics* such as echolalia [repeating others], palilalia [repeating oneself], and coprolalia [uttering profanities]). The frequency of the tics in an individual patient varies markedly over minutes, hours, days, weeks, and years.

TABLE 417-6 ETIOLOGIC CLASSIFICATION OF TICS

PRIMARY OR IDIOPATHIC TICS
Transient motor or phonic tics
Chronic motor or phonic tics
Adult-onset tics
Tourette's syndrome
SECONDARY TICS
Genetic disorders
Neuroacanthocytosis
Huntington's disease
Neurodegeneration with Brain Iron Accumulation 1 (NBIA 1) (previously Hallervorden Spatz disease)
Idiopathic dystonia*
Tuberous sclerosis*
Chromosomal disorders
Infections
Sydenham's chorea
PANDAS†
Encephalitis and postencephalitic disorders
Creutzfeldt-Jakob disease
Neurosyphilis
Drugs
Methylphenidate
Amphetamines
Cocaine
Levodopa
Carbamazepine
Phenytoin
Phenobarbital
Lamotrigine
Neuroleptics
Developmental disorders
Mental retardation
Pervasive developmental disorders/autism
Other causes
Head trauma
Stroke
Carbon monoxide poisoning
Cardiopulmonary bypass with hypothermia
RELATED DISORDERS
Mannerisms, stereotypies
Compulsions
Self-injurious behavior

*Tics have been described with these conditions but may simply be coincidental.
†Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. The existence of this disorder remains somewhat controversial.
Adapted from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

DIAGNOSIS

Various characteristics help to differentiate tics from other abnormal movements. Tics are often described by patients as being "semivoluntary" in response to an inner, irresistible urge. Premonitory sensory symptoms occasionally precede the tic, generally in the same general anatomic area as the tic itself. Relief is often associated with the production of the tic. Tics can be partially or completely voluntarily suppressed for variable periods, but often at the expense of mounting inner tension and psychological discomfort. Performing the tic or sometimes even substituting another more acceptable behavior for the socially inappropriate tic alleviates the tension. Many patients report that some tics occur in response to a typical urge, whereas the same or different tics may be unexpected and totally involuntary.

Tourette's Syndrome

EPIDEMIOLOGY AND PATHOBIOLOGY

The exact relationship between childhood tics and Gilles de la Tourette's syndrome remains uncertain. Tourette's syndrome is a common disorder, with prevalence estimates varying from 10 to 700 per 100,000. There is a male preponderance of 3:1 for the classic syndrome, but female patients manifest obsessive-compulsive features more often than tics. A functional mutation in the *HDC* gene encoding L-histidine decarboxylase can result in Tourette's syndrome, thereby suggesting a role for histaminic neurotransmission in its pathogenesis (Video 417-11).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The criteria for this disorder include the presence of multiple motor and at least one vocal tic beginning before the age of 21 years (typically between ages 2 and 10 years) and lasting for more than 1 year, waxing and waning symptoms over time (new tics replacing old ones; previous tics sometimes recurring years after they had originally resolved), and the absence of other explanatory medical conditions. Involuntary swearing (coprolalia), a highly publicized feature of the syndrome, is present in fewer than 10% of patients and is usually manifested by aborted forms such as "fu" and "shi." Patients commonly exhibit a variety of comorbid disorders including obsessive-compulsive disorder, attention-deficit disorder (with or without hyperactivity), impulse control problems, and other behavioral disturbances.

TREATMENT

Rx

Most patients who fulfill diagnostic criteria for Tourette's syndrome have mild symptoms that do not require treatment; education, reassurance, behavioral therapy, and follow-up are often sufficient. When tics (isolated or as part of Tourette's syndrome) interfere with social and physical function, low-dose clonazepam (0.5 to 4 mg/day) may be effective. Clonidine (0.05 to 0.5 mg/day) is variably effective in controlling tics and may be useful for impulse control and symptoms of attention-deficit/hyperactivity disorder (ADHD); alternatively, guanfacine (0.5 to 4 mg/day) can be used. The most effective treatments for disabling tics are the dopamine receptor blockers such as risperidone (0.5 to 16 mg/day), haloperidol (0.5 to 20 mg/day), pimozide (0.5 to 10 mg/day), fluphenazine (0.5 to 20 mg/day), and aripiprazole (5 to 15 mg/day), but caution is required in view of the potential for important side effects, including tardive dyskinesia, with long-term use. An alternative without this complication is the dopamine depleter tetrabenazine (50 to 200 mg/day dopamine). Injected botulinum toxin may be effective for simple motor tics of the face and neck and may also reduce the urge to perform the tic. Comorbid ADHD can be treated safely with stimulant therapy (e.g., methylphenidate, 2.5 to 60 mg/day) without a significant risk for increasing the severity of tics. Obsessive-compulsive symptoms may respond well to selective serotonin reuptake inhibitors (e.g., clomipramine, 25 to 250 mg/day; paroxetine, 10 to 60 mg/day; or citalopram, 10 to 40 mg/day). Behavioral disorders, which remain a major therapeutic challenge, may require a variety of psychotherapeutic or behavioral modification approaches. Promising preliminary reports of deep brain stimulation require confirmation in controlled clinical trials.

PROGNOSIS

The natural history of Tourette's syndrome is to stabilize and often improve in adolescence. Approximately 50% of patients have a complete or partial remission at this time.

TABLE 417-7 CLASSIFICATION AND CAUSES OF MYOCLONUS

PHYSIOLOGIC MYOCLONUS

Sleep myoclonus
Anxiety-induced myoclonus
Exercise-induced myoclonus
Hiccups
Benign infantile myoclonus during feeding

ESSENTIAL MYOCLONUS

Essential myoclonus*
  Hereditary
  Sporadic
Myoclonus dystonia*

EPILEPTIC MYOCLONUS

Fragments of epilepsy
  Isolated epileptic myoclonic jerks
  Photosensitive myoclonus
  Myoclonic absences
  Epilepsia partialis continua
  Idiopathic stimulus-sensitive myoclonus
Childhood myoclonic epilepsies
  Infantile spasms
  Lennox-Gastaut syndrome
  Cryptogenic myoclonus epilepsy
  Juvenile myoclonic epilepsy of Janz
Benign familial myoclonic epilepsy
Baltic myoclonus (Unverricht-Lundborg)

SYMPTOMATIC MYOCLONUS

Storage disease
  Lafora body disease
  Lipidoses
  Neuronal ceroid lipofuscinosis
  Sialidosis
Spinocerebellar degeneration
  Friedreich's ataxia
  Ataxia-telangiectasia
  Other spinocerebellar degenerations
Basal ganglia degenerations
  Wilson's disease
  Idiopathic torsion dystonia
  Neurodegeneration with Brain Iron Accumulation 1 (NBIA 1)
    (Hallervorden-Spatz disease)
  Progressive supranuclear palsy
  Corticobasal degeneration
  Parkinson's disease
  Multiple system atrophy
  Huntington's disease
  Dentatorubropallidoluysian atrophy
Mitochondrial cytopathies
Dementias
  Alzheimer's disease
  Creutzfeldt-Jakob disease
  Dementia with Lewy bodies
Viral encephalopathies
  Subacute sclerosing panencephalitis
  Encephalitis lethargica
  Herpes simplex encephalitis
  Arbovirus encephalitis
  Human immunodeficiency virus infection
  Postinfectious encephalitis
Metabolic disorders
  Hepatic failure
  Renal failure
  Dialysis dysequilibrium syndrome
  Hyponatremia
  Hypoglycemia
  Nonketotic hyperglycemia
  Infantile myoclonic encephalopathy
  Multiple carboxylase deficiency
  Biotin deficiency
Toxins
  Bismuth
  Heavy-metal poisoning
  Methylbromide, dichlorodiphenyltrichloroethane (DDT)
  Drugs (multiple)
Physical encephalopathies
  Posthypoxic myoclonus (Lance-Adams)
  Post-traumatic status
  Heat stroke
  Electric shock
  Decompression injury
Focal central nervous system damage
  Stroke
  Post-thalamotomy status
  Tumor
  Trauma
  Spinal cord lesions
Paraneoplastic syndromes
Psychogenic myoclonus

*Probably represents the same entity.
Adapted from Cloutier M, Lang AE. Movement disorders: an overview. In: Factor SA, Lang AE, Weiner WJ, eds. *Drug Induced Movement Disorders*. Malden, Mass: Blackwell; 2005:3-19.

MYOCLONUS

DEFINITION

Myoclonus (or myoclonic jerks) consists of sudden, brief, shocklike, involuntary movements that result from both active muscle contraction (positive myoclonic jerks) and brief inhibition of ongoing muscle activity (negative myoclonic jerks). The most common form of negative myoclonic jerk is *asterixis.*

PATHOBIOLOGY

Myoclonus generally arises in the central nervous system, although rare peripheral causes are described, and it is distinct from abnormal muscle activity associated with peripheral nervous system diseases, such as fasciculations or myokymia. Myoclonus can be classified according to origin (Table 417-7), including physiologic, essential, epileptic, and symptomatic forms. Physiologic myoclonus, such as hypnic (sleep) jerks and hiccups, occurs in normal healthy subjects. Patients with essential myoclonus, which may be sporadic or inherited, often have additional postural tremor or dystonia, and this disorder is probably the same as what is now referred to as *myoclonus dystonia* (see Dystonias, earlier). Epileptic myoclonus arises in the context of seizures (Chapter 410), including many inherited generalized epileptic syndromes and the progressive myoclonic epilepsies. Symptomatic myoclonus occurs in association with a large number of encephalopathic states.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Myoclonic jerks are very short, typically lasting less then 150 milliseconds. Myoclonus can be spontaneous, action induced, or reflex (induced by various sensory stimuli), or a combination. Spontaneous myoclonus occurs at rest, without any provocation. Action myoclonus occurs during purposeful movement and is often very disabling owing to its interference with volitional activity. Reflex myoclonus can be triggered by visual, auditory, or somesthetic stimuli. The distribution of myoclonus may be focal, segmental, multifocal, or generalized. When myoclonus involves more than one body area, the movements may be synchronous or asynchronous. Myoclonus can be intermittent or repetitive, and it sometimes is rhythmic (e.g., usually originating in the brain stem or spinal cord). *Palatal myoclonus,* recently redesignated as *palatal tremor,* is a rhythmic movement disorder originating in the brain stem and involving the soft palate as well as the eyes, facial muscles, neck, and limbs; it is commonly the result of a focal lesion (e.g., stroke, demyelination) in the connections between the dentate nucleus of the cerebellum and the inferior olives of the medulla (*symptomatic palatal tremor*).

DIAGNOSIS

Myoclonus can be classified according to the anatomic site of origin, usually with the assistance of detailed electrophysiologic assessments. These sites may be cortical, subcortical (e.g., thalamus; lower brain stem [reticular myoclonus]), or spinal (two types: spinal segmental and propriospinal).

TREATMENT

Rx

Management of myoclonus, when possible, should be directed specifically at the underlying cause. Drug treatment includes a variety of anticonvulsant medications, most notably clonazepam (1.5 to 15 mg/day), valproic acid (10 to 15 mg/kg/day), carbamazepine (600 to 1200 mg/day), and levetiracetam (1000 to 4000 mg/day). Postanoxic action myoclonus (the Lance-Adams syndrome) in some patients who survive severe cerebral anoxia may also respond to 5-hydroxytryptophan (400 to 2800 mg/day) given with carbidopa (75 to 300 mg/day). Acetazolamide (250 to 1000 mg/day) may be useful for patients with action myoclonus.

HYPEREXPLEXIA

A disorder related to myoclonus, known as *hyperexplexia,* manifests as excessive response to startle. It may be inherited (startle disease, most often caused by a mutation in the α_1-subunit of the glycine receptor gene). Some patients demonstrate only generalized body jerking or an exaggerated startle response that habituates poorly after repeated stimuli. Others also experience disabling stiffness in response to sudden unexpected stimuli such as loud sound. The disorder responds well to clonazepam (1.5 to 15 mg/day) therapy.

OTHER MOVEMENT DISORDERS

Drug-Induced Movement Disorders

All the movements listed in Table 417-1 can be induced by medications. Neuroleptic drugs, which block postsynaptic dopamine receptors, particularly the D2 subtype, can result in a variety of movement disorder syndromes, including acute dystonic reactions, akathisia, drug-induced parkinsonism (including "the rabbit syndrome" with perinasal and perioral rest tremor), the neuroleptic malignant syndrome, and a variety of later-onset, often persistent, movements referred to as *tardive dyskinesia.*

ACUTE DYSTONIC REACTIONS

Acute dystonic reactions are most often seen in young patients who are receiving potent antipsychotic agents (e.g., young male patients receiving high doses of haloperidol for acute psychosis), but they also occur in patients receiving dopamine receptor blockers, including metoclopramide as antiemetic therapy. Symptoms range from overt dystonic postures of the face and neck, to involuntary prolonged deviation of the eyes (oculogyric crises), to simple slurring of speech and difficulty coordinating the tongue. Symptoms often vary from moment to moment and can increase with anxiety and improve with relaxation or reassurance. Acute dystonic reactions are self-limited and respond rapidly to a parenteral injection of an anticholinergic drug such as benztropine (2 mg intravenously followed by 2 mg three times daily orally for a variable duration depending on neuroleptic use) or an antihistaminic such as diphenhydramine (50 mg intravenously followed by oral benztropine).

AKATHISIA

Akathisia refers to a sense of restlessness and a need to move. Typically, the patient performs a variety of purposeful or semipurposeful, often complex, movements in response to an uncomfortable subjective restlessness, including pacing when standing, marching in place, rocking, shifting weight, moving legs when sitting, picking at clothing or hair, rubbing body parts with hands, and other similar movements. Akathisia is most often a side effect of medications, especially neuroleptic drugs and selective serotonin reuptake inhibitors (Chapter 404). Symptoms occur in a dose-related fashion and usually resolve on drug withdrawal. Akathisia is a common reason for psychiatric patients to comply poorly with their medications; management includes adjustment of the dose or type of antipsychotic agent and trials of β-blockers (e.g., propranolol, 80 mg/day) or antiparkinson agents, such as anticholinergics (e.g., benztropine (6 mg/day) or amantadine (200 to 300 mg/day). Rare patients experience a very disabling and persistent form referred to as *tardive akathisia.* Akathisia is also sometimes seen in patients with Parkinson's disease.

NEUROLEPTIC MALIGNANT SYNDROME

The *neuroleptic malignant syndrome* (Chapters 440 and 442) is an uncommon but severe, sometimes fatal, complication of neuroleptic therapy. Patients usually manifest a combination of features including fever, marked rigidity, changes in level of arousal, and autonomic instability. Laboratory abnormalities include a marked increase in the serum creatine kinase level and the blood leukocyte count. Management involves early recognition, withdrawal of the causative agent, systemic supportive therapy, a dopamine agonist (most experience has been with the older agent bromocriptine, ≤60 mg/day), and, when necessary, dantrolene sodium (50 to 600 mg/day orally or ≤10 mg/kg/day intravenously) to reduce muscle contraction.

TARDIVE DYSKINESIA

EPIDEMIOLOGY AND PATHOBIOLOGY

The term *tardive dyskinesia* encompasses a wide variety of abnormal movements caused by chronic neuroleptic therapy. The cumulative 5-year incidence rate in patients taking classic neuroleptics is approximately 25%, and the incidence may continue to increase almost linearly beyond that point. The propensity to develop tardive dyskinesia on newer atypical neuroleptics appears to be much lower (Video 417-12).

CLINICAL MANIFESTATIONS

Tardive dyskinesia generally begins after a minimum of 6 weeks of treatment. One of the most common forms involves the lower facial muscles and has been given a variety of names, including *orobuccolinguomasticatory dyskinesia*. The movements generally include repetitive chewing and smacking movements with the tongue either protruding between the lips (fly-catching movements) or pushing into the cheek (bonbon sign). Although the movements are somewhat choreic, they are not as random as true chorea. The more stereotypical, repetitive nature of the movements, involving not only face but also the limbs (e.g., piano playing movements of the fingers, rocking or thrusting of the pelvis), has encouraged the more recent term *tardive stereotypies*. Many patients with classic orofacial tardive dyskinesia seem unaware of the presence of the movements and are not disabled by them, but others are embarrassed or otherwise impaired.

Tardive akathisia and tardive dystonia are less common but particularly disabling subtypes of tardive dyskinesia. Rarer forms include tardive tics (tourettism), tardive tremor, tardive myoclonus, and even tardive oral or genital pain.

TREATMENT AND PROGNOSIS

Rx

Treatment is often unsatisfactory, but the dopamine depleter tetrabenazine (50 to 200 mg/day) can be very effective. Prevention is the most important consideration. The physician must regularly reassess the need for ongoing neuroleptic therapy, consider switching to an atypical agent when possible (particularly quetiapine and clozapine; Chapter 404), and routinely evaluate the patient for the presence of early subtle clinical features, such as mild pursing of the lips or rolling movements of the tongue in the mouth. Unfortunately, tardive dyskinesia may persist for many years despite withdrawal of neuroleptic treatment in up to 50% of patients. Several atypical neuroleptics, such as risperidone and olanzapine, nevertheless block dopamine D2 receptors sufficiently to cause drug-induced parkinsonism and tardive dyskinesias.

Restless Legs Syndrome

EPIDEMIOLOGY

Restless legs syndrome (Chapter 412) is now recognized as an extremely common disorder affecting between 3 and 29% of the general population. Women are affected more frequently than men. Although the incidence increases with age, it can also affect children, in whom it may be confused with "growing pains" or ADHD.

PATHOBIOLOGY

Restless legs syndrome is most often primary or idiopathic, in which case it is frequently inherited in an autosomal dominant fashion. Five genetic loci associated with restless legs syndrome by recent genome-wide studies are variants in MEIS1, BTBD9, MAP2K5/LBXCOR1, and PTPRD. Restless legs syndrome also may be secondary to other causes, including peripheral neuropathy, uremia, pregnancy, and iron deficiency, and it may occur more commonly than by chance in some neurodegenerative disorders such as Parkinson's disease. The pathophysiology of restless legs syndrome is uncertain, but central iron dysregulation may somehow alter central dopamine. Serum ferritin levels are often low, even in the presence of normal values of hemoglobin, hematocrit, iron, and iron-binding capacity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In restless legs syndrome, as in akathisia, movements occur because of the subjective need to move. However, unlike in akathisia, the patient typically complains of a variety of sensory disturbances in the legs, including pins and needles, creeping or crawling sensations, aching, itching, stabbing, heaviness, tension, burning, or coldness. Occasionally, similar symptoms are appreciated in the upper limbs. These symptoms are usually experienced during periods of prolonged inactivity, especially with recumbency in the evening, and are often associated with insomnia (Chapter 412). The discomfort appears particularly during the transition from wake to sleep in the evening and often follows a circadian pattern, peaking between midnight and 4 AM. Symptoms are typically relieved only by movement or stimulation of the legs; although these maneuvers are effective while they are being performed, the discomfort usually returns as soon as the individual becomes inactive or returns to bed to try to sleep. Patients often have significant problems with immobility during long automobile drives or plane flights.

In approximately 80% of patients, this condition is associated with another movement disorder, periodic leg movements in sleep, sometimes inappropriately called nocturnal myoclonus. These periodic, slow, sustained (1 to 2 seconds) movements range from synchronous or asynchronous dorsiflexion of the toes and feet to triple flexion of one or both legs. In 15% of patients, more rapid myoclonic movements or slower, prolonged dystonic-like movements of the feet and legs are present while patients are awake. In the absence of evidence of a secondary cause of restless legs syndrome, the only useful routine test is a serum ferritin level.

TREATMENT Rx

Dopamine agonists (e.g., pramipexole, 0.125 to 1.5 mg at bedtime) and ropinirole (1 to 4 mg at bedtime) are the treatments of choice in moderate to severe restless legs syndrome and can be very effective.[1] Levodopa preparations (100 to 300 mg of levodopa at bedtime; consider controlled-release preparation) are also effective but are more often associated with disabling rebound symptoms early in the morning or during the day (*augmentation*). A new nondopaminergic agent, XP13512, is also effective, but is not yet approved in the United States.[2] Patients with milder symptoms may respond to gabapentin (300 to 2400 mg/day). Opiate agonists (e.g., oxycodone, 5 mg at bedtime; codeine, 30 mg at bedtime; propoxyphene, 65 mg or N-100 mg at bedtime) and less often benzodiazepines (e.g., clonazepam, 0.5 to 2 mg at bedtime) may also be effective. Tolerance or loss of original benefit may occur with all these treatments. Iron replacement is indicated in patients with reduced serum ferritin levels (325 mg ferrous sulfate two to three times per day for 3 to 4 months until ferritin levels exceed 50 mg/L and iron saturations surpass 20%).

Painful Legs and Moving Toes

Another uncommon but well-defined movement disorder of the lower limbs has been termed *painful legs and moving toes.* Patients typically complain of a deep pulling or searing pain in the lower limbs, associated with continuous involuntary wriggling or writhing of the toes. Occasionally, the ankle and less commonly more proximal muscles of the legs are involved. Rarely, a similar problem is seen in the upper limbs as well. Various treatments have been tried without much benefit to the pain, which is typically the major concern of the patient.

Other Abnormal Movements

Numerous abnormal movements are caused by dysfunction of the peripheral nerves (e.g., fasciculations, myokymia); these movements are usually easily separated from the movement disorders described earlier. *Hemifacial spasm* is a common disorder in which irregular clonic and tonic movements involve the muscles innervated by the facial nerve, usually owing to compression of the seventh nerve as it exits the brain stem, most often by a normal small artery or vein and less often by a mass lesion or inflammatory process. Eyelid twitching is usually the first symptom, followed at variable intervals by lower facial muscle involvement. A magnetic resonance image with careful assessment of the posterior fossa is necessary to exclude secondary causes. Treatment usually involves injections of botulinum toxin into selected facial muscles, although surgical decompression can be curative (Video 417-13).

Hereditary Cerebellar Ataxias and Spastic Paraplegias

CEREBELLAR ATAXIAS

The hereditary cerebellar ataxias, which may begin in childhood or adulthood, can progress at widely varying rates. These ataxias are divided into early-onset ataxias, which are usually inherited as autosomal recessive disorders, and adult-onset ataxias, which are usually autosomal dominant. A small number are X-linked. Because most of these ataxias are untreatable, it is important to recognize the rare causes of treatable or preventable progressive ataxias.

Friedreich's Ataxia

EPIDEMIOLOGY AND PATHOBIOLOGY

The most common progressive inherited ataxia in children is Friedreich's ataxia. Friedreich's ataxia is a trinucleotide-repeat disorder that affects the central and peripheral nervous systems, the heart, and many other organs. Friedreich's ataxia is an autosomal recessive disorder with no anticipation. It has an estimated carrier frequency in the population of about 1 in 100 and a resulting disease prevalence of about 1 per 50,000.

The normal length of the GAA repeat on the long arm of chromosome 9 (9q13-q21) is 10 to 21 copies, but expansion in individuals with Friedreich's ataxia results in 200 to 900 copies and disrupts the expression of the protein frataxin. GAA unstable expansion, which occurs on an intron, leads to gene silencing rather than to the production of an abnormal protein. Higher numbers of copies correlate with more severe neurologic deficits. Frataxin appears to be critical for iron export and mitochondrial function. Because accumulation of mitochondrial iron affects the production of oxygen radicals, loss of frataxin may lead to oxidative mitochondrial damage. The pathology of Friedreich's ataxia includes spinal cord atrophy, which often is evident on magnetic resonance imaging, with loss of neurons in Clarke's columns and the dorsal root ganglia. Degeneration occurs in spinocerebellar tracts, pyramidal tracts, dorsal column tracts, and peripheral nerves, with minor cell loss in the brain stem and cerebellum. Cardiomyopathy is associated with ventricular hypertrophy and chronic interstitial myocardial fibrosis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Typical Friedreich's ataxia first presents clinically during puberty with progressive ataxia, loss of lower extremity deep tendon reflexes, and extensor plantar responses (i.e., Babinski's signs). Other common clinical features include nystagmus, dysarthria, stocking-glove sensory loss, and weakness in the lower extremities. Patients frequently have kyphosis, scoliosis, and pes cavus. Interstitial myocardial disease may cause a typical hypertrophic cardiomyopathy (Chapter 60). A small number of patients have a later onset and less severely progressive course.

The diagnosis is made by genetic testing for the trinucleotide repeat expansion, which usually is present on at least one allele. Point mutations are sometimes present in the other allele and are more difficult to detect. Potentially treatable conditions with similar clinical manifestations include vitamin B_{12} deficiency (Chapter 225), abetalipoproteinemia (Chapter 142), and a selective defect in vitamin E absorption (Chapter 225).

TREATMENT AND PROGNOSIS Rx

Treatment consists of supportive measures. A randomized trial using idebenone showed no benefit. The disorder is progressive, and patients usually are wheelchair bound by their mid-20s. The average age at death is 37 years, and the major cause of death is hypertrophic cardiomyopathy (Chapter 60).

Other Spinocerebellar Ataxias

The hereditary spinocerebellar ataxias are routinely classified by their specific molecular diagnosis. At least 10 autosomal recessive and nearly 30 autosomal dominant cerebellar ataxias have been identified. Clinical features, ethnic origin, and family history may suggest an autosomal recessive, autosomal dominant, or X-linked inheritance and often narrow the search for the genetic mutation. As the molecular pathogenesis of many of the hereditary ataxias is unraveled, the current numerical classification, which largely reflects the chronology of the identification of causative mutations, is likely to be replaced

by a more pathophysiologic approach. Spinocerebellar ataxias 1, 2, 3, 6, 7, and 17 are caused by trinucleotide expansions in or adjacent to a protein-coding region of a gene. These expansions result in polyglutamine expansions in the protein product, which likely results in a toxic gain of function in a manner analogous to the pathogenesis of Huntington's disease.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The predominant clinical features of the spinocerebellar ataxias are ataxia and dysarthria. Other cerebellar signs include titubation, dysdiadochokinesia, and dysmetria. With increasing ataxia, patients can become wheelchair bound. Additional clinical signs include ophthalmoplegia, dementia, optic atrophy, retinal pigmentary degeneration, deafness, dysphagia, and peripheral neuropathy. Extrapyramidal features include masked facies, cogwheel rigidity, dystonia, athetosis, and chorea. Levodopa-responsive parkinsonism (Chapter 416) may be seen in some patients, particularly in spinocerebellar ataxia 2 and spinocerebellar ataxia 3. Pyramidal dysfunction includes spastic limbs, especially legs; hyperreflexia; and Babinski's response. Diagnosis is based on genetic testing.

TREATMENT AND PROGNOSIS Rx

No treatment is currently available. The spinocerebellar ataxias are progressive, with worsening gait, hand coordination, speech, and eye movements, but with preserved mental function. Pneumonia is a common cause of death.

HEREDITARY SPASTIC PARAPLEGIAS

Hereditary spastic paraplegia, also known as Strümpell's disease, can be an autosomal dominant disorder (70 to 80%), an autosomal recessive disorder, or an X-linked disorder. The prevalence of hereditary spastic paraplegia is about 1 per 10,000 in the population. At least 14 loci have been identified for autosomal dominant hereditary spastic paraplegias; 15 loci for autosomal recessive hereditary spastic paraplegias; and 3 loci for X-linked hereditary spastic paraplegias. The autosomal dominant spastic gait genes include *SPG4*, which encodes for spastin, and the less common *SPG3A* (atlastin) and *SPG31* (*REEP1*) genes.

At autopsy, patients with hereditary spastic paraplegia have axonal degeneration of the pyramidal tracts and dorsal column tracts with lesser involvement of the spinocerebellar tracts. The neurons of origin are intact. The peripheral nervous system is unaffected.

CLINICAL MANIFESTATIONS

Patients with hereditary spastic paraplegia have a progressive gait disturbance with spasticity of lower extremities, hyperreflexia, clonus, and extensor plantar responses. Cranial nerves, speech, swallowing, and upper extremities remain normal. Although patients can experience weakness of their lower extremities, spasticity is usually the disabling component. The progressively increased leg spasticity results in tripping and an inability to run. Strength is generally preserved, and pain is infrequent. Sensation is normal. Pure hereditary spastic paraplegia is limited to symptoms and signs of spasticity, whereas complex or complicated hereditary spastic paraplegia includes additional neurologic or other abnormalities. Other clinical features include pes cavus (30 to 50%), decreased vibratory sensation, and urinary frequency, urgency, and hesitancy.

DIAGNOSIS

Hereditary spastic paraplegia is diagnosed when patients meet clinical criteria and when other causes of spasticity are excluded. Magnetic resonance imaging may show spinal cord atrophy, but cerebrospinal fluid analysis and nerve conduction studies are normal. The differential diagnosis includes other genetic conditions, spinal cord disease from structural lesions, multiple sclerosis, and vitamin deficiencies or retroviral infections (Table 417-8). Even a positive family history does not obviate the need to exclude potentially treatable alternative diagnoses.

TREATMENT AND PROGNOSIS Rx

No specific treatment is available. Symptomatic therapy is aimed at decreasing disability and preventing complications, such as contractures. Antispastic agents, such as oral baclofen (usually 10 to 20 mg three times daily), improve spasticity but should be used with caution because they may worsen weakness. Some reports suggested an improved therapeutic response to intrathecal baclofen, but no controlled trials have addressed this issue. Preliminary data also raise the possible utility of injected botulinum neurotoxin type A injections for improving spasticity. Most patients become nonambulatory between 60 and 70 years of age. Patients with complicated hereditary spastic paraplegia often have other disabling features.

TABLE 417-8 DIFFERENTIAL DIAGNOSIS OF HEREDITARY SPASTIC PARAPLEGIAS

Hereditary
Dopa-responsive dystonia
Spinocerebellar ataxias
Adult-onset adrenoleukodystrophy
Structural lesions of the spinal cord
Cervical spondylosis
Tumor
Arteriovenous malformation
Syringomyelia
Multiple sclerosis
Primary lateral sclerosis
Vitamin B_{12} deficiency
Copper deficiency
Infections
Human immunodeficiency virus
Human T-lymphotropic virus type 1
Tertiary syphilis

Grade A

1. Zesiewicz TA, Elble R, Louis ED, et al. Practice parameter: therapies for essential tremor—report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2005;64:2008-2020.
2. Mestre T, Ferreira J, Coelho MM, et al. Therapeutic interventions for symptomatic treatment in Huntington's disease. *Cochrane Database Syst Rev*. 2009;8(3):CD006456.
3. Jankovic J, Esquenazi A, Fehlings D, et al. Evidence-based review of patient-reported outcomes with botulinum toxin type A. *Clin Neuropharmacol*. 2004;27:234-244.
4. Mueller J, Skogseid IM, Benecke R, et al. Pallidal deep brain stimulation improves quality of life in segmental and generalized dystonia: results from a prospective, randomized sham-controlled trial. *Mov Disord*. 2008;23:131-134.
5. Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. *JAMA*. 2010;303:1929-1937.
6. Trenkwalder C, Hening WA, Montagna P, et al. Treatment of restless legs syndrome. *Mov Disord*. 2008;23:2267-2302.
7. Kushida CA, Becker PM, Ellenbogen AL, et al. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. *Neurology*. 2009;72:439-446.

SUGGESTED READINGS

Abdo WF, van de Warrenburg BP, Burn DJ, et al. The clinical approach to movement disorders. *Nat Rev Neurol*. 2010;6:29-37. *Review*.

Gasser T, Finsterer J, Baets J, et al. EFNS guidelines on the molecular diagnosis of ataxias and spastic paraplegias. *Eur J Neurol*. 2010;17:179-188. *Current approach to identifying the specific mutation*.

Kurlan R. Tourette's Syndrome. *N Engl J Med*. 2010;363:2332-2338. *Review*.

Müller U. The monogenic primary dystonias. *Brain*. 2009;132:2005-2025. *Thorough review*.

Ostrem JL, Racine CA, Glass GA, et al. Subthalamic nucleus deep brain stimulation in primary cervical dystonia. *Neurology*. 2011;76:870-878. *Deep brain stimulation improved dystonia*.

Poon LH, Kang GA, Lee AJ. Role of tetrabenazine for Huntington's disease-associated chorea. *Ann Pharmacother*. 2010;44:1080-1089. *Review of benefits and side effects*.

Thevathasan W, Gregory R. Deep brain stimulation for movement disorders. *Pract Neurol*. 2010;10:16-26. *Review*.

418

AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES

PAMELA J. SHAW

DEFINITION

The motor neuron diseases (Table 418-1) are a heterogeneous group of disorders in which selective loss of function of upper motor neurons, lower motor neurons, or both results in impairment of the nervous system's control of voluntary movement. The most common acquired motor neuron disease, amyotrophic lateral sclerosis (ALS), is a combined upper and lower motor neuron disorder. The features of lower motor neuron involvement are muscle wasting, fasciculations, and flaccid weakness, with normal or depressed tendon reflexes. Upper motor neuron dysfunction may cause increased muscle tone, clonus, weakness in the pyramidal distribution, and extensor plantar responses. Recent advances in the molecular genetics of hereditary motor neuron diseases have improved their classification and enhanced the careful diagnosis that is essential for genetic counseling, guidance, treatment, and advising patients about prognosis.

TABLE 418-1 CLASSIFICATION OF THE MAJOR MOTOR NEURON DISEASES

COMBINED UPPER AND LOWER MOTOR NEURON DISORDERS
Amyotrophic lateral sclerosis
Familial adult onset
Familial juvenile onset
Sporadic
ALS-plus syndromes
ALS with frontotemporal dementia
Western Pacific ALS–parkinsonism-dementia complex
UPPER MOTOR NEURON DISORDERS
Primary lateral sclerosis
Hereditary spastic paraplegias
Neurolathyrism
Konzo
LOWER MOTOR NEURON DISORDERS
Hereditary
Spinal muscular atrophies (SMAs)
Proximal autosomal recessive SMA (associated with *SMN* mutations) types I to IV
Other forms of SMA not associated with *SMN* mutations
Distal spinal muscular atrophies/hereditary motor neuronopathies
Kennedy's disease (X-linked spinobulbar neuronopathy)
Hexosaminidase deficiency (GM2 gangliosidosis)
Acquired
Monomelic focal and segmental spinal muscular atrophies
Multifocal motor neuropathies
Acute motor axonal neuropathy (AMAN)
Postpolio syndrome
Postirradiation syndrome
Infective disorders
Acute poliomyelitis
West Nile fever
Other viral infections, e.g., enterovirus 71 and rabies virus
Human immunodeficiency virus–associated motor neuron disorder
Lyme disease
Creutzfeldt-Jacob disease (amyotrophic forms)
DISORDERS OF THE BULBAR MOTOR SYSTEM
Kennedy's disease (X-linked bulbospinal neuronopathy)
Brown-Vialetto-Van Laere syndrome
Fazio-Londe disease
TOXIC DISORDERS OF THE MOTOR NEURON
Neurolathyrism
Konzo
Heavy metal toxicity (lead, mercury)
Western Pacific ALS–parkinsonism-dementia complex
Postirradiation motor neuron injury
DISORDERS OF MOTOR NEURON OVERACTIVITY
Neuromyotonia
Stiff person syndrome
MISCELLANEOUS MOTOR NEURON DISORDERS
Endocrinopathies, e.g., hyperthyroidism, hyperparathyroidism, hypoglycemia
Copper deficiency syndrome
Benign cramp-fasciculation syndrome

AMYOTROPHIC LATERAL SCLEROSIS

EPIDEMIOLOGY

ALS is a neurodegenerative disorder that causes progressive injury and cell death of lower motor neurons in the brain stem and spinal cord, as well as upper motor neurons in the motor cortex. ALS has an incidence of about 2 per 100,000 and a prevalence of 6 to 8 per 100,000. The global incidence is fairly uniform, with the exception of a few high-incidence foci such as the Western Pacific island of Guam. The disease affects predominantly middle-aged and elderly individuals, with a mean age at onset of 55 to 60 years, although younger individuals can also be affected. Increasing age, male sex (male-to-female ratio ≈1.6:1), and genetic susceptibility are the only proven risk factors, although ongoing research is assessing the effects of athleticism/physical exercise and other potential environmental risk factors. Approximately 90% of cases of ALS occur sporadically, but 5 to 10% are familial, usually with an autosomal dominant mode of inheritance.

PATHOBIOLOGY

The process of neuronal degeneration in ALS is complex. The subtype of disease caused by *SOD1* mutations accounts for 20% of familial ALS cases and 2% of ALS overall. Mutant *SOD1* appears to trigger a complex interplay of multiple pathogenic processes, including oxidative stress, protein aggregation, mitochondrial dysfunction, excitotoxicity, and impaired axonal transport. Non-neuronal cells in the vicinity of motor neurons may contribute importantly to neuronal injury. Genetically engineered mouse models of *SOD1*-related ALS have shown that normal astrocytes can protect motor neurons expressing mutant *SOD1* and that removing the expression of mutant *SOD1* from microglia or astrocytes has a significant effect in slowing the progression of disease in these murine models. Astrocytes expressing mutant *SOD1* exert toxic effects on neighboring motor neurons through as yet undefined mechanisms.

Familial motor neuron disease has been linked to mutations in *SOD1,* alsin, senataxin, angiogenin, VAPB, dynactin, TDP-43, and FUS/TLS, with a suggestion that defective RNA processing may play a key role in the pathogenesis of ALS. In the sporadic disease, associations have been reported with alterations in at least eight other genes.

Pathology

At autopsy, the gross pathologic features of ALS consist of atrophy of the cerebral precentral gyrus, as well as sclerosis and pallor of the corticospinal tracts of the spinal cord. Thinning of the hypoglossal nerves and ventral spinal roots may be observed, and muscle atrophy is obvious. Microscopically, ALS patients will typically have lost 50% of their spinal motor neurons and have diffuse astrocytic gliosis in the spinal gray matter. By comparison, motor neurons in Onuf's nucleus in the sacral spinal cord, which innervate the pelvic floor muscles, and the motor nuclei of cranial nerves III, IV, and VI, which control eye movements, are relatively preserved. A cardinal feature in residual motor neurons is the presence of ubiquitinated proteinaceous inclusions, which may be compact or skeinlike. TDP-43 has recently been recognized as a major protein constituent of these aggregates. In the motor cortex, there is variable loss of upper motor neurons and astrocytic gliosis. In the descending corticospinal tracts, axonal loss, myelin pallor, and gliosis are seen. The atrophied skeletal muscle shows clusters of angular atrophic fibers and fiber-type grouping, which results from serial denervation and reinnervation. The selectivity of the disease process for the motor system is now recognized to be relative, and involvement of extramotor parts of the central nervous system can be found, especially in the sensory and spinocerebellar

pathways, substantia nigra neurons, and dentate granule cells in the hippocampus.

CLINICAL MANIFESTATIONS

ALS is characterized by a combination of upper and lower motor neuron degeneration. Lower motor neuron degeneration causes weakness, atrophy, and fasciculation of the limb and bulbar musculature. Features of upper motor neuron dysfunction include the incongruous presence of active or brisk tendon reflexes in a wasted limb, increased muscle tone, and sometimes the presence of Babinski's sign. Upper motor neuron bulbar disease causes pseudobulbar palsy, with emotional lability, a brisk jaw jerk, slowing of repetitive tongue movements, and strained effortful speech. Fatigue and weight loss are also common symptoms. With end-stage disease, most patients will have features of upper and lower motor neuron dysfunction affecting all four limbs and the bulbar musculature.

In approximately 75% of patients, the disease starts distally, focally, and asymmetrically in the upper limb, lower limb (Video 418-1), or bulbar territories, followed by progressive spread of injury in an anatomically logical progression to contiguous groups of motor neurons. Affected individuals may notice weakness, wasting or clumsiness of one hand, or unilateral footdrop. Muscle cramps may precede other clinical features, and fasciculations are most noticeable in the large proximal limb muscles. In the upper limbs, the thenar and intrinsic hand muscles tend to be severely affected, whereas the triceps and finger flexors are relatively spared until late in the disease. In the lower limbs, the pattern of weakness is often in a pyramidal distribution (flexors weaker than extensors), with early weakness of hip flexion and ankle dorsiflexion and severe involvement of the distal muscles.

Bulbar symptoms, which are the initial feature in approximately 25% of patients, are especially common in elderly women with ALS (Video 418-2). The first problem is usually slurring of speech, initially apparent only when the individual is tired. Patients often have a mixed spastic/flaccid dysarthria, in which speech develops a tight, strangled quality because of the upper motor neuron component, with a superimposed nasal quality as a result of the flaccid lower motor neuron weakness of the palate and nasopharynx. In patients with bulbar disease, examination often reveals weakness of the facial muscles; a spastic, weak, wasted, and fasciculating tongue; and a brisk jaw jerk. Dysphagia, initially more pronounced for liquids than for solids, usually follows the dysarthria within a few weeks or months (Video 418-3). Complications include weight loss and prolonged and arduous meal times with frequent episodes of coughing, drooling of saliva, and aspiration pneumonia.

Respiratory muscle weakness is rarely the initial feature of ALS. More commonly, respiratory muscle weakness develops insidiously and causes dyspnea and orthopnea. Diaphragmatic weakness may be apparent from the paradoxical movement of the abdominal wall during inspiration and a marked decline in forced vital capacity in the supine position. Symptoms of nocturnal carbon dioxide retention may develop, including morning headaches, anorexia, and daytime somnolence.

Neck muscle weakness, which is common later in the course of disease, causes difficulty holding the head upright (dropped head syndrome). Eye movements tend to be spared even in advanced disease, thereby permitting limited communication by movements of the eyes. Similarly, the strength of the pelvic floor muscles is relatively preserved, so patients with ALS usually remain continent throughout the course of the disease.

Overt features of frontotemporal dementia (Chapter 409), with progressive deterioration in personality and behavior, will develop in approximately 5% of patients with ALS. Cognitive dysfunction may precede, follow, or coincide with the features of motor dysfunction. Up to 50% of ALS patients without overt dementia may show more subtle features of frontal lobe dysfunction.

About 5 to 10% of ALS patients have the progressive muscular atrophy variant with clinical features reflecting only degeneration of lower motor neuron groups in the spinal cord. In primary lateral sclerosis, patients have pure upper motor neuron degeneration. Although severe spastic spinobulbar paresis ultimately develops in these patients, the duration of survival is commonly 10 to 15 years after the onset of symptoms. The progressive bulbar palsy variant usually progresses to involve the limbs, although limb signs may not be present initially.

Several ALS variants follow a more segmental pattern than is typical in ALS. Up to 10% of patients with ALS have flail arm syndrome, which is more common in men and is associated with a longer median survival than seen in those with typical ALS. A similar focal manifestation in the lower limbs, flail leg syndrome, is another recognized variant.

TABLE 418-2 REVISED EL ESCORIAL DIAGNOSTIC CRITERIA FOR AMYOTROPHIC LATERAL SCLEROSIS

The diagnosis of ALS requires:
- [A:1] Evidence of LMN degeneration by clinical, electrophysiologic, or neuropathologic examination
- [A:2] Evidence of UMN degeneration by clinical examination and
- [A:3] Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination

Together with the absence of:
- [B:1] Electrophysiologic and pathologic evidence of another disease that might explain the signs of LMN and/or UMN degeneration and
- [B:2] Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiologic signs

Levels of diagnostic certainty:

Definite ALS
- UMN signs and LMN signs in 3 regions

Probable ALS
- UMN signs and LMN signs in 2 regions with UMN signs rostral to LMN signs

Probable ALS—laboratory supported
- UMN signs in 1 or more regions *and* LMN signs defined by EMG in at least 2 regions

Possible ALS
- UMN signs and LMN signs in 1 region (together) or
- UMN signs in 2 or more regions
- UMN and LMN signs in 2 regions with *no* UMN signs rostral to LMN signs

UMN signs: clonus, Babinski's sign, absent abdominal reflexes, hypertonia, loss of dexterity.
LMN signs: atrophy, weakness. If only fasciculation, search with EMG for active denervation.
Regions reflect segmental motor neuron pools: bulbar, cervical, thoracic, and lumbosacral.
EMG = electromyography; LMN = lower motor neuron; UMN = upper motor neuron.

DIAGNOSIS

The diagnosis of ALS is essentially clinical, and there is no specific diagnostic test. Diagnosis requires evidence of *lower motor neuron degeneration* by clinical, electrophysiologic (Chapter 403), or neuropathologic examination; upper motor neuron degeneration by clinical examination; and progressive spread of symptoms or signs within a region or to other regions, as determined by the history or examination. The diagnosis also requires the absence of other disease processes as determined by electrophysiologic testing, neuroimaging, and if performed, biopsy. Generally accepted criteria (Table 418-2) classify patients as having definite, probable, or possible ALS. However, a number of other conditions may mimic ALS (Table 418-3), and about 8% of patients in whom ALS is initially diagnosed have other lower motor neuron syndromes such as multifocal motor neuropathy with conduction block, Kennedy's disease, or mixed spinal cord and root compression. Conversely, 10 to 15% of patients in whom ALS is ultimately diagnosed may first undergo inappropriate surgery for presumed spinal cord or root compression abnormalities.

Blood tests that may be helpful in distinguishing ALS from mimic syndromes (see Table 418-3) include a complete blood count and serum calcium level, thyroid function tests, serum protein electrophoresis, Venereal Disease Research Laboratory test, creatine kinase level, inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), and levels of anti-GM1 ganglioside and anti–myelin-associated glycoprotein (MAG) antibodies. Further testing, which is guided by the patient's clinical findings, might include acetylcholine receptor antibody; mutation screening in patients with familial disease, suspected Kennedy's disease, or spinal muscular atrophy (SMA); heavy metal screening; urinary porphyrins; serum hexosaminidase A and B levels; *Borrelia* titers; and testing for human immunodeficiency virus.

Typical features of ALS on electromyography (EMG) include evidence of active denervation (i.e., positive sharp waves, fibrillation, and fasciculation potentials) and chronic denervation, as evidenced by large motor unit potentials that cannot be explained by a single nerve, root, or plexus lesion. Neuroimaging of the brain and spinal cord is often needed to exclude structural pathology.

Baseline respiratory function tests should be performed on all patients. Muscle biopsy is indicated only in rare or atypical cases, when diagnostic uncertainty persists.

TABLE 418-3 DISORDERS THAT CAN MIMIC AMYOTROPHIC LATERAL SCLEROSIS/MOTOR NEURON DISEASE

FORM OF MOTOR NEURON DISEASE	MIMIC SYNDROMES	CLINICAL CLUES
Progressive muscular atrophy (PMA)/LMN-predominant phenotype	Multifocal motor neuropathy	Weakness out of proportion to wasting. Neurophysiology identifies conduction block. Anti-GM1 antibodies may be raised
	Kennedy's disease	Gynecomastia, distal sensory features, perioral fasciculation, indolent progression
	Spinal muscular atrophy	SMA can be adult onset. Pure LMN syndrome. Slower progression than PMA. Probably no family history
	Chronic idiopathic demyelinating polyneuropathy	Electrophysiology identifies peripheral nerve demyelination
	Benign cramp-fasciculation syndrome	Predominantly middle-aged men. Largely calf involvement. Failure to progress. No active denervation on EMG
	Postpolio syndrome	Pure LMN syndrome. Past history of an illness compatible with poliomyelitis. Indolent progression
	Lead poisoning	Extramotor clinical features, e.g., constipation, nail and buccal signs
	Acute motor axonal neuropathy (AMAN—a Guillain-Barré syndrome variant)	Acute onset, with progression ceasing after a few weeks. Nerve conduction studies show features of motor axonopathy
	Hereditary motor neuropathies	Pure LMN syndrome. Family history, clinical signs indicating chronicity, slower rate of progression
	Porphyria	Extramotor clinical features, family history, episodic exacerbations
	Compressive focal motor neuropathies	Pure motor disorders can result from compression of the deep palmar branch of the ulnar nerve and posterior interosseous branch of the radial nerve. Failure to extend beyond territory of one nerve. Electrophysiology with or without imaging helpful
Amyotrophic lateral sclerosis	Multilevel spinal cord and root compression by discs, osteophytes, or tumor	Sensory symptoms and pain are common. UMN signs often caudal to LMN signs
	Thyrotoxicosis	Systemic symptoms and signs
	Combined peripheral neuropathy and cervical myelopathy	MRI of the spine and electrophysiology will differentiate
	Inclusion body myositis	Rarer than ALS. Characteristic pattern of weakness with early involvement of the long finger flexors and quadriceps
	Paraneoplastic syndromes, especially lymphoma	History of malignancy or systemic features
	Sjögren's syndrome	Non–motor-related symptoms
	Radiation myelopathy	History of radiotherapy
	Structural lesions of the bulbar region, e.g., tumor of the tongue base	Pain, failure of features to extend outside the bulbar territory
Primary lateral sclerosis	Hereditary spastic paraplegia	Family history. Symptoms rarely extend beyond the lower limb territory. Prominent bladder dysfunction
	Multiple sclerosis	Non–motor-related symptoms and signs, e.g., eye, bladder, cerebellar, and sensory involvement
	Spinal cord compression by disc or tumor	Pain and sensory involvement usually present

ALS = amyotrophic lateral sclerosis; EMG = electromyography; LMN = lower motor neuron; MRI = magnetic resonance imaging; SMA = spinal muscular atrophy; UMN = upper motor neuron.

TREATMENT AND PROGNOSIS

Rx

ALS is best managed in specialized centers that offer multidisciplinary care. Teams typically include a neurologist, nurse specialist, occupational therapist, physical therapist, speech and language therapist, and dietitian. During the course of the disease, patients frequently require referral for placement of a gastrostomy tube and to provide respiratory support.

No therapy currently has a dramatic effect in slowing the progression of ALS. Riluzole, which is a sodium-channel blocker whose primary mechanism of action is to reduce excitotoxicity through inhibition of presynaptic glutamate release, prolongs survival by approximately 3 months when given at 50 mg twice daily.■ It may cause fatigue, nausea, and dizziness, but these effects are frequently transient. Liver function tests should be performed at baseline and monthly for the first 3 months of therapy.

Management must focus on symptoms and preservation of independence and quality of life. In patients with progressive bulbar problems, optimal positioning, attention to food and fluid consistency, and protective swallowing techniques are helpful. If weight loss continues, high-calorie nutritional supplements are added between meals. Placement of a gastrostomy tube via endoscopy or under radiologic guidance is recommended in patients in whom dehydration, weight loss of 10 to 15%, frequent distressing choking episodes, prolonged and tiring mealtimes, or aspiration pneumonia develops. Tube placement is higher risk in patients with respiratory insufficiency. Tubes should ideally be placed before the patient's forced vital capacity falls below 50% of expected.

Respiratory muscle weakness, which can develop insidiously during the course of ALS, causes breathlessness, orthopnea, daytime somnolence, morning headaches, and interrupted sleep. Management must emphasize detection and prevention of aspiration pneumonia, assistance in clearing of secretions by providing a suction machine, use of a mucolytic agent such as carbocysteine (in a dose of up to 750 mg three times daily), adoption of a semiupright position for sleep, and aggressive antibiotic therapy for bronchitis (Chapter 96) or pneumonia (Chapter 97). A small dose of sublingual lorazepam (0.5 to 1 mg) may be useful if the dyspnea is accompanied by extreme anxiety; opiate therapy (such as morphine, diamorphine, or fentanyl; see Table 29-4) may be given orally, transdermally, or by subcutaneous infusion to relieve respiratory distress during the later stages of the disease.

As respiratory function worsens, noninvasive ventilation can alleviate symptoms of chronic hypoventilation, significantly improve quality of life, and prolong survival,■ especially in patients with orthopnea, daytime hypercapnia, and nocturnal oxygen desaturation. Full 24-hour ventilation via a tracheostomy is an option that is chosen uncommonly by fully informed patients. Palliative care teams and hospices can contribute substantially to the care of ALS patients in the later stages of the disease. In the absence of ventilatory support, ALS patients will almost always die in their sleep from hypercapnic coma. In the terminal phases (Chapter 3), the aim of treatment is to ensure comfort by prescribing opiates and anxiolytic medications as required to alleviate discomfort or distress.

PROGNOSIS

Clinical features associated with a worse prognosis include older age at onset of symptoms, early compromise of respiratory function, bulbar symptoms, and more rapid need for medical attention. The mean duration from the onset of symptoms to death in patients with sporadic ALS ranges from 27 to 43 months. The average 5-year survival rate is 25%, and approximately 5% of patients will survive for more than 10 years. The usual cause of death is respiratory failure, which may be accompanied by bronchopneumonia.

SPINAL MUSCULAR ATROPHIES

DEFINITION

The term *spinal muscular atrophy* encompasses a group of pure lower motor neuron disorders that cause progressive, symmetrical muscle weakness and

wasting. Because the bulbar musculature may be affected, an alternative term, "hereditary motor neuronopathy," has been proposed. The time of onset is variable and ranges from in utero to adult life.

EPIDEMIOLOGY AND PATHOBIOLOGY

The most common type of SMA is caused by mutations in the survival motor neuron (*SMN*) gene and is inherited as an autosomal recessive disorder. The estimated carrier frequency of an *SMN* mutation is 1 in 50. Type 1 SMA (Werdnig-Hoffmann disease) has an incidence of 1 in 8000 births. SMA is divided into subtypes I to IV according to age at onset and severity of the phenotype.

The human *SMN* gene on chromosome 5q13 exists in two forms with 5–base pair differences between *SMN1* and its centromeric homologue *SMN2*. A change in exon 7 of *SMN2* leads to skipping of exon 7, and as a result, 80% of the protein encoded by *SMN2* is truncated and nonfunctional rather than full length. The majority of patients with SMA have homozygous absence of *SMN1* exon 7, but *SMN1* may be replaced by a copy of *SMN2* during DNA replication by a process known as gene conversion. An individual may have one to four copies of *SMN2*, with a proportional increase in the amount of full-length SMN protein. A molecular basis for the wide variation in the phenotypic severity of SMA, which can range from in utero onset (SMA type I) to adult onset (SMA type IV), is the number of copies of *SMN2* and the SMN protein levels, although other disease-modifying factors have also been implicated.

The SMN protein oligomerizes and associates with other proteins to form the SMN complex, which in turn has an important role in the assembly of spliceosomal small nuclear ribonucleoproteins that have a function in pre-mRNA splicing in the nucleus. These cellular processes are ubiquitous, so either the clinical features of SMA may be caused by a particular susceptibility of lower motor neurons to defects in RNA processing or SMN may have functions that are specific to the motor neuron, including axonal transport of mRNA molecules essential for the health of the distal axon.

At autopsy, patients with SMA have atrophic spinal cords with loss of α-motor neurons and evidence of motor neuron degeneration and gliosis. The ventral roots are atrophic, and muscle atrophy is apparent with microscopic evidence of denervation and reinnervation.

CLINICAL MANIFESTATIONS

Type I SMA (Werdnig-Hoffman disease) is characterized by severe generalized muscle weakness and hypotonia at birth or by the age of 6 months; affected children never sit or walk. Type II is an intermediate form with an onset of muscle weakness before the age of 18 months; patients can sit but are never able to walk unaided. Type III SMA (Wohlfart-Kugelberg-Welander disease) appears after 18 months of age; patients acquire the ability to stand and walk but often become wheelchair dependent in adolescence or adult life, although life expectancy is normal. Patients with type IV SMA have an onset of muscle weakness in adult life.

DIAGNOSIS

The diagnosis of SMA caused by changes in *SMN* can be made by genetic testing in a patient with appropriate clinical signs and symptoms. Ninety-five percent of affected individuals have *SMN* deletions. Prenatal diagnosis is available. Electrophysiology and muscle biopsy reveal evidence of denervation.

Other disorders that may be manifested in infancy or childhood as hypotonia and a pattern of weakness similar to *SMN*-related SMA can be distinguished by associated clinical features, such as early respiratory distress or vocal cord paralysis or an atypical distribution of motor features, such as upper limb– or lower limb–predominant or scapuloperoneal involvement. The etiologic relationship of these disorders to classic SMA can be clarified by testing for *SMN* mutations.

It is important to distinguish SMA type I from infantile botulism, which can have a similar initial clinical picture. EMG with high-frequency repetitive nerve stimulation shows a decrement in botulism, and testing for the presence of botulinum toxin can confirm the diagnosis. SMA II and SMA III can be distinguished from chronic inflammatory demyelinating polyneuropathy (Chapter 428) by the presence of normal cerebrospinal fluid protein and normal nerve conduction studies in SMA. Patients with SMA III can have clinical features that are similar to those of the hereditary motor and sensory neuropathies, but it can be distinguished by neurophysiologic assessment and genetic testing.

TREATMENT AND PROGNOSIS

Rx

No disease-modifying treatment of SMA is currently available, although experimental approaches to upregulate expression of the SMN protein are being explored. In SMA II and SMA III, children may benefit from passive and active physical therapy, lightweight braces, surgical correction of scoliosis, and respiratory support measures.

Patients with type I SMA usually die by the age of 18 months, patients with type II typically survive into adolescence, and patients with type III and type IV have a normal life expectancy.

SPINOBULBAR MUSCULAR ATROPHY/ KENNEDY'S DISEASE

EPIDEMIOLOGY

Kennedy's disease, or spinobulbar muscular atrophy (SBMA), is an X-linked degenerative disorder of the lower motor neurons. Though rare, it is important not to miss the diagnosis because of the genetic implications for the family and a more benign course than occurs with ALS. The diagnosis should be considered in any male patient with a pure lower motor neuron disorder, particularly when the disease course is relatively indolent, gynecomastia is present, or there is evidence of a mild accompanying sensory neuropathy.

PATHOBIOLOGY

SBMA is a trinucleotide repeat disorder in which a CAG expansion encodes for a polyglutamine tract in the first exon of the androgen receptor gene on chromosome Xq11-12. The androgen receptor, which contains three functional domains, is transported to the nucleus, where it binds to DNA and acts as a transcription factor. Expansion of the polyglutamine tract results in reduced target gene transactivation, and neurodegeneration occurs when the polyglutamine tract reaches a critical length of approximately 40 repeats. The neurodegeneration in patients with SBMA is considered to result from a ligand-dependent, toxic gain of function of the mutant androgen receptor protein. Complete loss of its function, as seen in testicular feminization syndrome (Chapter 241), does not lead to motor neuron degeneration. The toxicity has not been fully characterized, but protein aggregation, impairment of protein degradation pathways, disruption of gene transcription, impairment of axonal transport, and neurotrophic factor signaling may all contribute.

Pathologic examination reveals mild spinal cord atrophy, with ventral horn gliosis and loss of α-motor neurons. Misfolding of the polyglutamine (Q)-expanded protein leads to the formation of nuclear inclusions that contain the amino-terminal epitopes of the mutant androgen receptor within motor neurons and certain non-neuronal tissues.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The mean age at onset of SBMA is 30 years, with a range of 15 to 60 years, and the severity of the disease and its age at onset correlate with the size of the repeat expansion. Initial symptoms consist of hand tremors, fasciculations, and muscle cramps, followed by progressive weakness and atrophy of the limb and bulbar muscles. Limb muscle weakness tends to be proximal and predominantly involves the lower limbs. There are no clinical signs of upper motor neuron dysfunction. Weakness of the lower facial and tongue muscles causes dysarthria, and jaw weakness may cause the mouth to hang open. The presence of perioral fasciculations with quivering of the chin is a characteristic feature. Pharyngeal involvement can cause dysphagia, and respiratory muscle weakness causes breathlessness. Mild distal sensory loss is frequently present in the lower limbs. Features of mild androgen insensitivity with gynecomastia, testicular atrophy, and erectile dysfunction will often be apparent. Heterozygous female carriers of SBMA may show mild clinical manifestations of the disease.

EMG and muscle biopsy, which are often performed because the creatine kinase level tends to be elevated, reveal evidence of chronic denervation. Genetic screening for the CAG repeat expansion in exon 1 of the androgen receptor gene is diagnostic.

TREATMENT AND PROGNOSIS

Rx

Current therapy consists of supportive care. The course of the disease is slowly progressive in comparison to ALS and is compatible with normal life expectancy, although a proportion of patients may die of respiratory failure. Patients may become wheelchair dependent over a period of 2 to 3 decades, but some remain ambulatory until late in life.

Grade A

1. Miller RG, Mitchell JD, Lyon M, et al. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev*. 2007;24:CD001447.
2. Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized controlled trial. *Lancet Neurol*. 2006;5:140-147.
3. Bosboom WM, Vrancken AF, van den Berg LH, et al. Drug treatment for spinal muscular atrophy types II and III. *Cochrane Database Syst Rev*. 2009;1:CD006282.

SUGGESTED READINGS

Bede P, Oliver D, Stodart J, et al. Palliative care in amyotrophic lateral sclerosis: a review of current international guidelines and initiatives. *J Neurol Neurosurg Psychiatry*. 2011;82:413-418. *Highlights the importance of early palliative care for ALS patients and existing national differences in the availability of such care*.

Douglass CP, Kandler RH, Shaw PJ, et al. An evaluation of the neurophysiological criteria used in the diagnosis of motor neuron disease. *J Neurol Neurosurg Psychiatry*. 2010;81:646-649. *Highlights the usefulness of the new Awaji-shima neurophysiologic criteria in allowing earlier diagnosis of ALS*.

Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. *Lancet*. 2011;377:942-955. *Comprehensive review*.

TABLE 419-1 DISEASES OF MYELIN

IDIOPATHIC
Recurrent or chronic progressive demyelination (multiple sclerosis and its variants)
Monophasic demyelination (may be the first clinical episode of multiple sclerosis)
Optic neuritis
Acute transverse myelitis
Acute disseminated encephalomyelitis; acute hemorrhagic leukoencephalopathy
VIRAL INFECTIONS
Progressive multifocal leukoencephalopathy
Subacute sclerosing panencephalitis (Chapters 375 and 378)
NUTRITIONAL AND METABOLIC DISORDERS (Chapter 425)
Combined systems disease (vitamin B_{12} deficiency)
Copper deficiency (dorsal columns and subacute optic neuropathy)
Demyelination of the corpus callosum (Marchiafava-Bignami disease)
Central pontine myelinolysis
ANOXIC-ISCHEMIC SEQUELAE (Chapter 411)
Delayed postanoxic cerebral demyelination
Progressive subcortical ischemic encephalopathy
LEUKODYSTROPHIES PRIMARILY AFFECTING CENTRAL NERVOUS SYSTEM MYELIN
Adrenoleukodystrophy (Schilder's disease)
Pelizaeus-Merzbacher disease (sudanophilic leukodystrophies)
Spongy degeneration
Vanishing white matter disease
Others (Alexander's disease, Canavan's disease)
Leukodystrophies of the central and peripheral nervous system
Metachromatic leukodystrophy
Globoid cell leukodystrophy (Krabbe's disease)

419

MULTIPLE SCLEROSIS AND DEMYELINATING CONDITIONS OF THE CENTRAL NERVOUS SYSTEM

PETER A. CALABRESI

The disorders of myelin encompass a wide range of diseases in which either myelin is not formed in a normal fashion (dysmyelinating disease) or normally formed myelin is destroyed or not maintained appropriately (demyelinating disease) (Table 419-1). Dysmyelinating diseases are uncommon and include an array of leukodystrophies that have a genetic basis. Demyelinating diseases are much more common and include multiple sclerosis (MS), which represents more than 95% of all types of disorders of central nervous system (CNS) myelin.

Some disorders of myelin actually have a distinct pathogenesis in which the disruption of myelin is secondary. Further, in many of the diseases of myelin, the axon degenerates as a result of loss of trophic support from loss of myelin or because of increased susceptibility to injury in the absence of myelin. This observation has led to the recent hypothesis that axonal loss is the underlying substrate for permanent disability in MS, adrenoleukodystrophy, and perhaps other diseases of myelin.

MULTIPLE SCLEROSIS

DEFINITION

MS is a disease characterized by multifocal areas of demyelination in the brain and spinal cord, with associated inflammatory cell infiltrates, reactive gliosis, and axonal degeneration. It typically presents in young adults with episodic neurologic dysfunction. Although the exact origin of MS remains enigmatic, evidence suggests that it is an immune-mediated attack on myelin, with secondary disruption of axons leading to progressive disability over time in most afflicted patients.

EPIDEMIOLOGY

The annual incidence of MS varies by location and ranges between 1.5 and 11 per 100,000 people. MS is second only to trauma as the most common cause of neurologic disability in young adults. More recent studies suggest that the incidence rate has increased, in part because of better recognition of more cases at an earlier stage. The prevalence is estimated at 350,000 to 400,000 in the United States and more than 1,000,000 worldwide, but these numbers may be underestimates owing to incomplete recognition of the disease even in developed countries.

MS occurs 2- to 2.5-fold more frequently in women than in men, a sex predilection that is common in autoimmune diseases. The disease most often presents in the third to fourth decades of life, but with an incidence age range from postpubertal teenagers to persons in their 50s. Rare cases occur in infants or in patients in their 60s, but extreme caution is warranted in these situations to exclude alternative processes. In many of the late-onset cases, symptoms were present in younger years and were attributed to other causes.

MS is most common in people of Northern European descent, and whites acquire multiple sclerosis at nearly twice the rate of African Americans in the United States. In many areas of the world, MS is more prevalent in temperate latitudes (approaching 1 in 500 in some locations) and becomes less common toward the equator (1 in 20,000 or rare case reports only in some locations), perhaps explained, in part, by migration patterns of people with the same gene pools. However, the absence of complete genetic penetrance in monozygotic twin studies suggests an environmental component to the disease. Indeed, an outbreak of MS was documented on the Faroe Islands following World War II, and numerous other clusters have been reported, although an environmental trigger has not been identified.

Several studies have linked cigarette smoking with risk for MS. High levels of vitamin D and early exposure to excessive sunlight (sunburns) have been linked with lower risk for MS, possibly related to the beneficial effects of cholecalciferol on regulating immune cell responses.

PATHOBIOLOGY AND GENETICS

Monozygotic twins with MS show a concordance rate of between 15 and 50%, compared with only 3 to 5% concordance in dizygotic twins, consistent with a strong but incomplete role for genes in causing MS. The lifetime risk for MS is increased to 2 to 4% in individuals with a first-degree relative with

MS, compared with the general population risk of 0.1%. In addition, between 10 and 20% of patients with MS have a first-degree relative with another autoimmune disease, commonly rheumatoid arthritis, systemic lupus erythematosus, or autoimmune thyroid disease. Hashimoto's disease and Crohn's disease also may be more common in patients with MS. Genetic modeling of the disease strongly argues against a single MS gene and suggests that many different genes predispose to MS and account for its many phenotypes. Linkage and association studies have identified the human leukocyte antigen (HLA) or major histocompatibility complex (MHC) region on chromosome 6 as one genetic determinant for MS. The MHC class II region, involved in presentation of antigen to $CD4^+$ T cells, is the most strongly associated locus. The HLA-DR2 allele and, more specifically, the molecular haplotype HLA-DRB*1501 allele have repeatedly been implicated. Two single nucleotide polymorphisms in the interleukin-2 (IL-2) receptor α gene and the IL-7 receptor gene also appear to be associated with a higher risk for MS. Other loci of interest on other chromosomes, including chromosome 1, continue to be investigated, but the associations appear less strong.

Pathology

Pathologically, most cases are characterized by multifocal areas of demyelination and gross gliotic scar in the brain and spinal cord. Classic locations of these lesions, called *plaques,* are the optic nerves, periventricular white matter, deep white matter, juxtacortical white matter, corpus callosum, cerebellar peduncles, and dorsolateral spinal cord. However, there may be a bias toward recognition of lesions in white matter because of the relative ease of detecting demyelination and inflammation in white compared with gray matter. Indeed, more recent pathologic studies have confirmed demyelination, neuritic damage, and atrophy in the cortex and deep gray matter. At the microscopic level, one usually sees multiple areas of perivenular inflammatory cell infiltrates with extravasation into the surrounding tissue parenchyma. In the acute active plaque, CD4 helper T (T_H) cells are prominent in the perivenular areas. Proinflammatory cytokines released from T_H1 (interferon-γ [IFN-γ]) and T_H17 (IL-17) cells are thought to mediate damage. Increasingly large numbers of CD8 cytotoxic T cells have been documented in brain tissue, especially in the parenchyma, and these cells may mediate direct damage to axons through release of proteases such as granzyme B. Most parenchymal inflammatory cells are $CD68^+$ macrophages and microglia. In addition to the influx of circulating immune cells, prominent astroglial activation and even oligodendrocyte precursor cell proliferation occur in response to injury. Over time, the inflammation becomes less prominent in the center of the plaque, but a chronic active rim of inflammation with microglial activation exists at a well-demarcated border between abnormal and normal unharmed myelin. This characteristic of MS is seldom seen in other disorders of myelin. Although oligodendrocytes may survive, proliferate, and result in partial remyelination (shadow plaques) in some early cases, this process is hardly ever complete in MS. Over time, remyelination is less successful, and oligodendrocyte progenitor cells appear unable to differentiate into mature myelinating oligodendrocytes.

The number of damaged axons correlates with the extent of inflammation. Further, axonal damage and even neuronal apoptosis are seen in the cortex. Atrophy of both the brain and spinal cord, which occurs more rapidly in MS than in normal aging, reflects loss of both myelin and axons.

No consistent microbial cause has been discerned from careful examination of MS tissues for known infectious pathogens. Differential expression of human herpesvirus type 6, which is acquired by most people in childhood, has been noted in oligodendrocytes of patients with MS, but whether this virus is a cofactor in demyelination or just a bystander remains unclear. Evidence suggests the possibility that the earliest event in MS may be an insult to the oligodendrocytes, with subsequent activation of resident immune cells and secondary recruitment of other immune cells only at later stages.

Some pathologists believe that four distinct subtypes of MS can be discerned, in which the pathologic characteristics are consistent in every lesion, thereby allowing classification of patients with differing pathologic categories rather than just describing evolution of lesions over time. Type I lesions are characterized by typical perivenular inflammatory infiltrates consisting mainly of T cells, with early preservation of oligodendrocytes. Type II lesions are similar to type I but have an additional humoral component with immunoglobulin G (IgG) deposition and complement activation. Type III lesions are distinguished by not being based around venules and by prominent loss of myelin-associated glycoprotein, with evidence for oligodendrocyte apoptosis. Type IV lesions have inflammatory infiltrates more similar to types I and II but also have oligodendrocyte loss as in type III. These varying pathologic features may begin to explain clinical subtypes of the disease.

TABLE 419-2 CONDITIONS THAT CAN BE MISTAKEN FOR MULTIPLE SCLEROSIS AND OTHER DISEASES OF MYELIN

VASCULAR DISEASE
Small-vessel cerebrovascular disease
Vasculitides
Arteriovenous malformation
CADASIL
Antiphospholipid antibody syndrome
STRUCTURAL LESIONS
Craniocervical junction, posterior fossa, or spinal tumors
Cervical spondylosis or disc herniation
Chiari malformation or syrinx
DEGENERATIVE DISEASES
Hereditary myelopathy
Spinocerebellar degeneration
INFECTIONS
HTLV-1 infection
HIV myelopathy or HIV-related cerebritis
Neuroborreliosis (e.g., Lyme disease)
JC virus/progressive multifocal leukoencephalopathy
Neurosyphilis
OTHER INFLAMMATORY CONDITIONS
Systemic lupus erythematosus
Sjögren's syndrome
Sarcoidosis
MONOFOCAL OR MONOPHASIC DEMYELINATING SYNDROMES
Transverse myelitis
Optic neuritis
Neuromyelitis optica/Devic's disease
Acute disseminated encephalomyelitis
OTHER CONDITIONS
Hashimoto's thyroiditis with or without encephalopathy
Nonspecific MRI abnormalities related to migraine, aging, or trauma

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; HIV = human immunodeficiency virus; HTLV = human T-cell lymphotropic virus; MRI = magnetic resonance imaging.

Pathogenesis

It remains possible that the autoimmune hypothesis is wrong and that the inflammation observed in MS is secondary to an as yet uncharacterized primary degenerative process. Proponents of this theory cite evidence from pathologic features of hyperacute cases, in which the oligodendrocytes appear to die before any systemic immune response occurs, as well as recent data revealing neuronal and axonal death or demyelination in the absence of inflammation.

Macrophages and microglia, which make up the majority of cells within the parenchymal infiltrate in chronic MS plaques, are potent antigen-presenting cells and express HLA and costimulatory molecules. Activated macrophages and microglia also have effector functions, including release of cytokines that are partly (IL-6, tumor necrosis factor-α) or completely distinct from the T cells (IL-1β, IL-12, and IL-23). In high concentrations, these cytokines may damage oligodendrocytes and neurons and activate T cells.

CLINICAL MANIFESTATIONS

Presenting Symptoms

MS, which can present in many ways across a broad age range, may initially masquerade as a variety of different illnesses (Table 419-2; see Table 419-1). In a classic presentation, a young white person, more often a woman, will have the acute to subacute onset of impaired vision or sensation. Fatigue, depression, bladder urgency, weakness, impaired balance, and impaired coordination are also common symptoms. The often remarkably mild nature of the first symptoms often dissuades the patient from seeking medical attention

or is insufficiently impressive to stimulate the physician to order diagnostic tests. Furthermore, patients may initially have few objective neurologic findings, especially between attacks.

Paresthesias of a limb that are circumferential and do not follow a dermatome suggest a spinal cord lesion; these symptoms often manifest distally and then ascend to involve more proximal parts of the limb, spread to the contralateral limb, or progress from a leg to an arm. Similarly, bandlike sensations around a limb or the torso also suggest a myelopathic process.

Incomplete transverse myelitis is a focal (partial) spinal cord syndrome that is usually inflammatory and does not follow vascular territories. It is a common presentation of MS.

Lhermitte's symptom, an electrical sensation moving down the spine into the limbs on flexion of the neck, is characteristic of cervical myelitis from any cause, including MS. Frank loss of sensation is less common as an early symptom or sign but is seen in more advanced cases. Burning, electrical, or deep aching sensations are also common in MS.

Sensory Abnormalities

On examination, the most common sensory findings are loss of vibration perception, most prominent in the feet, and incomplete spinal cord levels to pin prick or vibration, which are often more notable in a graded fashion rather than at a distinct level. Such sensory levels may be asymmetrical and differ by sensory modality because of isolated demyelination in the dorsal columns compared with the spinothalamic tracts. Patchy or seemingly nonanatomic focal areas of impaired sensation can occur, and some patients describe bizarre sensations such as water dripping or bugs crawling on an area of the body.

Visual Effects

Optic neuritis (Chapter 432) is a classic presenting syndrome, typically with visual symptoms in one eye. In optic neuritis, patients often complain of pain over the lateral eyebrow and worsening on lateral eye movement. The visual impairment may be described as looking through frosted glass or a veil. The scotoma or area of greatest loss can often be mapped in a centrocecal distribution (central focal point to the blind spot laterally), which in mild cases may be evident only as desaturation to red color using the head of a pin. More severe cases may result in total loss of light perception. In most acute cases of optic neuritis, the inflammation is retrobulbar (behind the disc), so no immediate changes are visible on the optic disc, thereby leading to the aphorism "the patient sees nothing, and the doctor sees nothing." However, there should be a relative afferent papillary defect (Marcus-Gunn pupil; Chapter 432) with paradoxical dilation of the affected eye to direct light on swinging a flashlight from the unaffected eye in which consensual constriction was induced. In cases of bilateral optic neuritis (new or old), this abnormality may not be seen. Patients usually spontaneously recover substantial vision after weeks to months. Later, the optic disc may become pale, especially in the temporal region, a finding reflecting damage to the axons following inflammation and demyelination, even with recovery of normal visual acuity. Patients often have more subtle chronic visual impairment for colors, low contrast visual acuity, and contrast sensitivity. Visual testing using low contrast letter acuity charts commonly reveals substantial visual loss after clinical optic neuritis.

Visual impairment from impaired tracking of eye movements owing to brain stem or cerebellar disease most commonly occurs in the setting of an acute lesion affecting the medial longitudinal fasciculus, which is the neurologic pathway that yokes the eyes together on lateral saccades. Patients may experience frank diplopia or just blurred vision, especially when they look off to one side rapidly, such as when looking over one's shoulder while driving. The neurologic sign of this problem is called *internuclear ophthalmoplegia* (Chapter 432) and manifests as slowed or absent adduction of one eye with abducting nystagmus of the other eye. It may occur bilaterally or may exist in milder forms, such that the adduction lag is imperceptible to the human observer. Blurred vision from cerebellar damage with nystagmus is very common in MS and is often worse on extreme lateral or vertical gaze. *Oscillopsia,* the sensation that the environment is moving when it actually is not, is another symptom of impaired cerebellar coordination of the eyes. Saccadic eye movement or loss of smooth pursuit is also common in MS and also can be seen in numerous neurologic conditions or with aging.

Motor Symptoms

The most common motor symptoms of MS are weakness and impaired coordination in a leg, with ascending involvement from distal to proximal and commonly spreading to the contralateral leg or ipsilateral arm. The lesion causing these symptoms is more commonly in the cervical spinal cord rather than the thoracic spinal cord, even when the first sign is partial footdrop. It is likely that axons that must conduct impulses over the longest distance (entire length of the spinal cord) from a site of inflammatory demyelination will become symptomatic before axons delivering signals to closer synapses (adjacent anterior horn cells in the cervical cord). Clinically, the weakness may be severe and may result in an obvious paralysis or be so subtle as to be undetectable. Heat-induced fatigue and weakness, as manifested by focal symptoms (slapping of a foot or dragging a leg) occurring after 15 to 20 minutes of exercise and resolving with rest, are characteristic of early demyelinating disease. The early absence of associated hyperreflexia and plantar extensor responses (Babinski's sign) may make it difficult to document corticospinal tract involvement. Later, in more established MS, classic corticospinal tract signs are often evident and manifest clinically as spastic gait (either hemiparetic or paraparetic), muscle cramps, and clonus (sustained reflex loop), sometimes occurring with positional changes and mistaken for signs of a cerebellar tremor.

Ataxia may occur as a result of impaired delivery of sensory information up the spinal cord or from demyelination of cerebellar pathways in the brain stem or cerebellum. Often, the two are mixed and may be confounded further by visual loss and impaired ability to compensate by fixing on the environment; this combination commonly causes dizziness in crowds, in which fixation may be further obscured. Appendicular dysmetria resulting in tremor on reaching for an object is a common cause of impaired coordination and dexterity. Lower extremity and truncal ataxia may result in a wide-based (drunk) gait. Other movement disorders, such as postural tremor and titubation (head tremor), are much less common in MS. *Myokymia* (wormlike muscle movements) under the skin, especially around the face, however, is fairly common. Pseudoathetosis and parkinsonism can be seen in severe cases.

Organ Dysfunction

Bladder symptoms are extremely common, but often are not volunteered, so specific questions must be asked. A careful bladder history may reveal isolated or mixed patterns of urinary frequency, urgency, incontinence, or retention. Careful delineation of a spastic bladder (detrusor muscle spasm) causing incontinence from an atonic bladder or spasm of the external sphincter (the latter two are causes of retention) leading to overflow incontinence is critical to designing an appropriate therapeutic strategy (Chapter 25). Urinary tract infections (Chapter 292), which are commonly the result of bladder dysfunction, may aggravate the underlying symptoms of MS.

Bowel dysfunction commonly manifests as constipation (Chapter 138), which may be primary (related to spinal cord involvement) or secondary (related to self-induced dehydration to manage urinary frequency or to side effects of anticholinergic drugs). Bowel incontinence secondary to an incompetent anal sphincter is less common and most often occurs as an isolated episode of fecal urgency, sometimes related to dietary change or diarrheal illness.

Sexual dysfunction is also common and underdiscussed in MS. In men, erectile dysfunction is frequent. In women and men, loss of libido and inability to achieve orgasm can occur as a result of medication, loss of sensation, heat-induced worsening of symptoms, physical barriers to intercourse (impaired mucosal moisture, spasticity, and pain), depression, or disorders of body image.

Systemic Symptoms

Fatigue, which is common in MS, may be linked to depression but often occurs independently and can be the most disabling symptom of the disease. A sleep history is important to exclude daytime fatigue resulting from disrupted sleep secondary to pain, cramps, bladder frequency, sleep apnea, periodic limb movements, depression, or disrupted sleep-wake cycles. Daytime fatigue even after a good night of sleep may occur in midafternoon and may be described as being "unplugged" or completely drained. Many patients obtain benefit from a short daytime nap.

Sensitivity to heat, which is a classic symptom of MS, occurs only in some patients. Even minor elevations of the body temperature can dramatically worsen symptoms. Symptoms usually (but not always) improve on cooling. Cooling devices can prevent this phenomenon, but there is no persistent benefit of cooling below normal body temperature. Some patients complain of worsened symptoms in cold weather, likely related to increased dysfunction of already stiff muscles and increased pain.

Pregnancy

Many women with MS successfully have multiple children, and the activity of MS lessens during the course of pregnancy, especially by the third trimester, when the frequency of exacerbations is reduced by approximately two thirds. Relapses are more frequent in the first 6 postpartum months, but no evidence indicates that pregnancy changes the natural history of the disease. Whether breast-feeding alters the course of MS is debated, but it is contraindicated for patients who resume disease-modifying drugs following delivery.

Types of Multiple Sclerosis

The three major clinical types of MS are relapsing remitting, secondary progressive, and primary progressive. Approximately 85 to 90% of patients present with relapsing remitting MS, characterized by acute or subacute episodes of new or worsening old neurologic symptoms that increase in severity, plateau, and then partly or completely remit. Patients may have no detectable residual deficit, or they may accumulate significant permanent disability from an attack. Most patients with relapsing remitting MS convert to secondary progressive MS after 20 to 40 years. This stage of the disease, which is characterized by at least 6 months of progressive worsening without evidence of a relapse, can be diagnosed with confidence only retrospectively. Some patients with secondary progressive MS also have interposed relapses distinct from their periods of progressive worsening, although these episodes become less frequent with time. Primary progressive MS, which is characterized by progressive deterioration from the onset for at least 1 year without a history of distinct relapses, occurs in approximately 10 to 15% of patients. It is more common in middle-aged men and typically has more involvement of the spinal cord and fewer inflammatory brain lesions.

Several other uncommon types of MS also are described. Progressive relapsing MS refers to a fairly uncommon variant of MS (6%), in which a relapse ensues after an initially primary progressive course. Acute progressive MS (Marburg's disease) causes acute or subacute progressive neurologic deterioration leading to severe disability within days to a month in a patient with no prior history of MS. This rare form of the disease may progress to a quadriplegic, obtunded state with death as a result of intercurrent infection, aspiration, or respiratory failure from brain stem involvement.

DIAGNOSIS

The diagnosis of MS rests on demonstrating evidence of at least two inflammatory demyelinating lesions referable to different locations within the CNS, occurring at different times (usually ≥1 month apart), and for which no better explanation exists. Diagnostic criteria allow for the diagnosis to be made on clinical grounds alone as long as appropriate exclusionary testing is performed (Table 419-3). Clinical evidence of a lesion requires objective findings on examination, not just a symptom. Further, repeated episodes of neurologic dysfunction that could be explained based on one lesion (e.g., a cervicomedullary junction lesion causing brain stem, cerebellar, and corticospinal tract dysfunction) is not enough evidence to diagnose MS.

Laboratory Findings

Magnetic Resonance Imaging

No definitive diagnostic laboratory test exists for MS, but magnetic resonance imaging (MRI) of the brain is extremely useful and should be performed in all patients in whom MS is a diagnostic consideration. More than 95% of patients with clinically definite MS have an abnormal brain MRI, and the presence of high-signal, bright lesions is so characteristic of MS that a normal brain MRI should suggest an alternative diagnosis. Brain MRI is also useful in predicting future MS at the time of a clinically isolated demyelinating syndrome. Specific MRI findings allow for confirmation of disease disseminated in time and space (different parts of the brain or spine) as well as fulfilling evidence for dissemination in time (Table 419-4). MS plaques typically appear as high-signal (white) areas on fluid attenuation inversion recovery (FLAIR) T2-weighted images, which allow for the best discrimination of these lesions by suppressing high-signal from cerebrospinal fluid (CSF) in the ventricles (Fig. 419-1). Lesions generally range in size from 2 mm to 2 cm; larger plaques occasionally resemble a tumor. Features of an MRI lesion suggesting MS include an elliptical shape, discrete borders, lack of mass effect, and gadolinium enhancement. Typical locations include the periventricular area (perpendicular to or abutting the walls of the ventricles) (Fig. 419-2), the corpus callosum, the cerebellar peduncles, the brain stem, the juxtacortical area, and the dorsolateral spinal cord (Fig. 419-3). Cortical and deep gray matter lesions also occur but are less clearly seen on conventional MRI. Gadolinium enhancement, which suggests permeability of the blood-brain barrier, is correlated with new or active inflammation in lesions (Fig. 419-4). Lesions that enhance on a T1-weighted sequence usually have a concomitant lesion in the same location on a T2-weighted image. However,

TABLE 419-3 2010 REVISIONS TO THE MCDONALD DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR DIAGNOSIS OF MULTIPLE SCLEROSIS
Two or more attacks; objective clinical evidence of two or more lesions; or one lesion with a prior attack	None*
Two or more attacks; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: (1) MRI (see Table 419-4), or (2) Two or more MRI-detected lesions consistent with MS plus positive CSF, or (3) Await further clinical attack implicating a different site
One attack; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: (1) MRI (see Table 419-4), or (2) Second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	(1) Dissemination in space, demonstrated by: (a) MRI (see Table 419-4), or (b) Two or more MRI-detected lesions consistent with MS plus positive CSF, and (2) Dissemination in time, demonstrated by: (a) MRI (see Table 419-4), or (b) Second clinical attack

*Must rule out other causes (e.g., see Table 419-2).
CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MS = multiple sclerosis.
Adapted with permission from Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69:292-302.

TABLE 419-4 MAGNETIC RESONANCE IMAGING CRITERIA IN MULTIPLE SCLEROSIS (INTERNATIONAL PANEL RECOMMENDATIONS: 2010)

DISSEMINATION IN TIME
Detection of a new T2 or gadolinium-enhancing lesion if it appears at any time compared with a reference scan*
Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time
DISSEMINATION IN SPACE
At least one gadolinium-enhancing lesion in at least 2 of 4 areas: Periventricular Juxtacortical Infratentorial Spinal cord
DIAGNOSIS OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS
One year of disease progression (retrospectively or prospectively determined) plus two of the following: a. Positive brain magnetic resonance imaging (≥1 T2 lesion in at least one characteristic area: periventricular, juxtacortical, or infratentorial) b. Positive spinal cord magnetic resonance imaging (two focal T2 lesions) c. Positive cerebrospinal fluid (isoelectric focusing evidence of oligoclonal immunoglobulin G bands or increased immunoglobulin G index, or both)

*Caution: Determination that a T2 lesion is indeed new can be challenging. A new T2 lesion must be of sufficient size and location to reflect one that could not have been missed previously for technical reasons of slice orientation, thickness or spacing, tissue contract, patient motion, or other artifacts. This judgment requires standardized scanning procedures, with emphasis on careful repositioning, as well as input from qualified evaluators experienced in multiple sclerosis imaging.
From Polman Ch, Reingold SC, Banwell G, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;49:292-302.

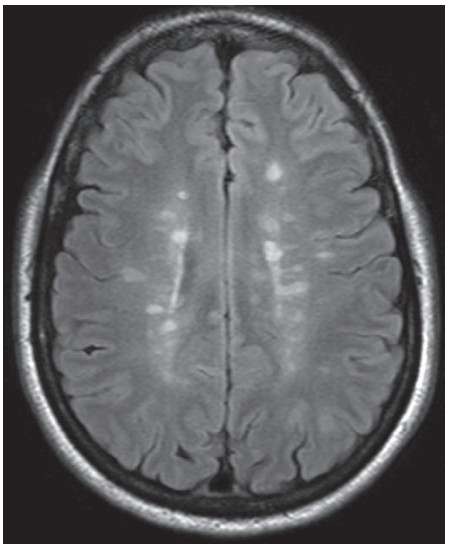


FIGURE 419-1. Axial fluid attenuation inversion recovery image of the brain from a patient with multiple sclerosis revealing classic multiple periventricular and deep white matter high signal lesions.

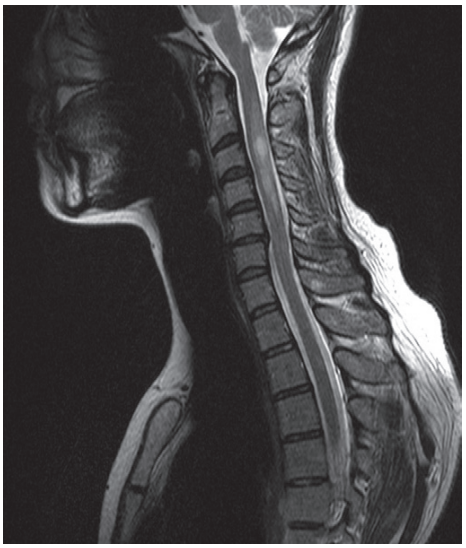


FIGURE 419-3. Sagittal T2-weighted image of the brain and cervical spine from a patient with multiple sclerosis. The image shows a high-signal plaque from C3-C5 in the spinal cord.

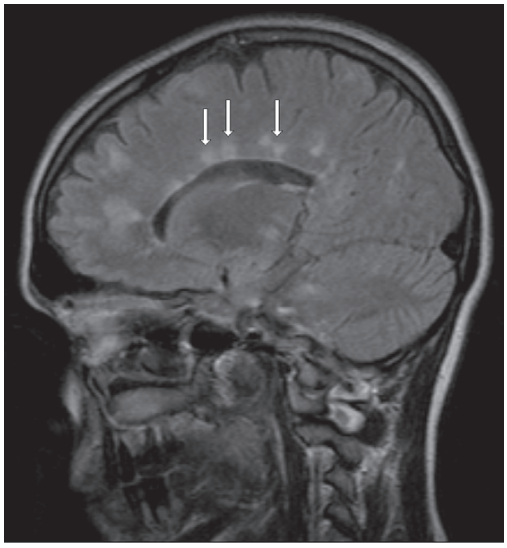


FIGURE 419-2. Sagittal fluid attenuation inversion recovery image of the brain from a patient with multiple sclerosis revealing classic periventricular lesions radiating outward from the ventricles *(arrows)*.

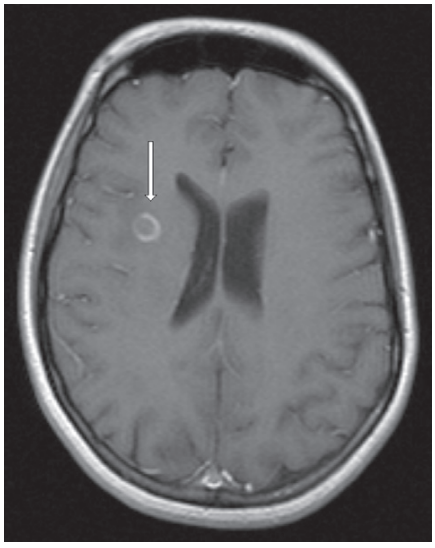


FIGURE 419-4. Axial T1-weighted image after gadolinium contrast showing an actively inflamed ring-enhancing lesion in a patient with multiple sclerosis.

T2-weighted lesions may form without evident enhancement. Gadolinium enhancement typically persists for 2 to 8 weeks and thus may be missed on intermittent scans. Persistent areas of low signal on T1-weighted images before contrast ("black holes") correlate with pathologic evidence of axonal loss and atrophy (Fig. 419-5).

Cerebrospinal Fluid

Examination of the CSF is useful in many cases but is not mandatory in patients with a typical clinical presentation and MRI evidence of disseminated disease. CSF evaluation includes cell counts, total protein, glucose, oligoclonal bands with a paired serum sample, and an IgG index. The presence of myelin basic protein is not specific for MS because it can be elevated secondary to any disruption of CNS tissue. Oligoclonal bands in the CSF or an elevated IgG index provides evidence for intrathecal production of immunoglobulins, and oligoclonal bands are common in MS but can occur with infection or other immune-mediated processes; the test lacks specificity for MS and has a sensitivity of only approximately 85 to 90% of patients with clinically definite MS. In clinically isolated demyelinating syndromes (see later), the sensitivity is even lower (~50%).

CSF evaluation is generally recommended if an alternative diagnosis is considered, especially if one suspects an infectious process (e.g., fever, sweats, unusual travel history, tick bite, or rash). CSF analysis may also be useful if clinical or MRI criteria are incomplete to provide confirmation of the diagnosis.

Evoked Potential Tests

Evoked potentials (Chapter 403) may also be useful in some situations to document objective evidence of slowed conduction owing to demyelination in locations different from those recognized clinically. However, visual evoked potentials (VEPs), brain stem auditory evoked potentials, and somatosensory

evoked potentials are less sensitive and less specific for MS than is high-resolution MRI. Multifocal VEPs may be more sensitive than global VEPs in revealing focal areas of abnormal conduction along the optic nerve.

Optical Coherence Tomography

Optical coherence tomography is an office-based device that uses the reflection of infrared light (from an exogenous source directed through the pupil) off the back of the eye to quantify the thickness of retinal tissues, including the retinal nerve fiber layer and macula. This test, which has been widely used in glaucoma, can monitor axonal damage, both in the setting of acute optic neuritis and in detecting subclinical axonal damage (Fig. 419-6). Retinal nerve fiber layer thinning correlates with brain atrophy and may be useful as a surrogate marker of more global neurodegeneration in MS.

Differential Diagnosis

The diagnosis of MS may be so clear that it is recognized by the patient and is readily confirmed by the primary physician or so obscure that even experienced specialists disagree. Many processes (see Table 419-2) can mimic the clinical, radiologic, and CSF findings associated with MS, and there is no "gold standard" diagnostic test that is 100% sensitive and specific for the disease.

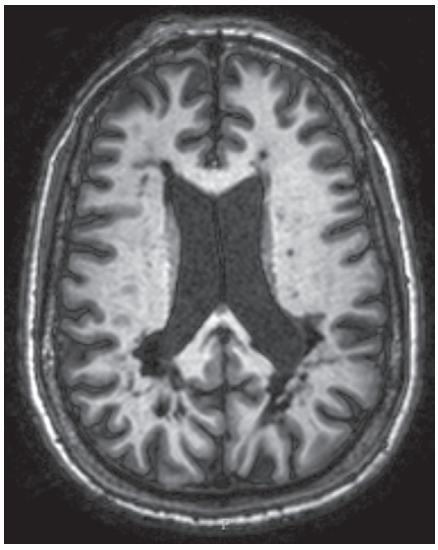


FIGURE 419-5. Axial T1-weighted image showing numerous areas of T1 low signal ("black holes"), ventricular enlargement, and diffuse atrophy.

Processes that mimic MS include structural lesions, especially of the base of the brain and of the spinal cord, in which one lesion can cause symptoms referable to many different tracts and at different perceived locations in the body. Chiari malformations with or without syrinx (Chapter 426), disc herniation (Chapter 407), cervical spondylosis, and low-grade tumors (Chapter 195) can produce symptoms of MS both in newly presenting patients and in patients who truly have MS but who also have a second process.

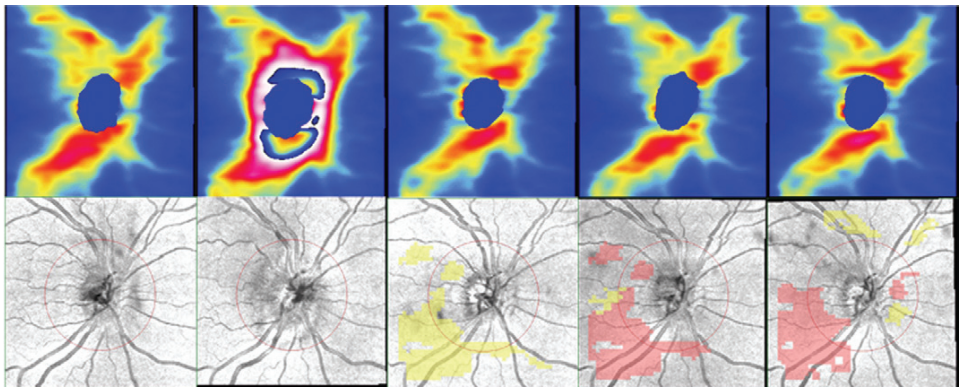
Various infectious diseases can mimic MS. Examples include human T-cell lymphotropic virus types I and II (virally associated myelopathy or tropical spastic paraparesis; Chapter 386), human immunodeficiency virus (neuropathy, myelopathy, cognitive impairment, CNS white matter changes; Chapter 401), neuroborreliosis (Lyme disease; Chapter 329), neurosyphilis (Chapter 327), Epstein-Barr virus (Chapter 385), cytomegalovirus (Chapter 384), herpes simplex virus (Chapter 382), varicella-zoster virus myelitis (Chapter 383), and JC virus (progressive multifocal leukoencephalopathy; Chapter 378).

Other inflammatory diseases that usually involve other parts of the body can concomitantly affect the CNS or rarely present in the CNS. Examples include sarcoidosis (Chapter 95), systemic lupus erythematosus (Chapter 274), Sjögren's syndrome (Chapter 276), and vasculitides (Chapter 278). Ischemic vascular disease secondary to any cause also can resemble MS. Metabolic and nutritional disorders that can mimic MS include vitamin B_{12} deficiency and methylmalonic acidemia (in some cases distinct from cyanocobalamin deficiency). Central pontine myelinolysis (Chapters 118 and 425) secondary to overly rapid correction of sodium is rarely mistaken for MS. Thyroid disease (Chapter 233) may mimic the fatigue of MS and may cause dysesthesias and disorders of the optic nerve and muscles. Nutritional deficiency (Chapter 222) and malabsorption have been associated with demyelination and may mimic MS. Copper deficiency can cause dorsal column pathology, neuropathy, anemia, and optic neuropathy. Vitamin D deficiency (Chapter 252), which is becoming increasingly common, can cause proximal weakness, fatigue, and asthenia, in addition to bone loss.

Monophasic demyelinating syndromes with or without multiple other lesions often, but not always, progress to become MS (see later). Spinocerebellar atrophy and hereditary myelopathy cause slowly progressive disease but do not cause sensory and visual abnormalities.

TREATMENT Rx

The treatment of MS can be divided into drugs designed to relieve symptoms, drugs designed to modify the course of the disease, and nondrug measures. In addition, numerous drugs can target specific aspects of MS: depression, fatigue, muscle spasticity, pain, insomnia, and bladder, bowel, and sexual dysfunction. Before considering a symptomatic therapy, the



Time from AON onset	− 3 Months	+ 2 Weeks	+ 3.5 Months	+ 8 Months	+ 10 Months
Average RNFL (microns)	108	164	98	99	97
Superior	131	197	131	123	125
Nasal	78	126	74	75	74
Inferior	141	246	118	130	126
Temporal	79	84	69	66	65

FIGURE 419-6. Serial optical coherence tomography (OCT) scans in a patient who developed unilateral optic neuritis. Immediate swelling and increased thickness of the retinal nerve fiber layer (RNFL) thinning can be seen followed by focal thinning, especially in the temporal quadrants, as depicted by the *yellow* and *red* regions. AON = acute optic neuritis.

patient should be educated about the purpose of the drug and its side-effect profile. On learning that these drugs have no long-term impact on disease activity, patients may elect not to use them for relief of symptoms alone. Symptomatic therapies are best started at low doses and frequently require titration to obtain the optimal balance between efficacy and side effects.

Treatment of Specific Symptoms

Depression and emotional lability are common symptoms of MS. In addition to appropriate supportive care and counseling, antidepressant therapy with one of the "activating" serotonergic or noradrenergic drugs (fluoxetine, sertraline, citalopram, escitalopram, venlafaxine, or bupropion) can be of benefit (see Table 404-5 in Chapter 404). If anxiety and panic symptoms predominate, a less activating drug such as paroxetine may be preferable. Patients with concomitant pain or insomnia may benefit more from a sedating antidepressant (amitriptyline, nortriptyline, or trazodone) given at bedtime.

Spasticity can be managed by physical therapy, stretching, and institution of either baclofen (5 to 160 mg in divided doses) or tizanidine (2 to 32 mg in divided doses). Either drug should be started as a single agent at a low dose, generally three to four times a day, but a larger dose at bedtime is often the best tolerated and may target nocturnal symptoms. Decreasing muscle tone can result in weakness. Baclofen should never be discontinued abruptly because of the potential for a severe withdrawal reaction.

Bladder urgency resulting from detrusor muscle spasm can be managed effectively with anticholinergics such as oxybutynin (5 to 20 mg in divided doses) or tolterodine (1 to 4 mg), but these agents can cause temporary urinary retention. Bladder ultrasonography permits accurate bedside assessment of postvoid residual volume to determine whether a patient is retaining excessive amounts of urine. Urinary retention may be improved by removing drugs known to induce it. Primary urinary retention is difficult to treat with drugs, but external sphincter spasm can be treated with α_{1a}-adrenergic receptor blockers such as tamsulosin (0.4 to 0.8 mg) and doxazosin (1 to 8 mg). Bethanechol (10 to 150 mg in divided doses) may be tried for an atonic bladder, but intermittent catheterization is often required. Alternative causes of bladder symptoms such as urinary tract infections, prostatic enlargement, or anatomic changes following pregnancy should be considered and managed separately.

Painful dysesthesias and paroxysmal dystonic spasms may be managed effectively with antiepileptic drugs (gabapentin, 300 to 5400 mg/day in divided doses; pregabalin, 75 to 600 mg/day in divided doses; or carbamazepine, 100 to 2400 mg/day in divided doses) or tricyclic antidepressants (amitriptyline, 10 to 150 mg; or nortriptyline, 10 to 50 mg). Patients with trigeminal neuralgia (Chapter 405) may respond to these drugs or to baclofen, misoprostol, botulinum toxin, or decompression surgery.

Sexual dysfunction in MS is often multifactorial. Patients with erectile dysfunction usually respond well to the phosphodiesterase inhibitors, which enhance penile vasodilation (Chapter 242). Education regarding the use of lubrication, alternative sensory stimulation, and the adverse effect of heat can improve sexual function.

Systemic Treatments

Corticosteroids (e.g., intravenous methylprednisolone, 1 g/day for 3 to 5 days) shorten the duration and severity of symptoms from an acute exacerbation but have no proven effect on long-term disability. Oral corticosteroids used in equivalent dosage are probably equally efficacious and safe. Intravenous immunoglobulin and plasma exchange have been reported occasionally to benefit steroid-refractory patients, but randomized placebo-controlled trials have failed to show consistent benefits, perhaps because only patients with type II disease (humoral component) are likely to respond.

Seven disease-modifying agents have been approved by the U.S. Food and Drug Administration (FDA): IFN-β1b (Betaseron and Extavia), IFN-β1a (Avonex), IFN-β1a (Rebif), glatiramer acetate (Copaxone), natalizumab (Tysabri), and mitoxantrone (Novantrone). The first six agents were approved for relapsing remitting MS, and mitoxantrone is indicated for worsening forms of MS and for secondary progressive MS.

The three IFN-β drugs[1–3] and glatiramer acetate[4] reduce the relapse rate by approximately one third. IFN-β1b (8 million IU, subcutaneously every other day [Betaseron and Extavia]) and IFN-β1a (30 μg intramuscularly weekly [Avonex] or 22 to 44 μg subcutaneously three times a week [Rebif]) appear to have a more rapid onset of action, perhaps based on their dosing regimen, compared with weekly IFN-β1a (30 μg weekly intramuscularly). However, weekly IFN-β1a Avonex is less immunogenic and results in only a 3% incidence of neutralizing antibodies, which reduce efficacy, compared with 20 to 30% for the other IFN-β preparations. The major side effects of IFN-β are a flulike reaction (low-grade fever, chills, and myalgias 6 to 24 hours after the injection), local reactions at the injection site (pain, erythema, and rarely necrosis), and elevated aminotransferase levels (rarely severe hepatitis). These side effects can be managed by initiating the drug slowly and by prophylaxis with acetaminophen and nonsteroidal anti-inflammatory agents, and they improve in most patients after 3 to 6 months.

Glatiramer acetate is a copolymer of four amino acids designed to mimic myelin basic protein; given as 20 mg/day subcutaneously, it also reduces relapses by about one third and is well tolerated by most patients.[4] Major side effects are local reactions at the injection site, swelling, hives, and a rare, self-limited (15 to 20 minutes) systemic reaction consisting of chest pain, palpitations, and anxiety. No monitoring of blood tests is required for this medication. The effect of glatiramer acetate on MRI T2-weighted and gadolinium-enhancing lesions is less dramatic than for the IFNs (30% reduction) perhaps because its primary effect is not at the blood-brain barrier.

Natalizumab is a monoclonal antibody directed against the α_4-integrin chain of the leukocyte adhesion molecule VLA-4. In a large phase III trial, this drug, at a dose of 300 mg intravenously every 4 weeks, reduced relapses by 68% compared with placebo and reduced gadolinium-enhancing lesions by 92%.[5] However, about 1 per 500 patients develop JC virus brain infection (Chapter 378) after 24 months of exposure, which causes progressive multifocal leukoencephalopathy.

In a randomized study, yearly courses of alemtuzumab (12 or 24 mg daily for 5 consecutive days in year 1 and for 3 days in years 2 and 3), which is a monoclonal antibody that targets CD52 in lymphocytes and monocytes, reduced relapse rates and disability by up to 75% compared with IFN-β1a given three times a week.[6] Serious side effects associated with alemtuzumab include an increased rate of autoimmune thyroid and thrombocytopenic purpura.

Mitoxantrone, which is an anthracenedione antineoplastic agent with potent immunosuppressive activity, has been approved to slow progression of neurologic disability and to reduce the relapse rate in patients with relapsing remitting MS and secondary progressive MS.[7] The recommended dose is a 5- to 12-mg/m^2 intravenous infusion every 3 months. In a phase III randomized, placebo-controlled, multicenter trial of 188 patients, the number of treated relapses was reduced by 67%. Side effects of mitoxantrone include nausea and alopecia. The lifetime use of this drug is limited to 2 to 3 years (or a cumulative dose of 120 to 140 mg/m^2) because of its cardiotoxicity. Heart failure or asymptomatic decreases in left ventricular ejection fraction (LVEF) can occur even after one to four doses, so careful monitoring of LVEF after each dose is mandatory. The risk for leukemia is increased and may be as high as 0.8%. A complete blood count, including platelets, should be done before each course of mitoxantrone therapy, and women of childbearing age should have a pregnancy test and should know the results before each dose, regardless of whether or not they are using birth control. Patients should be made aware that mitoxantrone may impart a blue-green color to the urine for 24 hours after administration. It also may cause bluish discoloration of the sclera. Rituximab (1000 mg intravenously 2 weeks apart every 6 months), which is a monoclonal antibody that depletes B-cell lymphocytes, can significantly reduce inflammatory brain lesions and relapse by about 50% for up to 48 weeks in patients with relapsing remitting MS,[8] but has not been effective in primary progressive MS. A trial of rituximab in primary progressive MS failed to show an effect on progression, although a post hoc analysis suggested that younger patients with enhancing lesions on MRI did have reduced progression after treatment compared with controls.

Fingolimod is a sphingosine-1 phosphate receptor modulator that is given orally once a day at 0.5 mg. Fingolimod reduces relapse rates and the progression of disease compared with placebo[9] and compared with IFN therapy.[10] Fingolimod's side effects include first-dose bradycardia, macular edema, and respiratory infections. Cladribine (2-chlorodeoxyadenosine, 3.5 or 5.25 mg/kg/day) given as a short course once a year reduced the annualized relapse rate by 55% and disease progression by one third compared with placebo in a phase III trial.[11] Both these drugs may have a role in treating MS but also have global immunosuppressive effects that increase the risk for serious infections and possibly other systemic complications.

In a phase 2 trial, treatment with 0.6 mg/day of laquinimod, a novel oral immunomodulatory agent, resulted in a 40% decrease in MR lesions in relapsing-remitting multiple sclerosis at 36 weeks.[12] In another phase II trial, oral fumarate, which also has anti-inflammatory effects, reduced new gadolinium-enhancing lesions by 69%.[13] In a randomized trial, sustained-release fampridine, a potassium-channel blocker at 10 mg twice daily, improved walking in 35% of patients compared with only 8% of patients receiving placebo, leading to its recent approval by the FDA.[14] Teriflunomide is an oral dihydro-orotate dehydrogenase inhibitor that reduced MRI activity in a phase II clinical trial. Other forms of immunosuppression, including methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide, also appear to have some efficacy in MS, although no definitive clinical trials have been done with these agents, and none is as yet approved for MS by the FDA.

MS patients are at high risk of developing osteopenia or osteoporosis, so prophylaxis with vitamin D and calcium and treatment with bisphosphonates or other proven approaches should be considered. Patients with suboptimal 25-OH vitamin D levels (<30 ng/mL) on standard 1000 IU cholecalciferol replacement therapy should consider increasing to 2000 to 4000 IU/day or 50,000 IU ergocalciferol every other week or, in some cases, weekly, with appropriate monitoring of vitamin D and calcium levels. If osteoporosis has already been diagnosed, bisphosphonate therapy, such as alendronate (10 mg daily or 70 mg weekly) or similar drug is generally indicated.

Nondrug Approaches to Well-Being

Nonmedical treatment of MS is a critical part of managing the disease. Patients derive benefit from a health care team approach consisting of an experienced MS physician, nurse, social worker, therapist, and counselor, with appropriate referral to other subspecialties as needed. Alternative and complementary therapies (Chapter 38) are commonly used by patients with MS, and the risks and benefits of these approaches must be discussed with the patient.

PROGNOSIS

The average lifespan of patients with MS is about 8 years less than normal, a finding reflecting a bimodal distribution in which many patients live a normal lifespan and a few die at a significantly younger age owing to aggressive disease, severe disability, infection, or suicide. Most patients presenting with relapsing remitting MS convert to secondary progressive MS after 20 to 40 years. Only one third of patients will require use of a wheelchair, but 50% may need assistive devices, and nearly two thirds will have disability that prevents them from working. African Americans and men of all races tend to have a more aggressive course and are more likely to become disabled. Institution of immunomodulating therapy early in the course of the disease may slow progression of disability, but no long-term follow-up data are available to quantify the extent of this benefit.

OTHER DISEASES OF MYELIN

Monofocal and Monophasic Demyelinating Processes

OPTIC NEURITIS AND TRANSVERSE MYELITIS

Optic neuritis (Chapter 432) and transverse myelitis are inflammatory processes that can occur as entities distinct from MS or as part of MS (see earlier). In addition, optic neuritis and transverse myelitis can occur together in the syndrome called *neuromyelitis optica* (Devic's disease).

Optic Neuritis

Optic neuritis (Chapter 432) is an inflammatory disease that usually involves the retrobulbar portion of the optic nerve and sometimes parts of the optic chiasm. Although optic neuritis is most often associated with MS (50 to 75%), it also can be seen as an isolated idiopathic disorder (25 to 50%), as part of neuromyelitis optica, or associated with other inflammatory and infectious diseases such as systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, Lyme disease, syphilis, and human immunodeficiency virus infection. The pathobiologic features are thought to be similar to those of MS and are characterized by idiopathic inflammatory demyelination followed by secondary axonal injury.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation, which typically is monocular visual loss with pain over the brow that worsens with lateral eye movement, is similar regardless of whether it presents as part of MS (see the earlier discussion of the visual effects of MS) or not. When it involves the optic nerve head, it is called *papillitis* and, in bilateral cases, can be impossible to differentiate from papilledema. Optic neuritis can also be mimicked by anterior segment, choroidal, or retinal diseases. Optic neuritis is distinguished from optic neuropathy, which is a chronic, generally noninflammatory condition of the optic nerve caused by tobacco or nutritional amblyopia, ischemia, Leber's disease, or other rare hereditary diseases (Chapter 432).

TREATMENT

Rx

Among patients with optic neuritis, the 15-year risk of developing MS is 25% in patients without lesions on their baseline brain MRI but 72% in patients with one or more baseline MRI lesions. Treatment with intravenous methylprednisolone as in MS may shorten the duration and severity of the attack, but no definitive evidence indicates that it changes the long-term outcome. Oral prednisone alone, without prior treatment with intravenous methylprednisolone, may increase the risk for recurrent optic neuritis and should be avoided. Data support the use of IFN-β drugs and glatiramer acetate in patients whose optic neuritis is at high risk for conversion to MS (one or more typical brain MRI lesions).

Transverse Myelitis

Transverse myelitis is a rare (~1 in 100,000 people) monophasic inflammatory process of the spinal cord that is usually distinct from MS in that it either involves the entire cross section or is longitudinally extensive along three vertebral body segments rostrocaudally. Transverse myelitis may be idiopathic or associated with inflammatory diseases (systemic lupus erythematosus, Sjögren's syndrome, vasculitis, or MS), infectious diseases, or vascular diseases (antiphospholipid antibody syndrome or dural venous fistula).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In its fulminant form, transverse myelitis causes complete loss of motor and sensory function below the affected level of the spinal cord and causes concomitant bowel, bladder, and sexual dysfunction. Autonomic involvement can be seen in cervical and high thoracic spine cases. Transverse myelitis may also manifest in an incomplete or partial form, which is more commonly associated with MS.

TREATMENT AND PROGNOSIS

Rx

Treatment is usually with methylprednisolone (1000 mg intravenously for 3 to 5 days), followed by specific treatment of any identifiable underlying disease process. The prognosis is worse than in MS in that significant recovery is seen in fewer than 50% of patients, and many patients remain completely paralyzed after the initial attack. Plasma exchange or cyclophosphamide may be considered in steroid-refractory cases.

NEUROMYELITIS OPTICA

Neuromyelitis optica is now recognized as a distinct entity from MS and is characterized by an optic neuritis, often bilateral and temporally associated with a fulminant multilevel transverse myelitis. A specific IgG directed against aquaporin 4 strongly predicts this process. Brain lesions may be seen on MRI and have a predilection for the brain stem. Neuromyelitis optica may be similar to what is called *opticospinal MS* in Japan. There is no proven effective treatment, but patients are usually given anti-inflammatory and immunosuppressive medications. Therapies directed against B cells or humoral factors are being explored. The prognosis is generally poor; most patients develop sustained disabling visual loss and weakness.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis and its hyperacute form, acute necrotizing hemorrhagic encephalopathy, are thought to be forms of monophasic immune-mediated inflammatory demyelination. They differ from MS in that they are typically monophasic, whereas MS is by definition multiphasic or chronically progressive. However, no reliable clinical or pathologic criteria are available to differentiate the two processes, which may represent a continuum. Patients may present with fever, headache, meningeal signs, and altered consciousness, which are exceedingly rare in MS. There is no known effective treatment. Large numbers of patients, especially children, make remarkable recoveries, but the necrotizing form can be severely disabling or fatal.

Leukodystrophies

The leukodystrophies represent a variety of diseases formerly characterized by their common clinical and pathologic characteristics of white matter and, presumably, myelin. Many of these diseases now have a defined biochemical and genetic basis, and some (e.g., Alexander's disease) are no longer considered dysmyelinating diseases.

ADRENOLEUKODYSTROPHY AND ADRENOMYELONEUROPATHY

Adrenoleukodystrophy and adrenomyeloneuropathy, which are caused by impaired ability of the peroxisomes to metabolize very long chain fatty acids, represent different phenotypes resulting from the same X-linked, incompletely recessive genetic defect. Impaired oxidation of very long chain fatty acids results from deficient function of the enzyme lignoceroyl–coenzyme A ligase. The defective gene maps to Xq28 and codes for a peroxisomal membrane protein (ALDP), which is a member of a large family of proteins referred to as the adenosine triphosphate–binding cassette (ABC) transporters, specifically *ABCD1*.

Childhood cerebral adrenoleukodystrophy, which is the most common form of the disorder, represents 45% of all cases; it is seen only in male patients, with an onset at ages 4 to 11 years. Adolescent (5%) and adult (3%) cerebral forms progress at a similar or slower rate compared with the childhood form.

CLINICAL MANIFESTATIONS

Adrenomyeloneuropathy begins in young men as slowly progressive paraparesis with hypogonadism, impotence, sphincter disturbances, variable adrenal insufficiency, and axonal neuropathy affecting mainly the lower extremities. A rare acute inflammatory form with rapid progression and dementia may occur. A similar, but usually milder, disorder can be seen in up to 20% of women who are hemizygous for the disease.

DIAGNOSIS

Diagnosis is established in male patients by finding elevated very long chain fatty acids in the plasma. DNA-based diagnosis in carriers is reliable and is recommended in women because of false-negative results using the plasma assay.

TREATMENT

Rx

Treatment is unsatisfactory. A 4:1 mixture of glyceryl trioleate and glyceryl trierucate (i.e., "Lorenzo's oil") normalizes plasma very long chain fatty acids within 4 weeks and has few side effects. Although clinical trials suggested that treatment in presymptomatic patients delayed or prevented the onset of disease, this treatment is ineffective after symptoms have begun, and the disease progresses relentlessly.

PELIZAEUS-MERZBACHER DISEASE

Pelizaeus-Merzbacher disease is an extremely rare, chronic, familial leukodystrophy usually caused by a genetic defect in the myelin proteolipid (PLP; lipophilin) protein gene. In classic Pelizaeus-Merzbacher disease, age at onset varies between 3 months and 9 years, the age at death varies between 6 years and 25 years, and the longest duration of the disease is approximately 24 years. The disease manifests as a slowly progressive myelopathy, often with cerebellar and cognitive involvement. The diagnosis is established by genetic testing for mutations in the *PLP* gene. No specific treatment exists for Pelizaeus-Merzbacher disease.

METACHROMATIC LEUKODYSTROPHY

Metachromatic leukodystrophy usually results from a recessively inherited defect in the lysosomal enzyme arylsulfatase A. Absence of arylsulfatase A results in the accumulation of sulfatide in both central and peripheral myelin and myelin-forming cells; instability of the myelin membranes results in the breakdown of myelin. Metachromatic leukodystrophy is generally divided into four subtypes: congenital, late infantile (most common), juvenile, and adult. It appears in all ethnic groups and has an overall frequency of 1 in 40,000.

The clinical manifestations are variable and may include progressive spastic paraparesis, extrapyramidal signs, seizures, and peripheral neuropathy. Brain MRI usually shows large confluent symmetrical high-signal areas in the cerebral white matter, brain stem, and cerebellum, but a more patchy appearance resembling MS is occasionally seen in adult cases. At present, no satisfactory treatment exists. Some evidence suggests that bone marrow transplantation delays the onset in presymptomatic patients and may slow progression of the disease.

GLOBOID CELL LEUKODYSTROPHY

Globoid cell leukodystrophy is characterized biochemically by accumulation of galactocerebroside in cerebral white matter as a result of deficient galactocerebroside β-galactosidase activity. The disease is transmitted as an autosomal recessive trait and affects infants in the first 2 to 3 months of life, initially manifesting with behavioral changes and failure to achieve developmental milestones. Rare late-onset cases present with progressive motor impairment and, less frequently, visual failure. Neuropathologic examination reveals marked loss of myelin throughout the brain, with the presence of round or oval macrophages and large, irregular, multinucleated cells, termed *globoid cells,* which are filled with galactocerebroside. Accumulation of galactosylsphingosine (psychosine) is thought to cause destruction of oligodendrocytes and marked reduction of myelin formation.

CANAVAN'S DISEASE

Canavan's disease is a fatal, progressive leukodystrophy with an autosomal recessive inheritance, caused by mutations in the gene for aspartoacylase, an enzyme that hydrolyzes *N*-acetylaspartate into L-aspartate and acetate. Aspartoacylase deficiency results in elevated levels of its substrate molecule, *N*-acetylaspartate, brain edema, and dysmyelination. Clinically, the disease manifests with retardation, seizures, and diffuse, symmetrical white matter degeneration in the subcortical areas, with involvement of the globus pallidum on MRI. No treatment is available.

Grade A

1. The IFN-β Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43:656-661.
2. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis: The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol*. 1996;39:285-294.
3. PRISMS Study Group (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis). Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet*. 1998;352:1498-1504.
4. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. *Neurology*. 1995;45:1268-1276.
5. Polman C, O'Connor PW, Havrdovra E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354:899-910.
6. Coles AJ, Compston DA, Selmaj KW, et al, for the CAMMS223 Trial Investigators. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med*. 2008;359:1786-1801.
7. Hartung H-P, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomized, multicentre trial. *Lancet*. 2002;360:2018-2025.
8. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med*. 2008;358:676-688.
9. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362:402-416.
10. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362:387-401.
11. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med*. 2010;362:416-426.
12. Comi G, Pulizzi A, Rovaris M, et al. Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet*. 2008;371:2085-2092.
13. Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate (240 mg thrice daily but not lower doses) in patients with relapsing-remitting acute multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet*. 2008;372:1463-1472.
14. Goodman AD, Brown TR, Krupp LG, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet*. 2009;373:732-738.

SUGGESTED READINGS

Fancy SP, Kotter MR, Harrington EP, et al. Overcoming remyelination failure in multiple sclerosis and other myelin disorders. *Exp Neurol*. 2010;225:18-23. *Overview of pathobiology*.

Frohman EM, Wingerchuk DM. Transverse myelitis. *N Engl J Med*. 2010;363:564-572. *Clinical review*.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69:292-302. *Review*.

Tremlett H, Zhao Y, Rieckmann P, et al. New perspectives in the natural history of multiple sclerosis. *Neurology*. 2010;74:2004-2015. *Review*.

420

MENINGITIS: BACTERIAL, VIRAL, AND OTHER

MORTON N. SWARTZ AND AVINDRA NATH

BACTERIAL MENINGITIS

DEFINITION

Meningitis is an inflammation of the arachnoid membrane, the pia mater, and the intervening cerebrospinal fluid (CSF). The inflammatory process extends

throughout the subarachnoid space around the brain and spinal cord and involves the ventricles. Pyogenic meningitis is usually an acute bacterial infection that evokes a polymorphonuclear response in CSF. By comparison, tuberculous meningitis (Chapter 332) is often subacute and characterized initially by a modest polymorphonuclear pleocytosis that rapidly evolves to lymphocytic predominance.

EPIDEMIOLOGY

The incidence of bacterial meningitis has dropped dramatically in developed countries since the introduction of vaccines against bacterial pathogens such as *Haemophilus influenzae* type b (Chapter 308), *Streptococcus pneumoniae* (Chapter 297), and *Neisseria meningitidis* (Chapter 306). Worldwide, however, bacterial meningitis remains a major cause of mortality and morbidity. Although all human microbes have the potential to cause meningitis, only a few organisms account for most cases of bacterial meningitis.

The clinical setting in which meningitis develops may provide a clue to the specific bacterial cause. *H. influenzae* (Chapter 308) affects primarily children, whereas *S. pneumoniae* (Chapter 297) causes meningitis in adults, especially those older than 50 years with comorbid conditions. Meningococcal meningitis (Chapter 306) most often occurs in outbreaks. In developed countries, *Listeria monocytogenes* (Chapter 301) is emerging as the most common cause of bacterial meningitis, with peak frequencies in the neonatal period and in persons 60 years of age and older. Simultaneous mixed bacterial meningitis is rare but occurs in the setting of neurosurgical procedures, penetrating head injury, head trauma with fracture of the cribriform plate, erosion of the skull or vertebrae by adjacent neoplasm, extension of osteomyelitis, or intraventricular rupture of a cerebral abscess; isolation of anaerobes should strongly suggest the latter two of these situations. Meningitis involving anaerobes may also occur very rarely as a result of an intestinal-meningeal fistula following surgery and radiation therapy for colorectal cancer. In approximately 10% of patients with pyogenic meningitis, the bacterial cause cannot be defined.

Over the past several decades, gram-negative bacillary meningitis has doubled in frequency in adults, a change reflecting more frequent and extensive neurosurgical procedures, as well as other nosocomial factors. *L. monocytogenes* has increased 8- to 10-fold as a cause of bacterial meningitis in large urban general hospitals. *Listeria* infections are most often food-borne via dairy products, processed meats, uncooked vegetables, and precut salads. Although *Listeria* meningitis may occur in immunocompetent individuals, it occurs mostly in organ transplant recipients, patients undergoing hemodialysis, patients receiving corticosteroids or cytotoxic drugs for treatment of cancer or autoimmune diseases, patients with liver disease, alcoholic patients, pregnant women, and neonates. Meningitis caused by coagulase-negative staphylococci, which represents approximately 3% of cases in large urban hospitals, occurs as a complication of neurosurgical procedures and is often caused by methicillin-resistant strains. *Streptococcus viridans*, *Pseudomonas*, and other gram-negative bacteria are the agents most often associated with meningitis that complicates diagnostic myelography and percutaneous trigeminal rhizotomy.

In large tertiary care hospitals, approximately 40% of cases of bacterial meningitis in adults are of nosocomial origin. The leading causes are gram-negative bacilli (primarily *Escherichia coli* and *Klebsiella*), which account for approximately 40% of nosocomial episodes, as well as various streptococci, *Staphylococcus aureus*, and coagulase-negative staphylococci, each responsible for approximately 10% of nosocomial cases.

Meningococcal disease, including meningitis, may occur sporadically and in cyclic outbreaks. High-risk groups include individuals who live in close quarters such as crowded classrooms, college dormitories, military barracks, or jails. The meningococcal vaccine is about 85% protective. In industrialized countries, serogroups B and C account for the majority of infections. In developing countries, serogroups A and, to a lesser extent, C are dominant. In sub-Saharan Africa, the so-called meningitis belt, recurrent yearly waves of serogroup A meningococcal infections can occur.

Predisposing factors for the development of pneumococcal meningitis include acute otitis media (Chapters 297 and 434), with or without mastoiditis, which is seen in approximately 20% of adult patients. Pneumonia is present in approximately 15% of patients with pneumococcal meningitis, a much higher frequency than in meningitis caused by *H. influenzae* or *N. meningitidis*. Acute pneumococcal sinusitis (Chapter 434) is occasionally the initial focus from which infection spreads to the meninges. A recent or remote major head injury (Chapter 406) precedes approximately 10% of episodes of pneumococcal meningitis, and CSF rhinorrhea (usually caused by a defect or fracture in the cribriform plate) is present in approximately 5% of patients. Cochlear implants, particularly those that include a positioner, have been implicated in cases of childhood bacterial meningitis, especially episodes resulting from *S. pneumoniae*. Occasionally, meningitis caused by *S. pneumoniae* develops in patients with central nervous system (CNS) shunts. Splenectomy or splenic dysfunction, as in sickle cell anemia (Chapter 166) or in cirrhosis (Chapter 156) with portal hypertension, or other defects in humoral immunity also predispose patients to pneumococcal meningitis. Alcoholism (Chapter 32) is an underlying problem in 10 to 25% of adults with pneumococcal meningitis in urban hospitals. The estimated annual incidence of bacterial meningitis (primarily pneumococcal) in patients infected with human immunodeficiency virus (HIV) is 150-fold higher than in the general population.

S. aureus meningitis is seen most commonly as a complication of a neurosurgical procedure, after penetrating skull trauma, or occasionally secondary to staphylococcal bacteremia and endocarditis. Meningitis attributable to gram-negative bacilli takes one of three forms: neonatal meningitis, meningitis after trauma or neurosurgery, or spontaneous meningitis in adults (e.g., bacteremic *Klebsiella* meningitis in a patient with diabetes mellitus). The most common causes of gram-negative bacillary meningitis in adults are *E. coli* (≈30%) and *Klebsiella-Enterobacter* (≈40%). Meningitis caused by group A streptococci is uncommon but occasionally occurs after acute otitis media, more often in children than in adults. *H. influenzae* type b meningitis in an adult should raise the question of the presence of an underlying anatomic or immunologic defect.

Patients with defects in cell-mediated immunity are susceptible to the development of CNS infections with intracellular organisms such as *L. monocytogenes*. Patients with defective humoral immunity and an inadequate antibody response are particularly vulnerable to meningitis with *S. pneumoniae* and *H. influenzae*. Patients with neutropenia are at higher risk for meningitis with *Pseudomonas aeruginosa* and members of the Enterobacteriaceae family.

PATHOBIOLOGY

Pathology

On gross examination, purulent exudate in the subarachnoid space is most abundant in the cisterns at the base of the brain and over the convexities of the rolandic and sylvian sulci, which are expansions of the subarachnoid space. Although neither the infecting organism nor the inflammatory exudate directly invades cerebral tissue, the subjacent brain becomes congested and edematous. The effectiveness of the pial barrier generally prevents bacterial meningitis from causing a cerebral abscess; when these two processes coexist, the sequence is usually that an initial abscess leaks its contents into the ventricular system and produces secondary meningitis.

The inflammatory exudate can extend around the perivascular spaces to adjacent structures, especially the arteries and veins that carry a layer of pia mater and arachnoid membrane as they enter the brain from the cortical surface. *Cortical thrombophlebitis* results from venous stasis and adjacent meningeal inflammation. Infarction of cerebral tissue may follow. *Involvement of cortical and pial arteries* by peripheral aneurysm formation and vascular occlusion or narrowing (related to spasm, arteritis, or both) of the supraclinoid portion of the internal carotid artery at the base of the brain occurs in approximately 15% of patients with meningitis. The anterior and middle cerebral arteries may have markedly increased intracerebral blood flow velocity (an index of stenosis or arterial spasm) on transcranial Doppler ultrasonography, a finding corresponding to focal cerebral signs. In fulminating cases, particularly meningococcal meningitis, *cerebral edema* may be marked even though the pleocytosis is only moderate. Rarely, temporal lobe herniation through the tentorium develops in such patients and compresses the midbrain, thereby leading to ipsilateral third nerve palsy and contralateral hemiparesis or cerebellar herniation through the foramen magnum with compression of the medulla, which results in apnea, hemodynamic instability, and coma. *Damage to cranial nerves* occurs in areas where dense exudate accumulates around the nerves; the third and sixth cranial nerves are also vulnerable to damage by increased intracranial pressure. *Ventriculitis*, which probably occurs in most cases of bacterial meningitis, rarely progresses to *ventricular empyema*. As the exudates continue to accumulate, obstruction of the flow of CSF may result in *hydrocephalus*. Obstruction of the foramina of Magendie and Luschka at the base of the fourth ventricle results in noncommunicating or obstructive hydrocephalus, whereas obstruction at the level of the arachnoid granulations in the venous sinuses results in communicating hydrocephalus. *Subdural effusions* are sterile transudates that develop over the

cerebral cortex and can be demonstrated readily by computed tomography (CT) as low-density areas about the cerebrum; rarely, such effusions become infected and produce subdural empyema.

Pathogenesis

Bacteria may gain access to the meninges by several routes: (1) hematogenous spread from a distant site, (2) direct ingress from the upper respiratory tract or skin through an anatomic defect (e.g., skull fracture, eroding sequestrum, meningocele, sequela of surgery), (3) passage intracranially through venules in the nasopharynx, or (4) spread from a contiguous focus of infection (infection of the paranasal sinuses, leakage of a brain abscess). Bacteremic spread of *H. influenzae*, *N. meningitidis*, and *S. pneumoniae* is probably the most frequent path of infection. Bacteremia is usually initiated by pharyngeal adhesion and colonization by an infecting strain. Adhesion of such strains, as well as of *S. pneumoniae*, to mucosal surfaces is abetted by their capacity to produce proteases that cleave immunoglobulin A, thus inactivating this local antibody defense. Adhesion of *N. meningitidis* to nasopharyngeal cells is affected by fimbriae or pili and promoted by previous damage to ciliated cells such as from smoking or viral infections. Meningococci invade the nasopharyngeal mucosal cells by means of endocytosis and are transported to the abluminal side in membrane-bound vacuoles. *H. influenzae*, in contrast, invades intercellularly by causing separation of the apical tight junctions between columnar epithelial cells. When these meningeal pathogens gain access to the blood stream, their intravascular survival is aided by the presence of polysaccharide capsules that inhibit phagocytosis and confer resistance to complement-mediated bactericidal activity.

The mechanism by which bacteria gain access to the subarachnoid spaces from blood appears to be related to specific adhesion molecules on brain endothelial cells. Once established in any part of the meninges, infection quickly extends throughout the subarachnoid space. Bacterial replication proceeds relatively unhindered because the low CSF levels of immunoglobulin and complement early in meningeal inflammation result in minimal or no opsonic or bactericidal activity and because surface phagocytosis of unopsonized organisms is meager in such a fluid environment. During meningitis, the concentrations of immunoglobulins in CSF increase but still remain relatively low. Secondary bacteremia may follow meningeal infection and may itself contribute to continuing further inoculation of CSF.

Bacterial meningitis following head trauma occurs because of a dural fistula from the nasal cavity, paranasal sinuses, or the middle ear to the subarachnoid space. The most frequent site is at the cribriform plate, where the bone is very thin and the dura is tightly adherent to the bone. Leakage of CSF results in CSF rhinorrhea and loss of smell.

Bacterial components (e.g., pneumococcal cell walls or lipoteichoic acid, *H. influenzae* lipopolysaccharide) are major elicitors of meningeal inflammation by causing release into the subarachnoid space of various pro-inflammatory cytokines such as interleukin-1 and tumor necrosis factor from endothelial and meningeal cells, macrophages, and microglia. Cytokines appear to enhance the passage of leukocytes by inducing several families of adhesion molecules that interact with the corresponding receptors on leukocytes. Cytokines can also increase the binding affinity of a leukocyte selectin, leukocyte adhesion molecule, for its endothelial cell receptor and may thereby further contribute to trafficking of neutrophils into the subarachnoid space.

In bacterial meningitis, neutrophils move into the subarachnoid space but are not able to control the bacterial infection because their phagocytic properties are inefficient as a result of a lack of opsonic and bactericidal activity. Within the subarachnoid space, neutrophils release products such as prostaglandins, matrix metalloproteinases, and free radicals that disrupt the endothelial intercellular tight junctions and the subendothelial basal lamina. The increased local vascular permeability of the blood-brain barrier may cause cerebral edema, which can also be caused by increased CSF pressure as a result of obstruction of CSF outflow because of interstitial inflammation at the level of the arachnoidal villi.

Cerebral blood flow, which depends on mean arterial pressure, appears to be increased in the very early stages of meningitis, but it subsequently decreases, substantially in some patients, in whom it may be responsible for ensuing neurologic injury. Localized regions of marked hypoperfusion, attributable to focal vascular inflammation or thrombosis, can occur in patients with normal blood flow. Impairment of cerebral blood flow autoregulation, as measured by transcranial Doppler ultrasonography of the middle cerebral artery, occurs in the early phase of acute bacterial meningitis and causes cerebral blood flow to correspond directly to mean arterial blood pressure, with attendant hyperperfusion or hypoperfusion of the brain. On recovery, the ability of the cerebral vasculature to maintain a constant level of perfusion despite variations in mean arterial pressure is restored.

CLINICAL MANIFESTATIONS

History

Acute-onset fever, generalized headache, vomiting, and stiff neck are common to many types of meningitis (Table 420-1). Most patients with community-acquired pyogenic meningitis have had an antecedent or accompanying upper respiratory tract infection or nonspecific febrile illness, acute otitis (or mastoiditis), or pneumonia. Myalgia, particularly in patients with meningococcal disease, backache, and generalized weakness are common symptoms. The illness usually progresses rapidly, with the development of confusion, obtundation, and loss of consciousness. Occasionally, the onset may be less acute, with meningeal signs being present for several days to a week.

General Physical Findings

Evidence of meningeal irritation is usually present as evidenced by a stiff neck, Kernig's sign, and Brudzinski's sign. Although the classic triad of fever, stiff neck, and change in mental status is present in only 44% of episodes, a combination of two of four symptoms (headache, fever, stiff neck, and altered mental status) is found in 95% of patients. The findings of meningitis may easily be overlooked in infants, obtunded patients, elderly patients with heart failure or pneumonia, or immunosuppressed individuals, who may have

TABLE 420-1 CHARACTERISTICS OF THE STUDY POPULATION*

CHARACTERISTIC	EPISODES OF MENINGITIS (*N* = 696)
Duration of symptoms <24 hr	48%
Predisposing conditions	
Otitis or sinusitis	25%
Pneumonia	12%
Immunocompromise†	16%
Symptoms at initial evaluation	
Headache	87%
Nausea	74%
Neck stiffness	83%
Triad of fever, neck stiffness, and change in mental status	44%
Focal neurologic deficits	33%
Aphasia	23%
Hemiparesis	7%
Indices of CSF inflammation	
Opening pressure (mm H_2O)‡	370 ± 130
White cell count§	
Mean (cells/mm^3)	7753 ± 14,736
<100/mm^3	7%
100-999/mm^3	14%
>999/mm^3	78%
Protein (g/L)	4.9 ± 4.5
CSF/blood glucose ratio	0.2 ± 0.2
Positive blood culture‖	66%
Blood tests	
ESR (mm/hr)¶	46 ± 37
C-reactive protein (g/L)**	225 ± 132
Platelet count (platelets/mm^3)††	198,000 ± 100,000

*The study included 671 patients who had a total of 696 episodes of community-acquired meningitis. Plus-minus values are means ± standard deviation.
†Immunocompromise was defined by the use of immunosuppressive drugs, a history of splenectomy, or the presence of diabetes mellitus or alcoholism, as well as patients infected with human immunodeficiency virus.
‡CSF pressure was measured in 216 patients.
§The CSF leukocyte count was determined in 659 patients; CSF specimens from 14 patients had too many leukocytes for an exact count to be performed.
‖Blood culture was performed in 611 patients.
¶The ESR was determined in 549 patients.
**C-reactive protein levels were determined in 394 patients.
††The thrombocyte count was determined in 653 patients.
CSF = cerebrospinal fluid; ESR = erythrocyte sedimentation rate.
Data from 696 cases reported in van de Beek D, de Gans J, Spanjaard L, et al. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med.* 2004;351:1849-1859.

meningitis without prominent meningeal signs; in such patients, lethargy should be investigated carefully, meningeal signs should be sought, and examination of CSF is indicated if any doubt exists. In elderly patients, neck stiffness may be difficult to evaluate because of osteoarthritis in the neck or stiffness of neck muscles secondary to basal ganglia disorders. When neck stiffness is caused by meningitis, the neck resists flexion but can be rotated passively from side to side; with cervical spine disease, however, resistance is present in all directions of neck movement. Neck stiffness disappears during coma.

The presence of a petechial or ecchymotic rash (see Fig. 306-3 in Chapter 306) in a patient with meningeal findings almost always indicates meningococcal infection and requires prompt treatment because of the rapidity with which this infection can progress (Chapter 306). Rarely, extensive petechial and ecchymotic lesions occur in meningitis caused by *S. pneumoniae*, *H. influenzae*, or echovirus type 9. Very rarely, skin lesions almost indistinguishable from those of meningococcal bacteremia occur in patients who have acute *S. aureus* endocarditis (see Fig. 76-1) and who also have meningeal signs and pleocytosis (secondary either to staphylococcal meningitis or to embolic cerebral infarction). Usually, one or two of the lesions in such a patient represent purulent purpura; aspiration of material reveals staphylococci on Gram staining. In the summer, viral aseptic meningitis may produce meningeal signs, macular and petechial skin lesions, and a pleocytosis of several hundred cells, sometimes with neutrophils predominating initially.

Fulminant meningococcal septicemia may cause hemorrhages within the adrenal glands and result in Waterhouse-Friderichsen syndrome (Chapter 234), a condition characterized by the sudden onset of a febrile illness, large petechial hemorrhages in the mucous membranes and skin, cardiovascular collapse, and disseminated intravascular coagulation. In contrast, hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone may develop in patients with meningitis attributable to *H. influenzae*. A concurrent respiratory tract infection or acute otitis media may be present with either *H. influenzae* or *S. pneumoniae*.

In patients with a basilar skull fracture, the potential for development of a dural fistula and bacterial meningitis is indicated by the presence of CSF rhinorrhea, periorbital ecchymoses, bruising behind the ear (Battle's sign), hemotympanum, or blood in the external auditory canal. Meningitis complicating neurosurgical procedures may be insidious in onset and difficult to distinguish from the altered consciousness and signs of meningeal irritation that are expected in the postoperative period. However, fever or prolonged obtundation is an indication for evaluation of CSF.

Neurologic Findings and Complications

Neurologic complications in patients with inadequately treated bacterial meningitis can be severe and disabling. Cranial nerve abnormalities, involving principally the third, fourth, sixth, or seventh nerve, occur in 5 to 10% of adults with community-acquired meningitis and usually disappear shortly after recovery. Persistent sensorineural hearing loss occurs in 10% of children with bacterial meningitis, and another 16% have transient conductive hearing loss. The most likely sites of involvement in patients with persistent sensorineural deafness appear to be the inner ear (infection or toxic products possibly spreading from the subarachnoid space along the cochlear aqueduct) and the acoustic nerve. In children, permanent hearing impairment is more common after meningitis caused by *S. pneumoniae* than by *H. influenzae* or *N. meningitidis*.

Seizures (focal or generalized; Chapter 410) occur in 20 to 30% of patients and may result from reversible causes (high fever or hypoglycemia in infants, penicillin neurotoxicity when large doses are administered intravenously to patients with renal failure) or, more commonly, from focal cerebral injury related to arterial hypoperfusion and infarction, cortical venous thrombosis, or focal edema and cerebritis. Seizures can occur during the first few days or can appear with associated focal neurologic deficits caused by vascular inflammation some days after onset of the meningitis. In adults with seizures accompanying meningitis, *S. pneumoniae* is more commonly the cause, but alcohol withdrawal is a confounding factor.

Increased CSF pressure, which can be caused by brain swelling or hydrocephalus, is associated with seizures, vomiting, sixth and third nerve dysfunction, abnormal reflexes, reduced consciousness or coma, dilated and poorly reactive pupils, and the Cushing response of decerebrate posturing, hypertension, bradycardia, and irregular respirations. In approximately a fourth of fatal cases of community-acquired meningitis in adults, cerebral edema accompanied by temporal lobe herniation is observed at autopsy.

Papilledema (see Fig. 431-27 in Chapter 431) occurs in less than 1% of patients with bacterial meningitis, even with high CSF pressure, probably because the patient is seen early in the process before changes in the nerve head have occurred. The presence of this sign should indicate the possibility of another associated or independent suppurative intracranial process, such as subdural empyema or brain abscess. Marked central hyperpnea sometimes occurs in patients with severe bacterial meningitis; CSF acidosis, which is principally due to increased lactic acid levels, provides much of the respiratory stimulus.

Focal cerebral signs (principally hemiparesis, dysphasia, visual field defects, and gaze preference) occur in approximately a third of adults with community-acquired bacterial meningitis. These signs may develop because of arterial or venous occlusion. In addition, cerebral blood flow velocity may be decreased in patients with increased intracranial pressure and may lead to temporary or lasting neurologic dysfunction. It is important to distinguish these vascular effects from postictal changes (Todd's paralysis), which usually persist for less than a day. Meningitis may also cause the syndrome of inappropriate secretion of antidiuretic hormone.

DIAGNOSIS

Bacterial meningitis is a medical emergency that requires immediate diagnosis and rapid institution of antimicrobial therapy. Delay in treatment is the most critical factor in determining the morbidity and mortality of patients with bacterial meningitis. The diagnosis of bacterial meningitis is not difficult in a febrile patient with meningeal symptoms and signs developing in the setting of a predisposing illness. The diagnosis may be less obvious in an elderly, obtunded patient with pneumonia or a confused alcoholic patient in impending delirium tremens.

When the diagnosis of bacterial meningitis is entertained, blood cultures should be performed, CSF examined and cultured, and antimicrobial therapy instituted promptly. If a mass lesion (cerebral abscess, subdural empyema) is suspected from the history, clinical setting, or physical findings (papilledema, focal cerebral signs), CT with or without contrast enhancement or magnetic resonance imaging (MRI) should be performed because of the danger of brain herniation with lumbar puncture. Antibiotics can and commonly should be started immediately, even before performing lumbar puncture, because it takes approximately 2 hours for antibiotics to affect CSF cultures. Diagnostic lumbar puncture should not be delayed to perform CT or MRI except in patients who have focal neurologic findings suggestive of a parameningeal collection or other intracranial mass lesions; in such patients, it is critical to initiate antimicrobial therapy for meningitis of unknown origin or brain abscess before CT or MRI is performed. Patients with community-acquired meningitis rarely have important abnormalities detected on CT in the absence of focal neurologic findings.

Laboratory Findings

Cerebrospinal Fluid Examination

Initial CSF pressure is usually moderately elevated (200 to 300 mm H_2O in adults). Striking elevations (≥450 mm H_2O) occur in occasional patients with acute brain swelling complicating meningitis in the absence of an associated mass lesion. Findings on CSF analysis are strikingly abnormal in patients with meningitis, and such findings help suggest the cause even before the results of culture are available (Table 420-2). In patients with skull fractures, CSF rhinorrhea can be distinguished from nasal secretions by the presence of glucose.

Gram-Stained Smear

By the time of hospitalization, most patients with pyogenic meningitis have large numbers (≥10^5/mL) of bacteria in their CSF. Careful examination of the Gram-stained smear of the spun sediment of CSF reveals the etiologic agent in 60 to 80% of cases. In most instances when gram-positive diplococci (or short-chain cocci) are observed on a stained CSF smear, they are pneumococci. In certain clinical settings, it is important to distinguish pneumococci from the relatively penicillin-resistant *Enterococcus*, an occasional cause of nosocomial meningitis, by latex particle agglutination. Rarely, three species may morphologically mimic *Neisseria* in CSF or may suggest a mixed infection with short gram-negative rods and meningococci: *Acinetobacter baumannii*, *Moraxella* sp, and *Pasteurella multocida*. Culture of CSF reveals the etiologic agent in 80 to 90% of patients with bacterial meningitis if CSF is obtained before or within 1 to 2 hours of the initiation of antibiotics.

TABLE 420-2 COMMON CEREBROSPINAL FLUID FINDINGS IN PATIENTS WITH MENINGITIS

MICROORGANISM	CSF OPENING PRESSURE (cm H_2O)	CELL COUNT (CELLS/mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)
Bacteria*	>20	>1000	>100	<10
Mycobacterium tuberculosis	>20	100-500	>100	10-45
Borrelia burgdorferi	<20	100-500	50-150	10-45
Treponema pallidum	<20	5-500	50-150	10-45
Fungi	<20	5-500	>100	10-45
Viruses	<20	5-500	50-150	Normal

*Group B streptococci, *Escherichia coli, Listeria monocytogenes, Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae* type b.
CSF = cerebrospinal fluid.
Adapted from Kim KS. Acute bacterial meningitis in infants and children. *Lancet Infect Dis*. 2010;10:32-42.

Special Testing Procedures

Broad-range polymerase chain reaction (PCR), which can be performed on CSF within 1.5 hours, can diagnose bacterial meningitis in patients in whom antimicrobial therapy was begun before lumbar puncture or when cultures are negative and a bacterial origin is still suspected. However, specific real-time PCR for the diagnosis of pneumococcal and meningococcal meningitis is currently available only in the research setting. The sensitivity and specificity of rapid antigen testing by latex agglutination are highest (>90%) for *H. influenzae*, lower for *S. pneumoniae*, and considerably lower for *N. meningitidis*. Gram-stained smears almost invariably show the causative microorganism when the latex agglutination test result is truly positive, so latex agglutination is not used routinely for the diagnosis of bacterial meningitis. However, latex agglutination testing may be very useful when the CSF cell count is abnormal, the Gram stain is negative, and blood and CSF cultures are unrevealing at 48 hours, at which time a stored sample of the initial CSF specimen can be tested. Occasionally, when only rare organisms of ambiguous morphology or Gram-staining properties are seen, latex agglutination may be helpful in providing a more specific diagnosis. Other promising new techniques include a nucleic acid amplification technique, which may be useful in resource-poor settings, and a rapid immunochromatographic test for *S. pneumoniae*.

Cell Count

Cells counts should be determined promptly because the cells will begin to lyse after 90 minutes. The normal CSF white blood cell count is less than 5/mm^3 (all mononuclear). The cell count in untreated meningitis usually ranges between 100 and 10,000/mm^3, with polymorphonuclear leukocytes predominating initially (>80%) and lymphocytes appearing subsequently.

The cell count in *L. monocytogenes* meningitis tends to be lower (median, 585/mm^3) than in other types of community-acquired pyogenic meningitis. Extremely high cell counts (>50,000/mm^3) should raise the possibility of intraventricular rupture of a cerebral abscess. Cell counts as low as 10 to 20/mm^3 may be observed early in bacterial meningitis, particularly that caused by *N. meningitidis* and *H. influenzae*. Occasionally, in granulocytopenic patients or in elderly persons with overwhelming pneumococcal meningitis, CSF may contain very few leukocytes and yet may appear grossly turbid because of the presence of a myriad of organisms and an elevated protein level. Meningitis caused by several bacterial species (*Mycobacterium tuberculosis*, *Borrelia burgdorferi*, *Treponema pallidum*, *Leptospira* sp, *Francisella tularensis*, *Brucella* sp) is characteristically associated with a lymphocytic pleocytosis. With *L. monocytogenes* meningitis in an adult, there is usually a polymorphonuclear response, but lymphocytes may predominate in rare instances.

Glucose

CSF glucose is reduced to values of 40 mg/dL or less (or <50% of the simultaneous blood level) in 50% of patients with bacterial meningitis; this finding can be valuable in distinguishing bacterial meningitis from most viral meningitides or parameningeal infections. However, a normal CSF glucose value does not exclude the diagnosis of bacterial meningitis. The blood glucose level should be determined simultaneously because patients with diabetes mellitus (or those who are receiving intravenous glucose infusions) have an elevated CSF glucose level that can be appreciated only by comparison with the simultaneous blood level; however, it may take 90 to 120 minutes for equilibration to occur after major shifts in the level of glucose in the circulation. The hypoglycorrhachia characteristic of pyogenic meningitis appears to result from interference with normal carrier-facilitated diffusion of glucose and increased utilization of glucose by host cells.

Protein

The level of protein in lumbar CSF is usually elevated to greater than 100 mg/dL, and higher values are more commonly observed in pneumococcal meningitis. Extreme elevations, 1000 mg/dL or greater, may indicate subarachnoid block with obstruction of CSF flow. Values higher than 15 mg/dL in ventricular CSF are considered abnormal. If the lumbar puncture is traumatic, the CSF protein level is corrected by subtracting 1 mg/dL for every 1000 red blood cells.

Other Abnormalities

Elevated levels of lactic acid occur in pyogenic meningitis, but other conditions (cerebral ischemia, metabolism of CSF neutrophils, hypoxia) may also increase CSF lactate concentrations. Although lactate dehydrogenase levels are higher in patients with bacterial meningitis than in patients with viral infections of the CNS, these alterations are not helpful in determining the specific etiologic agent.

Blood and Respiratory Tract Cultures

Bacteremia is demonstrable in approximately 80% of patients with *H. influenzae* meningitis, 50% of patients with pneumococcal meningitis, and 30 to 40% of patients with meningococcal meningitis. Hence, blood cultures should be performed routinely in patients suspected of having bacterial meningitis. Cultures of the upper respiratory tract are not helpful in establishing an etiologic diagnosis.

Determination of serum creatinine and electrolyte levels is important in view of the gravity of the illness, the occurrence of specific abnormalities secondary to the meningitis (syndrome of inappropriate secretion of antidiuretic hormone), and problems with therapy in patients with renal dysfunction (seizures and hyperkalemia with high-dose penicillin therapy). In patients with extensive petechial and purpuric skin lesions, evaluation for coagulopathy is indicated. Elevated serum procalcitonin levels have been used to distinguish bacterial meningitis from that of viral origin, but CSF examination (Gram stain, white blood cell count, glucose, culture) usually provides more direct and specific information.

Radiologic Studies

Because of the frequency with which pyogenic meningitis is associated with primary foci of infection in the chest, nasal sinuses, or mastoid, radiographs of these areas should be taken when clinically indicated at the appropriate time after antimicrobial therapy is begun. Initial head CT or MRI is not indicated in most patients with bacterial meningitis. For example, in patients who undergo head CT or MRI before lumbar puncture for suspected meningitis, only approximately 5% have a mass effect identified on CT. Baseline clinical features associated with abnormal findings on CT include age older than 60 years, history of CNS disease, seizure within the previous week, abnormal level of consciousness, abnormal visual fields, limb drift, and aphasia. In patients without any of these clinical findings, only approximately 1% have a mass effect identified on CT or MRI that would raise concern regarding lumbar puncture.

Specific changes that may be observed on CT or MRI during meningitis include cerebral edema and enlargement of the subarachnoid spaces, contrast enhancement of the leptomeninges and the ependyma, or patchy areas of diminished density as a result of associated cerebritis and necrosis. In patients

with meningitis whose clinical status deteriorates or fails to improve, CT or MRI may help demonstrate suspected complications: sterile subdural collections or empyema; ventricular enlargement secondary to communicating or obstructive hydrocephalus; prominent persisting basilar meningitis; extensive areas of cerebral infarction resulting from occlusion of major cerebral arteries, veins, or venous sinuses; or marked ventricular wall enhancement suggesting ventriculitis or ventricular empyema. MRI is superior to CT for visualizing these abnormalities. Rarely, cerebral hemorrhage identifiable on CT may complicate acute bacterial meningitis in adults. In approximately 10% of adults with bacterial meningitis, findings on cranial CT (mastoid or sinus wall defect, eroding retrobulbar mass, pneumocephalus) are indicative of disruption of the dural barrier.

Rarely, paraparesis or tetraparesis resulting from myelitis may complicate bacterial meningitis. In this situation, T2-weighted or short tau inversion recovery (STIR) sequences on MRI can be helpful to exclude spinal cord compression by an extramedullary mass.

Differential Diagnosis

Headache, fever, stiff neck, confusion, vomiting, and pleocytosis are features of meningeal inflammation and are common to many types of meningitis (e.g., bacterial, fungal, viral, chemical) and also to some parameningeal processes. The CSF findings are most helpful in distinguishing among these processes (Chapters 421 and 422). Although a lymphocyte-predominant pleocytosis without hypoglycorrhachia is characteristic of viral (usually enteroviral or herpes simplex virus type 2 [HSV-2]) meningitis or meningoencephalitis (HSV-1), the initial CSF finding may be a polymorphonuclear response (of ≤60%) that quickly becomes mononuclear. HSV-1 encephalitis is suggested by neurologic findings (dysphasia, hemiparesis, olfactory hallucinations, other temporal lobe signs, seizures), abnormalities in the orbitofrontal and medial temporal lobes on MRI, and distinctive electroencephalographic changes in the temporal lobe or lobes. The rash, fever, and headache of Rocky Mountain spotted fever (Chapter 335) may suggest meningococcal infection, but the geographic and seasonal predilections of the former can provide clues. Approximately 10% of patients hospitalized with Rocky Mountain spotted fever have CSF cell counts higher than 100/mm^3 (>70% polymorphonuclear), and thus the condition may initially be confused with bacterial meningitis. The rash associated with enteroviral infections typically consists of erythematous macules and papules on the face, neck, and trunk. Acute subarachnoid hemorrhage (Chapter 415) may be confused with bacterial meningitis because of headache, stiff neck, and vomiting. However, subarachnoid hemorrhage usually has a more abrupt onset without a prodromal fever but with evidence of subarachnoid blood on CT or CSF examination. In patients with neuroleptic malignant syndrome (Chapters 417 and 427), fever, generalized rigidity, and a fluctuating level of consciousness with autonomic instability and leukocytosis may develop. The most specific laboratory abnormality in these patients is a markedly elevated creatine kinase level.

In a patient with meningitis but whose CSF does not reveal the etiologic agent on a Gram-stained smear, particularly when the CSF glucose level is normal and the polymorphonuclear pleocytosis is atypical, certain treatable processes that can mimic bacterial meningitis should be considered in the differential diagnosis:

1. *Parameningeal infections.* The presence of infections (chronic ear or nasal accessory sinus infections, lung abscess) predisposing to brain abscess, epidural (cerebral or spinal) abscess, subdural empyema, or pyogenic venous sinus phlebitis should be sought (Chapter 421). Neurologic symptoms may appear in the course of primary bacterial meningitis, but their presence should alert the physician to the need for close scrutiny for the presence of a space-occupying infectious process in the CNS. Neurologic symptoms or findings antedating the onset of meningeal symptoms should suggest the possibility of a parameningeal infection. Isolation of an anaerobic organism should suggest the possibility of intraventricular leakage of a cerebral abscess.
2. *Bacterial endocarditis.* Bacterial meningitis may occur during bacterial endocarditis (Chapter 76) caused by pyogenic organisms such as *S. aureus* and enterococci. In subacute bacterial endocarditis, sterile embolic infarctions of the brain may produce meningeal signs and a pleocytosis consisting of several hundred cells, including polymorphonuclear leukocytes. A history of dental manipulation, fever, and anorexia antedating the meningitis should be sought; careful examination for heart murmurs and peripheral stigmata of endocarditis is indicated.
3. *"Chemical" meningitis.* The clinical and CSF findings (polymorphonuclear pleocytosis and even reduced glucose level) of bacterial meningitis may be produced by chemically induced inflammation. Acute meningitis after diagnostic lumbar puncture or spinal anesthesia may result from bacterial or chemical contamination of equipment or anesthetic agent. Chemical meningitis, characterized by polymorphonuclear pleocytosis, hypoglycorrhachia, and a latent period of 3 to 24 hours, occurs after 1% of metrizamide myelograms. Endogenous chemical meningitis resulting from material from an epidermoid tumor or a craniopharyngioma leaking into the subarachnoid space can produce polymorphonuclear pleocytosis and hypoglycorrhachia; birefringent material may be seen on polarizing microscopy of the CSF sediment.

Complications

Non-neurologic Complications

Shock

When shock occurs in patients with pyogenic meningitis, it is usually a manifestation of the accompanying intense bacteremia, as in fulminant meningococcemia, rather than a manifestation of the meningitis itself. Management is guided by the principles of septic shock therapy (Chapter 108), with appropriate modifications in patients with heart failure (Chapter 59).

Coagulation Disorders

Coagulopathies (Chapter 177) are frequently associated with the intense bacteremia (usually meningococcal, occasionally pneumococcal) and hypotension that can accompany meningitis. The changes may be mild, such as thrombocytopenia (with or without prolongation of the prothrombin and partial thromboplastin times), or more marked, with clinical evidence of disseminated intravascular coagulation (Chapter 178).

Septic Complications

Endocarditis

In patients with pneumococcal meningitis, particularly those with concomitant bacteremia and pneumonia, acute endocarditis (Chapter 76) can develop, most commonly on the aortic valve. In such patients, febrile relapse and a new cardiac murmur may appear shortly after the completion of antimicrobial therapy for meningitis.

Pyogenic Arthritis

Septic arthritis may result from the bacteremia associated with meningitis caused by *S. pneumoniae*, *N. meningitidis*, or *H. influenzae*.

Prolonged Fever

With appropriate antimicrobial treatment of community-acquired bacterial meningitis, patients become afebrile within 2 to 5 days. Sometimes, however, the fever persists or recurs after an afebrile period. In a patient with persisting headache, obtundation, and cerebral findings, inadequate drug therapy or neurologic sequelae (cortical venous thrombophlebitis, ventriculitis, subdural collections) are important considerations. Re-evaluation of CSF, particularly Gram-stained smear and culture, is essential in these circumstances. Drug-induced fever (Chapters 262 and 288) should be suspected in patients who continue to show clinical improvement in all other respects. Metastatic infection (septic arthritis, purulent pericarditis, thoracic empyema, endocarditis) may be the cause of continuing or recurrent fever. A syndrome, probably immunologic, consisting of fever, arthritis, and pericarditis 3 to 6 days after the initiation of effective antimicrobial therapy for meningococcal meningitis occurs in approximately 10% of patients (Chapter 306).

Recurrent Meningitis

Repeated episodes of bacterial meningitis generally indicate a host defect, either in local anatomy or in antibacterial and immunologic defenses (e.g., recurrent *N. meningitidis* infections in patients with congenital or acquired deficiencies of complement, particularly the late-acting components). Approximately 10% of episodes of pneumococcal meningitis in adults are recurrent meningitis, but only 0.5% of patients with community-acquired meningitis caused by other microorganisms have recurrent attacks. *S. pneumoniae* is the cause of a third of episodes of community-acquired recurrent meningitis; various streptococci, *H. influenzae*, and *N. meningitidis* are the cause of another third of episodes. In contrast, in nosocomial recurrent meningitis, gram-negative bacilli and *S. aureus* are the cause of approximately 60% of episodes. A history of head trauma is much more frequent in patients with recurrent meningitis. Organisms may enter the subarachnoid space directly, through a defect in the cribriform plate (the most common site),

in association with the empty sella syndrome, by means of a basilar skull fracture, through an erosive sequestrum of the mastoid, through congenital dermal defects along the craniospinal axis (usually evident before adult life), or as a consequence of penetrating cranial trauma or neurosurgical procedures. The anatomic defect may produce a frank CSF leak (rhinorrhea or, less commonly, otorrhea) or may entrap a vascular cuff of meninges that may subsequently serve as a direct route for organisms to reach the meninges. CSF rhinorrhea may be intermittent, and meningitis may occur months or years after head injury.

Any patient with bacterial meningitis, particularly if the meningitis is recurrent, should be evaluated carefully for congenital or post-traumatic defects. The presence of CSF rhinorrhea should be sought at admission and subsequently (rhinorrhea may clear during active meningitis only to recur when the inflammation has resolved). Clinical clues suggesting the presence of a CSF fistula through the cribriform plate, pericranial air sinuses, or temporal bone include (1) a salty taste in the throat, (2) positionally dependent rhinorrhea (rhinorrhea only in the lateral recumbent or prone position suggests an otic or sphenoid origin), (3) anosmia (cribriform plate leak), and (4) hearing loss or full feeling in the ear, often with a finding of fluid or bubbles behind the tympanic membrane (leakage into the middle ear). Quantitative determination of the glucose and chloride content of nasal secretions and detection of a transferrin band unique to CSF by protein electrophoresis can definitively establish the presence of CSF rhinorrhea.

Recurrent pneumococcal meningitis may develop without apparent predisposing circumstances, and cryptic CSF leaks should be sought actively in such patients by CT of the frontal and mastoid regions and by radioisotope techniques. Radioiodine-labeled albumin is introduced intrathecally, and pledgets of cotton placed in the nares are subsequently examined for the radionuclide. Intrathecal introduction of fluorescein as a visual tracer (under ultraviolet light) can similarly be used to detect active leaks. Surgical closure of CSF fistulas should be performed to prevent further episodes of meningitis. Extracranial approaches through the ethmoidal sinuses can be used to repair cribriform plate or sphenoidal sinus dural defects and avoid the higher morbidity associated with craniotomy.

In most patients with CSF otorrhea and rhinorrhea after an acute head injury, the leak ceases in 1 or 2 weeks. *Persistent rhinorrhea for more than 4 to 6 weeks is an indication for surgical repair.* Prolonged administration of penicillin does not prevent pneumococcal meningitis and may encourage infection with more drug-resistant species.

TREATMENT

Antimicrobial Agents

Antimicrobial therapy should be initiated promptly in this life-threatening emergency. Subsequent management should be undertaken with close monitoring, often in an intensive care unit. Treatment should be aimed at the most likely causes based on clinical clues, such as the age of the patient, the presence of a petechial or purpuric rash, a recent neurosurgical procedure, and CSF rhinorrhea. However, it is difficult to distinguish among the various causes of bacterial meningitis on clinical grounds alone, although patients with pneumococcal meningitis frequently have altered mental status and progress rapidly to coma, often with recurrent seizures and the rapid development of focal neurologic deficits. If the infecting organism is observed on examination of a Gram-stained smear of the CSF sediment, specific therapy is initiated. If the etiologic agent is not seen on a smear from a patient with suspected bacterial meningitis or if lumbar puncture is delayed because head CT is needed, empirical antimicrobial therapy should be initiated (Table 420-3).

Adequate CSF bactericidal activity, which is critical to cure the meningitis, depends on the ability of the antibiotic to penetrate CSF and to maintain its activity in the purulent exudate, as well as on its metabolism and rate of clearance from CSF. The ability of the antibiotic to penetrate CSF depends on its lipid solubility, protein binding in serum, molecular size, and the status of the blood-CSF barrier. For example, chloramphenicol has very high lipid solubility, whereas β-lactam antibiotics have poor solubility. With the exception of rifampin and chloramphenicol, the commonly used antimicrobial agents do not readily penetrate the normal blood-brain barrier, but the passage of penicillin and other antimicrobial agents is enhanced in the presence of meningeal inflammation (Table 420-4). Antimicrobial drugs should be administered intravenously throughout the treatment period; the dose should not be reduced as the patient improves because normalization of the blood-brain barrier during recovery reduces the achievable CSF drug levels. Bactericidal drugs (penicillin, ampicillin, third-generation cephalosporins) are preferred whenever possible, and CSF levels of antibiotics at least 10 to 20 times the minimal bactericidal concentration are needed for optimal therapy. Some antibiotics are removed from CSF by active transport into blood via the epithelium of the choroid plexus; by comparison, third-generation cephalosporin antibiotics persist in CSF for longer periods. Antimicrobial drugs (first- or second-generation cephalosporins, clindamycin) do not provide effective levels in CSF and should not be used.

Empirical Treatment

Initial treatment of presumed bacterial meningitis when the etiologic agent cannot be identified on a Gram-stained smear of CSF is based on the available clinical clues. In older children and adults, therapy with vancomycin and a third-generation cephalosporin (cefotaxime or ceftriaxone) is recommended (see Table 420-3). In adults older than 50 years and in high-risk groups, ampicillin is also added because of penicillin-resistant pneumococci, the increased frequency of aerobic gram-negative bacilli in nosocomial meningitis and meningitis in immunocompromised patients, and the possibility of *L. monocytogenes*, which is susceptible to ampicillin but not to third-generation cephalosporins. In a penicillin-allergic individual, trimethoprim-sulfamethoxazole is a suitable alternative for *Listeria* meningitis. In special settings, such as nosocomial meningitis associated with neurosurgical procedures or penetrating head trauma, more resistant species such as methicillin-resistant *S. aureus*, coagulase-negative staphylococci, and *P. aeruginosa* may be responsible; in these situations, vancomycin in addition to cefepime is indicated as initial therapy.

Meningitis of Specific Bacterial Cause

Pneumococcal Meningitis

The treatment of choice for pneumococcal meningitis in adults has historically been penicillin, with vancomycin (or chloramphenicol) being a reasonable alternative in patients allergic to penicillin (see later). However, penicillin-resistant pneumococcal strains are found worldwide, including 25% of clinical isolates in the United States. Thus, antimicrobial susceptibilities should be determined for all pneumococcal isolates from CSF, blood, or sterile body fluids (see Table 420-4). Approximately 9% of pneumococcal isolates from patients with meningitis in the United States are resistant to third-generation cephalosporins, with a minimal inhibitory concentration of 2 μg/mL or greater. If the minimal inhibitory concentration for cefotaxime or ceftriaxone (≤1.0 μg/mL) indicates a susceptible isolate, cefotaxime or ceftriaxone would be the drug of choice. If the isolate is highly penicillin resistant or is resistant to 1.0 μg/mL ceftriaxone or cefotaxime, alternative therapy (vancomycin with or without rifampin intravenously) is indicated. Because of the increasingly wide distribution of highly resistant strains, initial therapy (pending susceptibility testing) with cefotaxime (or ceftriaxone) in addition to vancomycin intravenously is recommended. When initial adjunctive therapy with dexamethasone is used (see later) along with vancomycin, it should be borne in mind that vancomycin levels in CSF may be reduced by concomitant corticosteroid use.

Although resistance to chloramphenicol is unusual in pneumococcal isolates from the United States, chloramphenicol has poor bactericidal activity against penicillin-resistant isolates from children with meningitis in South Africa. The relative chloramphenicol resistance of such strains may not be discerned on usual laboratory testing, but it is revealed when the minimum bactericidal concentration is determined. For this reason, vancomycin is preferred over chloramphenicol for the initial treatment of pneumococcal meningitis in a highly penicillin-allergic patient.

The β-lactam antibiotic meropenem is as effective as cefotaxime for meningitis caused by *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* in adults and in children. Cefepime is also similar to ceftriaxone and cefotaxime for infection with *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*, and it has greater activity than these antibiotics against *Enterobacter* sp and *P. aeruginosa* (Table 420-5).

Meningococcal Meningitis

Intravenous administration of penicillin G and ampicillin, in doses used to treat meningitis caused by penicillin-susceptible pneumococci, successfully treats *N. meningitidis* meningitis resulting from susceptible strains. Meningococci resistant to penicillin have occasionally been isolated in Spain (≤50% of strains), South Africa, and Canada but rarely in the United States. Most of these isolates have been only intermediately resistant to penicillin (minimal inhibitory concentration of 0.1 to 1.0 μg/mL), although rare strains have had high-level resistance related to β-lactamase production and require third-generation cephalosporins such as ceftriaxone, which is as effective as the potentially more toxic chloramphenicol. Nevertheless, "meningitis doses" of penicillin or ampicillin may provide CSF levels that are sufficient for infections with some strains of intermediately penicillin-resistant *N. meningitidis*. Usually, a 7-day course of antibiotics is sufficient.

Haemophilus influenzae Meningitis

At present, 25 to 35% of isolates of *H. influenzae* type b in the United States are β-lactamase producers and are ampicillin resistant; cefotaxime or ceftriaxone is the initial therapy of choice (see Table 420-5). Alternatives include cefepime or the combination of chloramphenicol and ampicillin; if the isolate proves susceptible to ampicillin, chloramphenicol may be discontinued. Although more than 50% of isolates are chloramphenicol resistant in some

TABLE 420-3 INITIAL EMPIRICAL THERAPY FOR COMMUNITY-ACQUIRED AND NOSOCOMIAL PURULENT MENINGITIS BASED ON AGE AND CLINICAL SETTING

PREDISPOSITIONS	LIKELY PATHOGENS	PREFERRED ANTIMICROBIALS	ALTERNATIVE ANTIMICROBIALS
Age			
<1 mo	Group B streptococcus, *Escherichia coli, Listeria monocytogenes, Klebsiella* sp	Ampicillin plus cefotaxime	Ampicillin plus aminoglycoside
1-23 mo	*Streptococcus pneumoniae, Neisseria meningitidis,* group B streptococci, *Haemophilus influenzae, Escherichia coli*	Vancomycin* plus ceftriaxone or cefotaxime	Meropenem (? plus vancomycin*)
2-50 yr	*Neisseria meningitidis, Streptococcus pneumoniae*	Vancomycin* plus ceftriaxone or cefotaxime	Meropenem (? plus vancomycin*)
>50 yr	*Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes*	Vancomycin* plus ceftriaxone or cefotaxime plus ampicillin	Vancomycin* plus ceftriaxone or cefotaxime plus trimethoprim-sulfamethoxazole
Impaired immunity	*Listeria monocytogenes*, gram-negative bacilli, *Streptococcus pneumoniae*	Ampicillin plus ceftazidime plus vancomycin*	Trimethoprim-sulfamethoxazole plus meropenem
Cerebrospinal fluid leak or basilar skull fracture	*Streptococcus pneumoniae*, various streptococci, *Haemophilus influenzae*	Vancomycin* plus cefotaxime or ceftriaxone	Vancomycin* plus meropenem
After neurosurgery or penetrating trauma	*Staphylococcus aureus*, coagulase-negative staphylococci, aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin* plus cefepime	Vancomycin* plus ceftazidime or vancomycin* plus meropenem
Cerebrospinal fluid shunts (external or internal)	Coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*), *Propionibacterium acnes*	Vancomycin* plus cefepime	Vancomycin* plus ceftazidime or vancomycin* plus meropenem

*If dexamethasone is also administered, consideration should be given to the addition of rifampin.
Modified from Tunkel AR, Hartman BJ, Kaplan SL, et al. IDSA practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39:1267-1284.

TABLE 420-4 PERMEABILITY OF ANTIBIOTICS INTO CSF

GOOD CONCENTRATIONS IN CSF WITH AND WITHOUT MENINGITIS	ADEQUATE CONCENTRATIONS IN CSF IN MENINGITIS	FAIR TO POOR CONCENTRATIONS IN CSF IN MENINGITIS
Chloramphenicol	Penicillin	Early cephalosporins
Sulfonamides	Ampicillin	Cephalothin
Cephalosporins	Methicillin	Cefoxitin
Cefotaxime	Oxacillin	Aminoglycosides
Ceftriaxone	Nafcillin	Gentamicin
Ceftazidime	Carbenicillin	Tobramycin
Moxalactam	Ticarcillin	Amikacin
Cefepime	Tetracycline	Clindamycin
Metronidazole	Erythromycin	Benzathine penicillin
Trimethoprim-sulfamethoxazole	Ethambutol	
Isoniazid	Rifampin	
	Vancomycin	
	Meropenem	

CSF = cerebrospinal fluid.
Courtesy Allen Aksamit, Mayo Clinic, Rochester, Minn.

TABLE 420-5 ANTIMICROBIAL THERAPY FOR COMMUNITY-ACQUIRED BACTERIAL MENINGITIS OF KNOWN CAUSE IN ADULTS OR CHILDREN

ORGANISM	PREFERRED ANTIMICROBIAL THERAPY	ALTERNATIVE ANTIMICROBIAL THERAPY
Streptococcus pneumoniae		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Cefotaxime, or ceftriaxone, or vancomycin, or chloramphenicol
Penicillin MIC 0.1-1 μg/mL	Ceftriaxone or cefotaxime	Vancomycin,* or meropenem, or cefepime
Penicillin MIC ≥2.0 μg/mL	Vancomycin* (plus cefotaxime or ceftriaxone)	Moxifloxacin or gatifloxacin
Cefotaxime or ceftriaxone MIC ≥1.0 μg/mL	Vancomycin* (plus cefotaxime or ceftriaxone)	Moxifloxacin or gatifloxacin
Neisseria meningitidis		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Ceftriaxone, or cefotaxime, or chloramphenicol
Penicillin MIC 0.1-1.0 μg/mL	Ceftriaxone or cefotaxime	Chloramphenicol, or meropenem, or gatifloxacin, or moxifloxacin
Haemophilus influenzae		
β-Lactamase negative	Ampicillin	Ceftriaxone, or cefotaxime, or cefepime, or chloramphenicol
β-Lactamase positive	Ceftriaxone or cefotaxime	Cefepime, or chloramphenicol, or gatifloxacin, or moxifloxacin
Listeria monocytogenes	Ampicillin† or penicillin G†	Trimethoprim-sulfamethoxazole or meropenem
Streptococcus agalactiae (group B streptococci)	Ampicillin† or penicillin G†	Cefotaxime or ceftriaxone

*Addition of rifampin should be considered. Consider intrathecal (or intraventricular vancomycin, 5 to 20 mg/day) if not responding to intravenous therapy.
†Addition of intravenous gentamicin should be considered.
MIC = minimal inhibitory concentration.
From Tunkel AR, Hartman BJ, Kaplan SL, et al. IDSA practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39:1267-1284.

areas of Spain, less than 1% of isolates have been found to be resistant in the United States. A 10-day course of antibiotics is usually sufficient.

Staphylococcal Meningitis

For the treatment of adult meningitis caused by methicillin-susceptible *S. aureus* or in a penicillin-allergic patient, vancomycin is the alternative of choice (Tables 420-6 and 420-7). Because penetration of vancomycin into CSF is limited, adjunctive intrathecal (or intraventricular) therapy with vancomycin (without preservative) is occasionally used when CSF cultures have remained positive after 48 hours of intravenous therapy alone and CSF levels can be monitored. For adult meningitis caused by methicillin-resistant *S. aureus*, intravenous vancomycin (with adjunctive intrathecal vancomycin as needed) is the treatment of choice. In severe or refractory cases, the addition of rifampin is warranted.

Listeria Meningitis

Ampicillin is the drug of choice for *Listeria* meningitis. When combined with gentamicin, it can have a synergistic bactericidal effect. Third-generation cephalosporins and vancomycin are not effective. In patients allergic to

TABLE 420-6 THERAPY FOR NOSOCOMIAL MENINGITIS OF KNOWN BACTERIAL CAUSE IN ADULTS

ORGANISM	THERAPY OF CHOICE	ALTERNATIVE THERAPY
Staphylococcus aureus		
Methicillin susceptible	Nafcillin or oxacillin; in difficult cases may add rifampin	Vancomycin or meropenem
Methicillin resistant	Vancomycin; in difficult cases may add rifampin	Linezolid or trimethoprim-sulfamethoxazole
Coagulase negative	Vancomycin; may consider addition of rifampin	Linezolid
Enterococcus sp		
Ampicillin susceptible	Ampicillin plus gentamicin	Vancomycin plus gentamicin
Ampicillin resistant	Vancomycin plus gentamicin	Linezolid
Ampicillin and vancomycin resistant	Linezolid	
Escherichia coli and other	Cefotaxime or ceftazidime	Meropenem or aztreonam or ampicillin or trimethoprim-sulfamethoxazole
Enterobacteriaceae*		
*Pseudomonas aeruginosa**	Cefepime or ceftazidime	Meropenem or aztreonam or ciprofloxacin

*Selection of specific antimicrobial drug should be based on in vitro susceptibility results, with consideration given to the addition of an aminoglycoside (e.g., tobramycin, gentamicin, or amikacin).

TABLE 420-7 DOSES OF ANTIMICROBIAL DRUGS FOR TREATMENT OF BACTERIAL MENINGITIS*

ANTIMICROBIAL DRUG	ADULTS (24-HR DOSE)	INFANTS AND CHILDREN (24-HR DOSE)
β-LACTAMS		
Penicillin G	24 million U, q4h aliquots	300,000 U/kg, q4h aliquots
Ampicillin	12 g, q4h aliquots	300 mg/kg, q4h aliquots
Nafcillin	10-12 g, q4h aliquots	200 mg/kg, q4h aliquots
Oxacillin	10-12 g, q4h aliquots	200 mg/kg, q4h aliquots
Aztreonam (a monobactam)	6-8 g, q6-8h aliquots	
Meropenem (a carbapenem†)	6 g, q8h aliquots	120 mg/kg, q8h aliquots
CEPHALOSPORINS		
Cefotaxime	12 g, q4h aliquots	200-300 mg/kg, q6h aliquots
Ceftriaxone‡	4 g, q12h aliquots	80-100 mg/kg, q12h aliquots
Ceftazidime	6 g, q8h aliquots	150 mg/kg, q8h aliquots
Cefepime	6 g, q6-8h aliquots	150 mg/kg, q8h aliquots
AMINOGLYCOSIDES		
Gentamicin§	5 mg/kg, q8h aliquots	7.5 mg/kg, q8h aliquots
Tobramycin§	5 mg/kg, q8h aliquots	7.5 mg/kg, q8h aliquots
Amikacin§	15 mg/kg, q8h aliquots	20-25 mg/kg, q8h aliquots
FLUOROQUINOLONES		
Ciprofloxacin	800-1200 mg, q8-12h aliquots	—
Gatifloxacin‖	400 mg, q24h dosing	—
Moxifloxacin‖	400 mg, q24h dosing	—
OTHERS		
Chloramphenicol	4-6 g, q6h aliquots	75-100 mg/kg, q6h aliquots
Vancomycin¶	2-3 g, q6-8h aliquots	50-60 mg/kg, q6h aliquots
Rifampin	600 mg, q24h dosing	10-20 mg/kg, q12-24h aliquots
Trimethoprim-sulfamethoxazole**	20 mg/kg, q6h aliquots	20 mg/kg, q6h aliquots
Linezolid	1200 mg, q12h aliquots	30 mg/kg, q8h aliquots

*Dosages are intravenous and for patients with normal renal and hepatic function.
†Use may be associated with seizures, but much less so than with imipenem.
‡Four-gram maximum daily dose.
§Peak and trough serum levels should be monitored.
‖No data are available on the optimal dosage required for bacterial meningitis.
¶Monitoring of trough serum levels is advisable; they should be maintained at concentrations of 15 to 20 μg/mL. If the patient is not responding well, one may need to monitor cerebrospinal fluid levels and, if low, temporarily increase the daily dose accordingly or add adjuvant intrathecal vancomycin (5 to 20 mg), as for the treatment of methicillin-resistant *Staphylococcus aureus* meningitis.
**Dosage based on the trimethoprim component of the combination.

ampicillin, intravenous trimethoprim-sulfamethoxazole may be used, followed by oral trimethoprim alone.

Gram-Negative Bacillary Meningitis

Cefotaxime or ceftriaxone (see Tabless 420-6 and 420-7) is used to treat meningitis known to be caused by susceptible gram-negative bacilli (e.g., *E. coli*, *Klebsiella*, *Proteus*), but they should not be used to treat meningitis caused by less susceptible species such as *P. aeruginosa* and *Acinetobacter*. After identifying the specific pathogen and determining its drug susceptibilities, alterations in antimicrobial therapy may be indicated. Although experience is limited, fluoroquinolones can also be used. If the organism is *P. aeruginosa*, ceftazidime or cefepime is recommended and may be combined with vancomycin (see Tables 420-6 and 420-7).

Zoonotic Meningitis

Uncommonly, systemic or bacteremic zoonotic infections are complicated by bacterial meningitis. *F. tularensis* (Chapter 319) meningitis, a rare complication of tularemia, develops approximately a week after the onset of infection. Illness is acquired from direct (or airborne) contact with wild rabbits or squirrels, with domestic animals, or through tick bites. Tularemia occurs throughout the United States, particularly in the Southeast and Midwest. CSF usually exhibits a lymphocytic pleocytosis (several hundred to 2000 cells/mm^3), hypoglycorrhachia, and increased protein concentration. Treatment of adults consists of chloramphenicol (4 g/day intravenously in 6-hour aliquots) in addition to either gentamicin (3 to 5 mg/kg/day intravenously in 8-hour aliquots) or streptomycin (15 mg/kg intramuscularly every 12 hours for 3 days followed by 7.5 mg/kg every 12 hours for the remainder of treatment). The duration of therapy is 14 days or longer.

Brucella meningitis (Chapter 318) is a subacute or chronic process that is often accompanied by other manifestations of neurobrucellosis (encephalitis, polyradiculitis, myelitis). Infection is transmitted to humans in endemic areas (Central and South America, Mediterranean littoral, Arabian peninsula) from the ingestion of unpasteurized milk or cheese or direct contact with domestic animals. Neurobrucellosis occurs in 2 to 5% of patients with brucellosis. CSF findings consist of a lymphocytic pleocytosis (<500 cells/mm^3), hypoglycorrhachia, and an elevated protein level, findings that could mistakenly suggest tuberculous meningitis. The diagnosis is based on demonstration of antibody in serum and CSF or by isolation of *Brucella* from blood; the microorganism is isolated from CSF in only a minority of cases. Treatment of adults involves the three-drug combination of doxycycline (200 mg/day), rifampin (600 mg/day), and trimethoprim-sulfamethoxazole (20 mg/kg/day, based on trimethoprim component, in 6-hour aliquots) intravenously for several months, depending on the clinical and CSF responses.

Streptococcus suis is an uncommon cause of meningitis seen in pig breeders, butchers, and abattoir workers in Europe, Canada, and China. *S. suis* meningitis, which is an acute illness with a brisk neutrophilic pleocytosis, is often initially mistaken for pneumococcal meningitis on the basis of Gram stain of CSF. Treatment of adults consists of penicillin (12 to 24 million U/day in 4-hour aliquots) or ampicillin (12 g/day in 4-hour aliquots) intravenously for 10 to 14 days.

Bacillus anthracis (Chapter 302) is a rare cause of meningitis that most often develops as a complication of inhalation anthrax following exposure to aerosols of anthrax spores in the setting of large-scale processing of wool and hides or a bioterrorism attack (Chapter 20). Anthrax meningitis is an acute process characterized by hemorrhagic or serohemorrhagic CSF with a neutrophilic predominance (several thousand cells per cubic millimeter), hypoglycorrhachia, an elevated protein level, and prominent large gram-positive bacilli on stained smear. Treatment of adults initially includes ciprofloxacin (400 mg at 12-hour intervals) in addition to penicillin (24 million U/day in 4-hour aliquots) and chloramphenicol (4 g/day in 6-hour aliquots) intravenously. Whether all drugs are continued (or treatment is narrowed to one or two antimicrobials) and the duration of treatment depend on whether the meningitis is of suspected bioterrorist origin (Chapter 20) or caused by cutaneous anthrax resulting from animal (or animal product) exposure (Chapter 302). Consultation with infectious disease and public health authorities should be sought.

Duration of Therapy

The frequency of CSF examination depends on the clinical course, but examination should be repeated in 24 to 48 hours if there has not been satisfactory improvement or if the causative microorganism is a more resistant gram-negative bacillus or a highly penicillin-resistant (or cephalosporin-resistant) *S. pneumoniae* strain, especially in patients who are receiving adjunctive dexamethasone therapy. Routine "end-of-treatment" CSF examination is unnecessary in most patients with the common types of community-acquired bacterial meningitis. Meningococci are rapidly eliminated from the circulation and CSF with appropriate antimicrobial therapy, which should be continued for 4 to 7 days after the patient becomes afebrile. If the patient has responded well, a follow-up lumbar puncture is not necessary. *H. influenzae* meningitis should be treated for 7 to 10 days. Follow-up CSF examination may be omitted in patients who have responded with rapid clinical resolution of the meningitis. In pneumococcal meningitis, antimicrobial treatment should be continued for 10 to 14 days and follow-up examination of CSF should be performed, particularly when the patient has coexistent mastoiditis. More prolonged therapy is indicated with concomitant parameningeal infection. Meningitis caused by *L. monocytogenes* should be treated for 21 days. Treatment of gram-negative bacillary meningitis with parenteral antimicrobials is prolonged, usually for a minimum of 3 weeks (particularly in patients after a recent neurosurgical procedure) to prevent relapse. Repeated examinations of CSF are necessary both during and at the conclusion of treatment to determine whether bacteriologic cure has been achieved. When treating meningitis resulting from vancomycin-resistant *Enterococcus faecium* with linezolid, an antibiotic that is bacteriostatic, approximately 4 weeks of therapy is indicated.

Other Aspects of Treatment

Adjunctive Corticosteroids

In children, the routine use of dexamethasone administered intravenously (either 0.15 mg/kg every 6 hours for 4 days or 0.4 mg/kg every 12 hours for 2 days), either at the time of or 10 to 20 minutes before initiating antimicrobial therapy (third-generation cephalosporin), has no effect on mortality but reduces the incidence of neurologic sequelae (primarily bilateral sensorineural hearing loss). However, the benefits are seen predominantly in *H. influenzae* type b meningitis, the incidence of which has been sharply reduced by the use of protein-conjugate vaccines. In a randomized double-blind study in adults with community-acquired bacterial meningitis, adjunctive dexamethasone therapy (10 mg every 6 hours intravenously for 4 days) significantly reduced the proportion of patients with an unfavorable neurologic outcome from 25 to 15% or a fatal outcome from 15 to 7%.[■] Adverse events were not increased in those receiving dexamethasone. Notably, the risk for gastrointestinal bleeding was not increased in the dexamethasone-treated group. The beneficial effect of dexamethasone was most evident in the subgroup of patients with pneumococcal meningitis, in whom the rate of unfavorable outcomes was reduced from 52 to 26% and deaths from 34 to 14%. In this trial, adjuvant dexamethasone was not beneficial in patients with meningococcal meningitis, but the number of patients in this subgroup was small. In a study of adolescents and adults with bacterial meningitis in Vietnam, dexamethasone significantly reduced death and disability by approximately 54% at 6 months in patients with confirmed disease but not in those with suspected disease.[■] By comparison, adjunctive corticosteroids were not effective in treating bacterial meningitis in a large trial of predominantly HIV-positive patients in sub-Saharan Africa.[■] Based on these data, adjunctive dexamethasone (0.15 mg/kg every 6 hours for 2 to 4 days, with the initial dose given 10 to 20 minutes before or simultaneously with the initial dose of antimicrobial therapy) is recommended in adults with suspected or demonstrated pneumococcal meningitis and perhaps routinely in all cases of bacterial meningitis,[■] at least in non–HIV-infected patients in high-income countries.[■] Continuation of dexamethasone requires demonstration of gram-positive diplococci on the CSF Gram stain or positive blood or CSF cultures for *S. pneumoniae*. When vancomycin is used for treatment of meningitis resulting from highly cephalosporin-resistant *S. pneumoniae*, as is recommended in the United States, the addition of rifampin should be considered because dexamethasone may reduce the CSF concentration of vancomycin (see Table 420-4).

Elevated Cerebrospinal Fluid Pressure (Brain Swelling)

Occasional patients with acute bacterial meningitis experience marked brain swelling (CSF pressure >450 mm H_2O), which may lead to temporal lobe or cerebellar herniation after lumbar puncture. To decrease the possibility of this complication when the pressure is found to be this high, only a small amount of CSF should be removed for analysis (the amount present in the manometer), and a 20% solution of mannitol (0.25 to 0.5 g/kg) should be infused intravenously over a period of 20 to 30 minutes while monitoring (if possible) for a decline in CSF pressure to a lower level before the spinal needle is removed. Continued control of increased intracranial pressure, if needed thereafter, may be effected with additional mannitol; dexamethasone (10 mg intravenously, followed by 0.15 mg/kg every 6 hours) should be used in patients with brain swelling regardless of the suspected bacteriologic cause of meningitis.

In a stuporous patient or one with respiratory insufficiency and markedly increased intracranial pressure, use of a ventilator to reduce the arterial carbon dioxide pressure to between 25 and 32 mm Hg is reasonable, and the patient's head should be elevated 30 to 45 degrees. Intubation should be performed with minimal stimulation to avoid an appreciable further rise in pressure; pharmacologic aids to intubation are recommended, such as succinylcholine and opioids, with the possible use of adjunctive intravenous lidocaine. Subsequently, transient increases in intracranial pressure associated with hyperactive airway reflexes can be mitigated by intratracheal instillation of lidocaine before vigorous suctioning. With continued marked and fluctuating elevations in intracranial pressure, use of a continuous intracranial monitoring device may be warranted.

Hypotension

Initial hypovolemia or hypotension, if present, should be treated with fluid to prevent significantly decreased cerebral blood flow. Over the next 24 to 48 hours, inappropriate secretion of antidiuretic hormone may contribute to

further brain swelling; in such cases, fluid should be restricted to 1200 to 1500 mL daily in adults if possible, although a study in children suggests that routine fluid restriction does not improve outcome and that the resulting decrease in extracellular water may increase the likelihood of hypovolemia and an adverse outcome.

Supportive Care

Patients with acute bacterial meningitis should receive constant nursing attention in an intensive care unit to ensure prompt recognition of seizures and to prevent aspiration. If seizures occur, they should be treated acutely in adults with diazepam (administered slowly intravenously at a dose of 5 to 10 mg) or lorazepam (4 to 8 mg). Maintenance anticonvulsant therapy can be continued thereafter with intravenous phenytoin (Chapter 410) until the medication can be administered orally. Sedation should be avoided because of the danger of respiratory depression and aspiration.

Surgery

Surgical treatment of an accompanying pyogenic focus such as mastoiditis should be undertaken when recovery from the meningitis is as complete as possible but under continuing antibiotic administration. Rarely, the mastoid infection (e.g., Bezold's abscess) is so hyperacute that early drainage may be required after 48 hours or so of antibiotic therapy when the acute meningeal process has subsided somewhat.

PROGNOSIS

Prompt treatment of bacterial meningitis usually results in rapid recovery of neurologic function. Persistent or late-onset obtundation and coma without focal findings suggest brain swelling, subdural effusion, hydrocephalus, loculated ventriculitis, cortical thrombophlebitis, or sagittal sinus thrombosis. The last three conditions are commonly associated with fever and continuing pleocytosis.

The mortality rate for community-acquired bacterial meningitis in adults varies with the etiologic agent and the clinical circumstances. With current antimicrobial therapy, the mortality rate for *H. influenzae* meningitis is less than 5% and that for meningococcal meningitis is approximately 10%. The highest mortality is seen with pneumococcal and *L. monocytogenes* meningitis, for which the rates are approximately 20% and 20 to 30%, respectively.

The mortality rate for gram-negative bacillary meningitis, commonly nosocomial in origin, has been 20 to 30% in adults, but it appears to be decreasing. The mortality rate for recurrent community-acquired meningitis in adults (≈5%) is strikingly lower than the 20% rate for nonrecurrent episodes. Poor prognostic factors include advanced age, the presence of other foci of infection, underlying diseases (leukemia, alcoholism), obtundation, seizures within the first 24 hours, and delay in instituting appropriate therapy.

Residual neurologic damage is seen in 10 to 20% of patients who recover from bacterial meningitis. Approximately 25% of adults considered clinically well recovered (expected to function independently and to resume activities of daily life, including work) from pneumococcal meningitis show neuropsychological abnormalities, mainly loss of cognitive speed, when they are examined 6 to 24 months after hospital discharge. Developmental delay and speech defects are each observed in approximately 5% of children. In infants surviving neonatal meningitis, significant sequelae are much more frequent (15 to 50%).

PREVENTION

Vaccination

Effective vaccines are now available for many subtypes of *H. influenzae* type b (Chapter 308) and many meningococcal (Chapter 306) infections that cause meningitis. Adherence to recommended vaccination (Chapter 17) substantially reduces meningitis from each of these organisms.

Chemoprophylaxis

Prompt prophylaxis of close contacts (individuals who frequently slept and ate in the same household with the patient, girlfriend, or boyfriend) is warranted because up to a third of secondary cases of meningococcal disease develop within 2 to 5 days of illness in the initial case. Only hospital personnel who were in close contact with a patient (mouth-to-mouth resuscitation, initial examination before institution of respiratory precautions) are at special risk. Commonly, rifampin orally is used for prophylaxis: for adults (other than pregnant women), 600 mg twice daily for 2 days; for children, 10 mg/kg twice daily for 2 days. Alternatively, for adults, ciprofloxacin (500 mg), ofloxacin (400 mg), or azithromycin (500 mg), each given orally as a single dose, may be used. Another choice is ceftriaxone intramuscularly as a single dose in adults (250 mg) or children (125 mg).

Widespread use of *H. influenzae* type b polysaccharide protein-conjugate vaccine in developed countries has largely eliminated the need for chemoprophylaxis of close childhood contacts of patients with *H. influenzae* meningitis or invasive infection. However, prophylaxis would be indicated for unimmunized close household contacts of an index patient (e.g., recent immigrant) younger than 6 years. If two or more cases of invasive *H. influenzae* type b disease occur in children at a daycare center, prophylaxis of other unimmunized attendees is warranted. Rifampin (20 mg/kg orally) once daily for 4 days is recommended for such children.

VIRAL MENINGITIS

DEFINITION

The nonspecific term *aseptic meningitis* describes an inflammatory process involving the meninges, usually accompanied by a mononuclear pleocytosis, without evidence of pyogenic bacterial infection on Gram stain or culture. The definition encompasses various processes that produce similar clinical pictures and inflammatory responses: *viral meningitis, atypical and nonpyogenic bacterial and fungal meningitis, chemically induced meningitis, drug-induced meningitis, neoplastic meningitis, meningeal inflammation caused by adjacent pyogenic infections,* and *meningitis associated with autoimmune hypersensitivity diseases.* Aseptic meningitis, which is usually an acute or subacute process, can be further divided into types by the duration of illness (*chronic versus chronic-intermittent*) and by distinctive cellular responses in CSF (e.g., *eosinophilic meningitis*).

Many of the viruses causing meningitis may also cause infection of the brain parenchyma (encephalitis; Chapter 422) or spinal cord. Sometimes, parenchymatous involvement and meningeal involvement occur simultaneously in the same patient and are referred to as meningoencephalitis and meningomyelitis, respectively.

EPIDEMIOLOGY

Most cases of community-acquired aseptic meningitis are the result of viruses, principally enteroviruses, which account for more than 60% of viral meningitides and for 90% of those for which an etiologic agent is identified (Table 420-8). Enteroviruses are members of the Picornaviridae (small RNA) family, which consists of more than 60 serotypes: 28 echoviruses, 23 group A and 6 group B coxsackieviruses, 4 numbered enteroviruses (68 to 71), and 3 polioviruses. The most common serotypes implicated in viral meningitis from year to year have been echoviruses 4, 6, 9, 11, 16, and 30 (most recently 13 and 33) and coxsackie B serotypes 2 to 5. Currently, poliovirus infections (Chapter 423) are limited to parts of Asia and Africa, although rare cases occur secondary to attenuated vaccine strains.

Many viruses that produce the clinical picture of aseptic meningitis, such as arthropod-borne viruses, HSV-1, enterovirus 71, lymphocytic choriomeningitis virus, mumps virus, HIV-1, cytomegalovirus, and Epstein-Barr virus, can also produce the clinical picture of meningoencephalitis and encephalitis (Chapter 422). In addition, some viruses involve the spinal cord, including the anterior horn cells (poliovirus, West Nile virus) or the dorsal root ganglia (HSV-2).

Enterovirus

An estimated 10 to 15 million clinical enteroviral infections (Chapter 387) occur annually in the United States, and these include an estimated 50,000 to 75,000 cases of enteroviral meningitis. In temperate climates, enteroviral meningitis peaks during the summer and fall, especially in children. Serotypes tend to cycle with varying periodicity, and outbreaks are related to lack of previous exposure to a particular serotype. Serotype-specific protective antibodies develop following infection, so subsequent episodes of enteroviral meningitis are uncommon and are caused by a different serotype.

Humans are the only known reservoir of enteroviruses. Enteroviral infection is spread predominantly by the fecal-oral route and occasionally by the respiratory route.

Herpes Simplex Virus

HSV (Chapter 382) accounts for 1 to 3% of all episodes of aseptic meningitis and occurs most commonly in sexually active adults or adolescents. In individuals with primary genital herpes (HSV-2) infection, up to 36% of women

TABLE 420-8 AGENTS OF VIRAL MENINGITIS

COMMON
Nonarthropod Viruses
Picornavirus (RNA)
Enterovirus
Echovirus
Coxsackie A
Coxsackie B
Enterovirus 70, 71
Poliovirus
Herpes simplex virus type 2 (HSV-2) (DNA)
Arthropod-Borne Viruses (Arboviruses)
Togavirus (alphavirus, RNA)
Eastern equine encephalitis (EEE)
Western equine encephalitis (WEE)
Venezuelan equine encephalitis (VEE)
Flavivirus (RNA)
St. Louis encephalitis (SLE)
West Nile virus (WNV)
Bunyavirus (RNA)
California encephalitis
UNCOMMON
Arenavirus (RNA)
Lymphocytic choriomeningitis (LCM)
Paramyxovirus (RNA)
Mumps
Retrovirus (RNA)
Human immunodeficiency virus (HIV-1)
RARE
Herpesvirus (DNA)
Herpes simplex virus type 1 (HSV-1)
Epstein-Barr virus (EBV)
Cytomegalovirus (CMV)
Varicella-zoster virus (VZV)
Human herpesvirus type 6 (HHV-6)
Adenovirus (DNA)
Coltivirus (RNA)
Colorado tick fever
Bunyavirus (RNA)
Toscana virus (a Phlebovirus)

and 13% of men have symptoms of aseptic meningitis. Recurrences of genital herpes are common and are sometimes accompanied by aseptic meningitis. More than 80% of cases of benign recurrent aseptic meningitis are caused by HSV-2. In contrast, HSV-1 CNS infection is almost always manifested as encephalitis rather than aseptic meningitis. Herpesviruses may also be reactivated in patients taking immunomodulatory drugs, which are often used to treat autoimmune diseases.

Arboviruses

Although the most common form of CNS infection caused by arboviruses (Chapters 391 and 422) is encephalitis, aseptic meningitis may also occur. These vector-borne viruses are introduced subcutaneously by a mosquito (e.g., West Nile virus), tick (e.g., Colorado tick fever), or sandfly (e.g., Toscana virus). Birds, which are vectors of mosquito-borne arboviruses, may not be obviously sick, although West Nile virus may cause prominent die-offs of corvine species, especially crows and blue jays, which can provide clues to an outbreak affecting humans.

The geographic spread of alphavirus infections (Eastern equine encephalitis, Western equine encephalitis, Venezuela equine encephalitis) in the United States is determined by the range of their individual mosquito vectors. Eastern equine encephalitis occurs sporadically or as focal outbreaks in the summer in the eastern and Gulf coasts, most frequently in children and elderly persons. Western equine encephalitis occurs predominantly in the western states, and Venezuela equine encephalitis is found in Florida. St. Louis encephalitis infections were originally recognized in the Midwest, but sporadic cases and outbreaks have occurred more recently in most parts of the United States; it is the most common arbovirus causing aseptic meningitis in the United States. West Nile virus infections first appeared in the United States in 1999 and now account for approximately 3000 cases of meningitis and another 3000 cases of encephalitis annually.

Mumps

Mumps virus (Chapter 377) was the leading identifiable cause of viral meningitis before widespread immunization in the 1960s. Episodes occurred most frequently in the winter and spring. It is now an uncommon cause of viral meningitis in the United States.

Lymphocytic Choriomeningitis

Lymphocytic choriomeningitis virus is transmitted to humans by rodents through direct contact, through ingestion of animal-contaminated food, or via aerosol or an animal bite. Cases tend to occur in early winter when mice seek shelter in homes. Outbreaks have occurred following exposure to pet or laboratory hamsters. Currently, lymphocytic choriomeningitis virus is infrequently a cause of aseptic meningitis.

PATHOBIOLOGY

The two basic routes for virus to gain access to the CNS are hematogenous (enteroviral infection) or neuronal (HSV infection). Enteroviruses pass through the stomach, where they resist the acid pH, and proceed to the lower gastrointestinal tract. Some virus also undergoes replication in the nasopharynx and spreads to regional lymphatics. After presumably binding to specific enterocyte receptors, the virus breaches the epithelial lining and undergoes primary replication in a permissive cell. From there, the virus progresses to Peyer's patches, where further replication occurs. A minor enterovirus viremia then seeds the CNS, heart, liver, and reticuloendothelial system. Following extensive replication at the latter sites, a major viremia ensues, often accompanying the onset of clinical illness. The mechanism by which enterovirus enters the CNS is presumed to involve crossing the blood-CSF barrier's tight endothelial junctions and then entering CSF, probably at the choroid plexus.

In contrast, HSV infections may reach the CNS via the neuronal route: in HSV-1 encephalitis, from oral sites via the trigeminal and olfactory nerve; in HSV-2 (and the rare HSV-1) aseptic meningitis, by spread from a primary genital lesion and ascent along the sacral nerve roots to the meninges. After subsidence of the primary infection, HSV-1 may remain dormant in the trigeminal or olfactory root ganglia only to reactivate at a later date, enter the temporal lobe, and produce encephalitis. Similarly, HSV-2 may remain latent in the sacral root ganglia until subsequent reactivation causes later episodes of aseptic meningitis.

CLINICAL MANIFESTATIONS

Enteroviral Meningitis

The clinical features of enteroviral meningitis (Chapter 387) in older children and adults often begin abruptly with headache (85 to 100%), fever (80 to 100%), and stiff neck (50 to 80%). In some patients the course is biphasic, with the initial prodromal phase being characterized by low-grade fever and nonspecific symptoms (malaise, sore throat, diarrhea), followed by a second phase at which time the meninges are seeded, with the development of higher fever, nausea, vomiting, myalgia, photophobia, and stiff neck. Other enteroviral syndromes may coexist, particularly pleurodynia or pericarditis resulting from coxsackieviruses. Rash may be a manifestation of infections caused by echoviruses, particularly echovirus type 9, coxsackieviruses A9 and A16, and enterovirus 71; the latter three cause hand-foot-and-mouth disease, which may occur alone or accompany aseptic meningitis. Echovirus 9 epidemics often produce syndromes of exanthem, enanthem (small, grayish white lesions resembling Koplik's spots on the buccal mucosa), and aseptic meningitis, either alone or in combination; a macular and petechial rash in the presence of a meningitic syndrome must be differentiated from meningococcal meningitis.

Neurologic abnormalities affecting the cerebrum are rarely observed because such cases would be defined as encephalitis or meningoencephalitis rather than enteroviral meningitis. In agammaglobulinemic individuals in whom enteroviral CNS infection develops, meningitis may progress to a chronic meningoencephalitis with multiple neurologic features, including headache, seizures, ataxia, weakness, hearing loss, obtundation, and coma.

The clinical course of enteroviral meningitis is benign, even in the minority of patients in whom the onset is acute and even fulminant. Symptoms subside within a week in children but may continue for several weeks in adults.

Herpes Simplex Virus Type 2 Meningitis

Aseptic meningitis is a common complication of primary genital HSV-2 infection (Chapter 382); up to 36% of women and 13% of men have

headache (developing over a period of 2 to 3 days), stiff neck, and photophobia. Clinical features of meningitis occur 3 to 12 days after the appearance of genital lesions and usually last for 4 to 7 days. Neurologic complications occur in up to 37% of patients and include dysesthesia or paresthesia in the perineum or sacral area, urinary retention, and constipation; evidence of transverse myelitis with motor weakness in the lower extremities, hyporeflexia, and paraparesis occasionally ensues. Recurrent episodes of HSV-2 meningitis may occur at intervals of months or years in 20% of patients. In recurrent HSV-2 meningitis, fever may develop but is not as prominent as in bacterial or acute enteroviral meningitis. Recurrent vesicular lesions, paresthesia, or dysesthesia in areas of previous genital herpes may or may not precede individual recurrences of meningitis. Between recurrences, CSF findings and clinical manifestations return to normal. In patients who have had neurologic complications with a first episode of HSV-2 meningitis, the findings subside within 6 months.

Mumps Meningitis

Symptomatic CNS disease, principally meningitis or meningoencephalitis, occurs in 1 to 10% of patients with mumps parotitis (Chapter 377), but pleocytosis occurs in more than 50% of patients with mumps, most of whom lack CNS symptoms. When meningitis occurs in patients with mumps, it usually follows parotitis by 4 to 10 days, but it may precede parotitis by up to 1 week. The typical features of viral meningitis (headache, fever, vomiting) are each present in 50 to 100% of patients. Stiff neck (40 to 90%) is common, and abdominal pain (perhaps complicating pancreatitis or oophoritis) or orchitis (in ≤20% of men with mumps) may be present. Other complications of mumps may involve the nervous system (eighth nerve damage, transient facial nerve paralysis, and rarely, fifth nerve palsy) but are usually independent of mumps meningitis or meningoencephalitis. The incubation period for mumps is 18 to 21 days. When mumps meningitis occurs in the absence of clinical parotitis, it is difficult to distinguish it from other forms of viral meningitis.

When meningitis complicates mumps, fever, which had been low grade, rises to 103° F or higher and persists at this level for 3 or 4 days. Most cases are uncomplicated, with approximately a 10-day duration of illness and then complete recovery. However, symptomatic mumps meningitis may persist for more than 14 days in some patients.

Meningitis Caused by Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus infections are uncommon, and clinical illness occurs after an incubation period of 1 to 3 weeks. Illness begins with a grippe-like syndrome of fever, rigors, malaise, myalgia, anorexia, and photophobia. Sore throat and arthralgia or arthritis of the digits are noted by some patients. Orchitis or parotitis occurs rarely. This grippe-like illness lasts 1 to 3 weeks in humans, but 15% of patients have a biphasic illness consisting of transient improvement and then recrudescence, 1 to 2 days later, of fever, photophobia, and more prominent headache. Meningeal signs are observed during the second phase. The duration of meningitis caused by lymphocytic choriomeningitis virus, like that of mumps meningitis, tends to be longer than the 7 to 10 days for enteroviral meningitis.

Meningitis Caused by Human Immunodeficiency Virus

Initial infection with HIV-1 (Chapter 392) is symptomatic in 40 to 90% of patients but is frequently overlooked. The interval between exposure and onset of symptoms is 2 to 4 weeks. This acute illness resembles mononucleosis, with fever, malaise, lymphadenopathy, arthralgia, myalgia, anorexia, nausea, headache, and morbilliform rash. A few patients with this initial syndrome have manifestations of aseptic meningitis (headache, photophobia, nausea, vomiting, and stiff neck). Occasionally, encephalopathy or cranial nerve palsies (seventh, eighth, and fifth) develop. Symptoms of the initial HIV-1 aseptic meningitis syndrome last several weeks and then subside. Occasionally, manifestations similar to those of the initial infection may appear later in the course of untreated infection.

DIAGNOSIS

Cerebrospinal Fluid Examination

CSF findings in all types of viral meningitis are similar and consist of a predominantly lymphocytic pleocytosis, usually 50 to 1000/mm^3 but occasionally up to several thousand per cubic millimeter, a normal glucose concentration, and a mildly elevated protein level, usually less than 150 mg/dL. During the first 24 to 48 hours of enteroviral meningitis, a predominance of neutrophils (55 to ≤90%) is observed in approximately 50% of patients; subsequently, the principal cells in CSF change to lymphocytes. Occasionally, no pleocytosis is noted in patients proved by culture or PCR to have early enteroviral meningitis. Rarely, hypoglycorrhachia occurs in meningitis resulting from mumps or lymphocytic choriomeningitis virus or in infants with enterovirus.

Polymerase Chain Reaction versus Culture or Antibody Detection

The recent development of reverse-transcription PCR for enteroviruses can reduce detection time to as little as 5 hours, thereby shortening hospital stay and minimizing the unnecessary use of antimicrobial agents. Its sensitivity in CSF is 85 to 100%, with a specificity of 90 to 100%, depending on the laboratory. The test is available in research settings, large hospitals, and commercial laboratories. By comparison, viral culture of enterovirus from CSF has a sensitivity of only 65 to 75% and takes 4 to 8 days.

HSV-2 can be cultured from CSF in approximately 75% of patients with aseptic meningitis during an initial episode of genital HSV-2 infection, but it is rarely isolated from CSF during meningitis associated with recurrent genital herpes. PCR for HSV-2 DNA is usually positive in the CSF of patients with initial episodes of meningitis and is positive in approximately 80% of patients with benign recurrent meningitis caused by lymphocytic choriomeningitis virus.

The diagnosis can be made retrospectively by demonstrating seroconversion in antibody to gG-2 antigen in HSV-2 meningitis. A four-fold rise in titer to mumps or lymphocytic choriomeningitis virus between acute and convalescent sera is also diagnostic. Serodiagnosis is not practical for sporadic enteroviral meningitis because of the specificity of antibodies to individual serotypes.

Differential Diagnosis

The most important process to distinguish from viral meningitis is bacterial meningitis. A predominance of CSF neutrophils, hypoglycorrhachia, and bacteria on Gram-stained smear or culture indicate bacterial meningitis. An early neutrophilic predominance in CSF combined with a macular and petechial rash in enteroviral meningitis may mimic meningococcemia with meningitis. Occasional bacteria and fungi cause meningitis with a predominantly lymphocytic pleocytosis similar to that of most viral meningitides (Table 420-9). Epidemiologic considerations and clinical findings aid in distinguishing leptospiral, Lyme *Borrelia*, and syphilitic meningitis, whereas hypoglycorrhachia suggests tuberculous and cryptococcal meningitis.

TABLE 420-9 NONVIRAL INFECTIOUS CAUSES OF ASEPTIC MENINGITIS

UNCOMMON	RARE
Bacterial	
Leptospira interrogans serovars	*Mycoplasma pneumoniae*
Borrelia burgdorferi	*Ehrlichia chaffeensis*
Treponema pallidum	*Listeria monocytogenes*
Mycobacterium tuberculosis	*Borrelia recurrentis* and *Borrelia hermsii*
Brucella sp	*Chlamydia psittaci*
Parameningeal infections	Staphylococcal enterotoxin or TSST-1
Subacute bacterial endocarditis	*Rickettsia rickettsii* and *Rickettsia prowazekii*
Partially treated bacterial (pyogenic) meningitis	
Fungal	
Cryptococcus neoformans	*Blastomyces dermatitidis*
Coccidioides immitis	*Sporothrix schenckii*
Histoplasma capsulatum	*Candida* sp
Protozoan	
	Trypanosoma brucei sp
	Toxoplasma gondii
	Acanthamoeba sp

TSST-1 = toxic shock syndrome toxin 1.

PREVENTION AND TREATMENT

Rx

The introduction of live attenuated mumps vaccine in the United States reduced mumps from the leading cause of aseptic meningitis and meningoencephalitis to the point at which it occurs only rarely. Chronic enteroviral meningitis and meningoencephalitis in agammaglobulinemic patients have been controlled by parenteral (even intrathecal) administration of immune globulin.

No approved antiviral chemotherapy is available for enteroviral meningitis. Pleconaril, a drug that prevents attachment of virus to host cells, can produce clinical improvement in agammaglobulinemic patients with chronic enteroviral meningoencephalitis.

Intravenous acyclovir (5 to 10 mg/kg every 8 hours) is used to treat hospitalized, symptomatic patients with HSV-2 meningitis, particularly when the disease is associated with primary genital herpes, although it has not been shown in clinical trials to alter the course of illness. In patients with frequent recurrences of HSV meningitis, it is reasonable to attempt prophylaxis with oral antivirals: valacyclovir (500 mg once daily), famciclovir (250 mg twice daily), or acyclovir (400 mg twice daily).

PROGNOSIS

The course and outcome in patients with enteroviral meningitis are almost always benign, although approximately 1% of patients have subsequent abnormalities, probably reflecting a meningoencephalitic process. Most viral meningitides are self-limited, but some cause chronic or recurrent illness. Persistent meningitis or meningoencephalitis, sometimes fatal, can occur in individuals with hereditary (usually X-linked agammaglobulinemia or common variable immunodeficiency) deficiencies in B-lymphocyte function. HIV-1 may produce a prolonged meningeal inflammation. HSV-2 infection is the most common viral cause of recurrent episodes of aseptic meningitis.

OTHER MENINGITIDES

Nonviral Infectious Causes of Aseptic Meningitis

Categories of aseptic meningitis other than the viral meningitides include nonviral infectious processes (see Table 420-9), noninfectious processes (Table 420-10), chronic meningitides (Table 420-11), recurrent meningitis (Table 420-12), and eosinophilic meningitis (Table 420-13). Nonviral infectious causes are uncommon or rare in comparison to viral or acute suppurative meningitis. Some of the bacterial causes (e.g., *Leptospira* serovars, *B. burgdorferi*, *Brucella* sp, *T. pallidum*) produce a lymphocytic pleocytosis; others (partially treated bacterial meningitis, subacute bacterial endocarditis with embolic cerebral infarcts) produce a mixed neutrophilic-mononuclear pleocytosis; and *M. tuberculosis*, though producing a lymphocytic response with developing hypoglycorrhachia, may show a predominantly neutrophilic response in a minority of patients early in the disease. Although patients with *L. monocytogenes* infection usually have neutrophilic pleocytosis, this infection may suggest aseptic meningitis because of its sometimes indolent onset and, occasionally, an early predominantly lymphocytic response in young children. Fungal (e.g., *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*) meningitides are associated with a predominantly mononuclear response, sometimes with a small percentage of eosinophils, particularly in coccidioidal meningitis (Chapter 341). Patients with Rocky Mountain spotted fever (Chapter 335), an acute disease with a macular and petechial rash, may exhibit confusion. When examined, the CSF in

TABLE 420-10 NONINFECTIOUS CAUSES OF ASEPTIC MENINGITIS

Drug hypersensitivity
Systemic disease
Systemic lupus erythematosus
Familial Mediterranean fever
Behçet's syndrome
Wegener's granulomatosis
Cogan's syndrome
Sarcoidosis
Still's disease
Kawasaki disease
Lead poisoning
Neoplastic disease
Metastatic carcinomatous meningitis
Central nervous system tumors (meningeal gliomatosis, dysgerminomas, ependymomas)
Tumors that leak inflammatory material into cerebrospinal fluid (squamous cells in epidermoid tumors of the posterior fossa, cholesteatomas)
Inflammatory processes involving central nervous system structures primarily
Chemical meningitis following myelography (water-soluble nonionic contrast material)
Continuous spinal and epidural anesthesia, inflammation after neurosurgery
Granulomatous cerebral vasculitis
Vogt-Koyanagi-Harada syndrome

TABLE 420-11 INFECTIOUS CAUSES OF CHRONIC (PERSISTENT) LYMPHOCYTIC MENINGITIS

CAUSATIVE CONDITIONS	OTHER CSF FINDINGS
Bacterial	
Mycobacterium tuberculosis	Usually <500 white blood cells/mm^3, low glucose, high protein
Borrelia burgdorferi (Lyme disease)	Normal glucose, elevated protein
Treponema pallidum (secondary syphilitic meningitis, tertiary meningovascular syphilis)	Elevated protein; Venereal Disease Research Laboratory positive in CSF and serum
Brucella sp (uncommon)	Often low glucose; elevated protein
Tropheryma whippelii (rare)	Periodic acid–Schiff–positive cells on meningeal biopsy
Partially treated bacterial meningitis	Mixture of PMNs and lymphocytes, bacteria on Gram stain and culture
Parameningeal infections	Lymphocytes or mixed lymphocytic-PMN response, normal glucose
Fungal	
Cryptococcus neoformans	Low glucose, elevated protein, budding yeast on India ink or fungal wet mount, antigen detectable
Coccidioides immitis	Often low glucose, may have 10-20% eosinophils, elevated protein, presence of complement-fixing antibody
Histoplasma capsulatum	Low glucose; complement-fixing antibodies in CSF; antigen detectable in urine, CSF, serum
Blastomyces dermatitidis	Low glucose
Candida sp	Low glucose, may have PMN or lymphocyte predominance, fungal stain may be positive
Aspergillus sp	Lymphocytes or PMNs predominate
Sporothrix schenckii (sporotrichosis)	Low glucose; protein, 200-800 mg/dL
Protozoal	
Toxoplasma gondii	Usually, picture is that of an encephalitis; often in patients with AIDS; pleocytosis is mild (<60 cells/mm^3) and protein is mildly elevated
Trypanosoma gambiense or *Trypanosoma rhodesiense*	Meningoencephalitis is stage II of disease, elevated protein and immunoglobulin M, trypanosomes on Giemsa-stained smear
Viral	
Mumps	Rarely, low glucose
Lymphocytic choriomeningitis	Rarely, low glucose
Echovirus (in patients with congenital agammaglobulinemia)	Occasionally, low glucose
HIV-1	Cell counts lower (10-20/mm^3) than in acute self-limited meningitis at clinical onset of HIV infection or may develop during course of AIDS

AIDS = acquired immunodeficiency syndrome; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; PMN = polymorphonuclear leukocyte.

TABLE 420-12 CAUSES OF CHRONIC (RECURRENT) MENINGITIS

Infections
Herpes simplex virus type 2
Leakage of contents from central nervous system tumors (chemical meningitis)
Epidermoid tumors
Craniopharyngiomas
Cholesteatomas
Drug hypersensitivity with repeated use of agent
Inflammatory processes
Behçet's syndrome
Systemic lupus erythematosus
Mollaret's meningitis
Vogt-Koyanagi-Harada syndrome

TABLE 420-13 CAUSES OF EOSINOPHILIC MENINGITIS*

CAUSATIVE CONDITIONS	SOURCE
Parasitic Disease	
Angiostrongylus cantonensis	Ingestion of raw shellfish; Pacific
Taenia solium (cysticercosis)	Fecal-oral transmission of *T. solium* eggs
Gnathostoma spinigerum	Ingestion of raw fish; Japan, Southeast Asia
Baylisascaris procyonis	Accidental ingestion of *B. procyonis* eggs from raccoon feces
Trichinella spiralis (trichinosis)	Ingestion of poorly cooked pork
Schistosoma sp	Exposure of skin to fresh water; Africa, Middle East
Echinococcus granulosus	Contact with infected dogs passing eggs in feces
Toxoplasma gondii	Ingestion of meat containing cysts or food contaminated with oocysts from cat feces
Toxocara canis (visceral larva migrans)	Ingestion of infective eggs from dog feces
Fungal Infections	
Coccidioides immitis	Southwestern United States
Neoplastic Disease	
Lymphoma, leukemia, metastatic carcinoma	
Hypereosinophilic syndrome (myeloproliferative disorder)	
Inflammatory Processes	
Sarcoid	
Drug hypersensitivity	
Presence of foreign body in the central nervous system	

*The percentage of eosinophils varies from as little as 6% to the majority of cells.

approximately 20% of such patients shows a pleocytosis of 10 to 100 or more cells/mm^3, with either a neutrophilic or lymphocytic predominance. The clinical picture may suggest either enteroviral or meningococcal disease.

Epidemiologic factors are important in raising suspicion for nonviral aseptic meningitis. Leptospirosis (Chapter 331) may be suggested by a history of recent direct or indirect exposure to animals (e.g., dogs, rodents, dairy cattle) and their urine. Neurobrucellosis (Chapter 318) is suggested by the recent ingestion of unpasteurized cheese from the Mediterranean littoral, Middle East, or Mexico or by work as a veterinarian or in an abattoir. Specific endemic mycoses may be a consideration with residence in the southwestern United States (coccidioidomycosis; Chapter 341) and the Mississippi River valley (histoplasmosis; Chapter 340). The setting of immunosuppression by drugs or illness such as acquired immunodeficiency syndrome would raise the possibility of *C. neoformans* (Chapter 344) or *L. monocytogenes* (Chapter 301). Sexual promiscuity and the macular rash of secondary syphilis could suggest *T. pallidum* (Chapter 327) as the cause in a patient with lymphocytic meningitis.

Noninfectious Causes of Aseptic Meningitis

Noninfectious causes fall into four principal categories (see Table 420-10): drug hypersensitivity; systemic processes such as systemic lupus erythematosus and other collagen-vascular diseases; neoplastic disease, primary or metastatic, infiltrating the leptomeninges; and inflammatory processes primarily involving the CNS. Although a mononuclear cell predominance is found in the CSF in most noninfectious aseptic meningitides, there are several important exceptions. Drug hypersensitivity meningitis usually causes a neutrophilic response, although occasionally mononuclear cells or eosinophils predominate. In systemic lupus erythematosus (Chapter 274), the pleocytosis may be predominantly lymphocytic or neutrophilic (sometimes several thousand per cubic millimeter) with a normal CSF glucose level. Hypoglycorrhachia is a feature of few noninfectious aseptic meningitides and suggests malignant disease or sarcoidosis. Various drugs, most commonly the nonsteroidal anti-inflammatory drugs, have also been implicated in aseptic meningitis.

Chronic (Persistent) Meningitis

Chronic meningitis is defined by the clinical syndrome of headache, stiff neck, altered mental status, nausea and vomiting, evidence of myelopathy or radiculopathy with or without cranial nerve palsies (e.g., III, IV, VI, VII, VIII), and an inflammatory response in the CSF for 4 weeks or longer. Obstruction of CSF flow may produce hydrocephalus and papilledema.

Infectious Causes

Among the more common bacterial causes of chronic meningitis, *M. tuberculosis* (Chapter 332) is the most important to identify because if untreated, it is almost always fatal within 4 to 8 weeks (see Table 420-11). Similarly, parameningeal infections (Chapter 421) must be recognized and treated promptly because surgery is often necessary to provide a specific bacteriologic diagnosis and prevent neurologic residua. Tuberculosis should be suspected in patients with a previous history of a tuberculous illness, a history of recent exposure, HIV infection or another immunosuppressed state, fever and night sweats, sixth cranial nerve palsies, stroke related to arteritis, or lesions on the chest radiograph. The purified protein derivative skin test may be negative in patients with recently acquired or overwhelming disease. Acid-fast smear and culture of concentrated CSF can provide the diagnosis, and PCR can be very helpful. When clinical and CSF findings suggest the diagnosis, treatment (Chapter 332) should be initiated while one awaits the results of culture.

Parameningeal infections (Chapter 421) should be suspected when chronic meningitis with focal neurologic signs develops in the setting of chronic otitis media or sinusitis, pleuropulmonary infection, or right-to-left cardiopulmonary shunting. Contrast-enhanced CT or MRI of the head is important to delineate brain abscess, sinus infection, and epidural or subdural infections.

Meningitis may accompany the skin, mucous membrane, and lymph node features of secondary syphilis (Chapter 327), or it may occur alone. Individual cranial nerves (II to VII) may be involved; visual abnormalities, hearing loss, and facial palsy are most frequent. The fluorescent treponema antibody absorption test or microhemagglutination *T. pallidum* serologic studies are helpful in distinguishing the process from biologic false-positive Venereal Disease Research Laboratory (or rapid plasma reagent) results in serum.

Lyme disease meningitis (Chapter 329) should be suspected on the basis of epidemiologic grounds (geographic location, season, tick exposure) and associated clinical features (erythema chronicum migrans rash, Bell's palsy, radiculopathy). The diagnosis is made by enzyme-linked immunosorbent assay with Western blot confirmation.

Noninfectious Causes

Noninfectious causes of meningitis include malignant disease, chemical meningitis, and primary inflammatory conditions (Table 420-14). Malignant disease may be diagnosed by cytologic examination of large volumes of CSF. Contrast-enhanced MRI may disclose thickening of the meninges and nerve roots, but meningeal biopsy may be required for diagnosis. Chemical meningitis from previous subarachnoid injection may persist, with xanthochromia noted in CSF; meningeal inflammation may be identified on contrast-enhanced CT or MRI.

Meningeal or CNS sarcoid (Chapter 95) may be isolated or occur with other organ involvement, such as pulmonary granulomas, lymphadenopathy, or myopathy. Neurologic findings can include diabetes insipidus and cranial nerve palsies. Wegener's granulomatosis (Chapter 278) may produce

TABLE 420-14 NONINFECTIOUS CAUSES OF CHRONIC (PERSISTENT) LYMPHOCYTIC MENINGITIS

CAUSATIVE CONDITIONS	OTHER CSF FINDINGS
Neoplasms	
Metastatic: lung, breast, stomach, pancreas, lymphoma, melanoma, leukemia	Low glucose; elevated protein, cytologic examination; polarizing microscopy; clonal lymphocyte markers
Central nervous system: meningeal gliomatosis, meningeal sarcoma, cerebral dysgerminoma; epidermoid tumors/cysts	
Chemical Inflammation	
Endogenous: epidermoid tumor, craniopharyngioma	Low glucose, elevated protein
Exogenous: recent injection into the subarachnoid space	Low glucose, elevated protein
Primary Inflammatory Processes	
Central nervous system sarcoid	Often low glucose, elevated protein, elevated angiotensin-converting enzyme levels in CSF (and serum)
Wegener's granulomatosis	Elevated protein
Behçet's syndrome	Elevated protein
Isolated granulomatous angiitis of the central nervous system	Elevated protein
Systemic lupus erythematosus	Elevated protein
?Chronic idiopathic benign meningitis	Elevated protein

CSF = cerebrospinal fluid.

TABLE 420-15 CAUSES OF CHRONIC (PERSISTENT) MENINGITIS WITH NEUTROPHIL PREDOMINANCE

UNCOMMON	OTHER CSF FINDINGS
Bacterial	
Nocardia asteroides	Low glucose, markedly elevated protein, culture positive
Actinomyces israelii	Low glucose, elevated protein, anaerobic culture positive
Arachnia propionica	Low glucose, elevated protein, anaerobic culture positive
Fungal	
Candida sp	Low glucose, elevated protein, culture positive
Aspergillus sp	Low glucose, elevated protein, enzyme immunoassay or enzyme-linked immunosorbent assay for *Aspergillus* galactomannan
Zygomycetes	Low glucose, elevated protein
Dematiaceous fungi	Low glucose, protein may be markedly elevated
Noninfectious	
Systemic lupus erythematosus	Low glucose, elevated protein
Chemical meningitis	Low glucose, protein may be markedly elevated
VERY RARE	
Bacterial	
Brucella sp	Low glucose, elevated protein
Mycobacterium tuberculosis	Low glucose, elevated protein, polymerase chain reaction positive for *M. tuberculosis* DNA
Fungal	
Pseudoallescheria boydii	Low glucose, protein may be markedly elevated
Coccidioides immitis	Low glucose, elevated protein, presence of complement-fixing antibody
Blastomyces dermatitidis	Low glucose, protein elevated, antigen detection possible in CSF and urine
Histoplasma capsulatum	Low glucose; protein mildly elevated; complement-fixing antibodies in CSF; antigen detectable in CSF, urine, serum

CSF = cerebrospinal fluid.

meningeal inflammation and cranial nerve palsies, often in association with air sinus disease. The diagnosis is suggested by lesions on the chest radiograph, microscopic hematuria, skin lesions, peripheral neuropathy, and serum antineutrophil cytoplasmic antibodies. Aseptic meningitis associated with systemic lupus erythematosus (Chapter 274) may be accompanied by other neurologic manifestations (seizures, encephalopathy, stroke, transverse myelopathy), systemic manifestations (rash, arthritis), and antinuclear and anti-DNA antibodies.

Chronic (Intermittent) Meningitis

In chronic intermittent meningitis, all clinical and CSF abnormalities resolve completely between episodes without antimicrobial therapy (see Table 420-11). Uncommonly, a patient may have several episodes resulting from different viral agents. The major causes of recurrent aseptic meningitis are infections (almost always viral and resulting from HSV-2), endogenous chemical meningitis, drug hypersensitivity with meningitis following each use, and inflammatory and autoimmune diseases.

In HSV-2 recurrent meningitis, lymphocytes predominate, with the cell numbers being approximately 40% higher in the initial episode than in recurrences. Leakage of material from intracranial epidermoid cysts produces 1000 to 5000 cells/mm^3 (≈80% polymorphonuclear leukocytes) initially, with a subsequent mononuclear cell predominance. Occasionally, polarizing microscopy may demonstrate keratin and cholesterol crystals in the CSF of patients with endogenous chemical meningitis. In Behçet's syndrome (Chapter 278), the CSF may have predominantly mononuclear cells or polymorphonuclear leukocytes. Mollaret's meningitis, a syndrome of benign recurrent meningitis usually caused by HSV-2, is initially associated with neutrophils and monocytes in the CSF without hypoglycorrhachia but subsequently transitions to a predominantly lymphocytic pleocytosis. Vogt-Koyanagi-Harada syndrome, a rare uveomeningoencephalitis, consists of recurrent meningitis/meningoencephalitis and anterior or posterior uveitis, followed by vitiligo, poliosis, alopecia, and dysacousia; the CSF cellular response is mononuclear, and an autoimmune origin, directed against a melanocyte antigen, has been suggested.

Chronic Meningitis with Predominantly Neutrophilic Pleocytosis

Chronic persistent neutrophilic meningitis (Table 420-15) is defined by the following combination: (1) clinical features consistent with meningitis; (2) initial CSF examination showing greater than 50% neutrophils, hypoglycorrhachia, and elevated protein concentration; (3) antimicrobial therapy that would be appropriate for the usual causes of bacterial meningitis; (4) negative smears and cultures for bacteria on the initial CSF specimen; and (5) repeated CSF examination 7 days or more after initial analysis showing 50% or greater neutrophils, hypoglycorrhachia, and elevated protein concentration.

Among the bacterial causes (see Table 420-15) are organisms (*Actinomyces israelii* and *Arachnia propionica* [Chapter 337]) that can be isolated by culture only under anaerobic conditions. Coexisting pulmonary lesions may suggest *Nocardia* (Chapter 338) or *M. tuberculosis* (Chapter 332) as the cause, although the initial polymorphonuclear pleocytosis present in some cases uncommonly persists much beyond a week before changing to a lymphocytic predominance. *Brucella* (Chapter 318) and endemic invasive mycotic infections would be suggested by epidemiologic considerations. Other fungal causes may be diagnosed, particularly in immunocompromised patients, by antigen testing with enzyme-linked immunosorbent assay (*Aspergillus* sp galactomannan; Chapter 347), or meningeal biopsy may be required.

Occasionally, exogenous chemical meningitis secondary to intrathecal injection of antimicrobials, chemotherapeutic agents, or contrast media may produce persisting pleocytosis and hypoglycorrhachia resulting from sclerosing arachnoiditis well after the inciting medication has been withdrawn. Systemic lupus erythematosus (Chapter 274) can produce a variety of meningitides, including acute lymphocytic or neutrophilic aseptic meningitis, as well as chronic persistent lymphocytic or neutrophilic CSF responses.

Eosinophilic Meningitis

The presence of 5% or greater eosinophils in CSF is uncommon and suggests parasitic disease, certain fungal infections such as coccidioidal or candidal meningitis, neoplastic diseases, or a few inflammatory processes (see Table 420-13). In most cases, eosinophils are mixed with lymphocytes, which predominate; the highest percentage of eosinophils is seen with meningitis caused by migrating larvae of the raccoon ascarid *Baylisascaris procyonis* (Chapter 365) and the rat lung worm *Angiostrongylus cantonensis* (Chapter 365). In fungal meningitides, particularly those resulting from *C. immitis* (Chapter 341), the CSF response is primarily mononuclear with 6 to 20% eosinophils; hypoglycorrhachia may be a feature of *C. immitis* and *Candida* meningitis (Chapter 346) and of neoplastic processes and sarcoid.

Most patients with eosinophilic meningitis, except those with cases resulting from trichinosis (Chapter 365) or drug hypersensitivity, have prolonged symptoms suggesting chronic meningitis. Most patients with meningitis of parasitic or neoplastic origin have evidence of cerebral involvement as well.

1. Nathan N, Borel T, Djibo A, et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. *Lancet*. 2005;366:308-313.
2. van de Beek D, Farrar JJ, de Gans J, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. *Lancet Neurol*. 2010;9:254-263
3. Nguyen TH, Tran TH, Thwaites G, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med*. 2007;357:2431-2440.
4. Scarborough M, Gordon SB, Whitty CJ, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med*. 2007;357:2441-2450.
5. Vardakas KZ, Matthaiou DK, Falagas ME. Adjunctive dexamethasone therapy for bacterial meningitis in adults: a meta-analysis of randomized controlled trials. *Eur J Neurol*. 2009;16:662-673.
6. Assiri AM, Alasmari FA, Zimmerman VA, et al. Corticosteroid administration and outcome of adolescents and adults with acute bacterial meningitis: a meta-analysis. *Mayo Clin Proc*. 2009;84:403-409.

SUGGESTED READINGS

Edmond K, Clark A, Korcczak VS, et al. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10:317-328. *Review*.

Kallio-Laine K, Seppanen M, Kautiainen H, et al. Recurrent lymphocytic meningitis positive for herpes simplex virus type 2. *Emerg Infect Dis*. 2009;15:1119-1122. *Describes the epidemiology, clinical manifestations, management, and outcome of HSV-2–associated meningitis.*

Sinner SW. Approach to the diagnosis and management of tuberculous meningitis. *Curr Infect Dis Rep*. 2010;12:291-298. *Comprehensive review*.

van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med*. 2010;362:146-154. *Review of pathophysiology and treatment*.

421 BRAIN ABSCESS AND PARAMENINGEAL INFECTIONS

AVINDRA NATH AND JOSEPH BERGER

Brain abscess affects the brain's parenchyma directly, whereas parameningeal infections produce suppuration in potential spaces covering the brain and spinal cord (epidural abscess and subdural empyema) or produce occlusion of the contiguous venous sinuses and cerebral veins (cerebral venous sinus thrombosis).

BRAIN ABSCESS

EPIDEMIOLOGY

The frequency of various causes of brain abscess (Table 421-1) in the population has been difficult to ascertain because of wide variations among case series, in part as a result of referral patterns. In addition, case series of children with brain abscesses contain a sizable contingent of cases related to cyanotic congenital heart disease or otogenic infection. Cryptogenic abscesses account for a greater percentage of cases in more recent series, perhaps related to the presence of a patent foramen ovale. On average, 90% of brain abscesses occur as a consequence of a focus of suppuration elsewhere in the body, with the remainder due to introduction of the infection from head wounds or neurosurgical procedures. Males predominate in virtually all series of brain abscess. Terminally ill patients in whom medical care may be withdrawn may be found to have abscesses at autopsy, but these abscesses are of little clinical importance.

TABLE 421-1 CONDITIONS THAT PREDISPOSE TO THE DEVELOPMENT OF BRAIN ABSCESS

Otogenic
Otitis media
Mastoiditis
Dental
Cardiac
Cyanotic heart disease
Tetralogy of Fallot
Patent foramen ovale
Infective endocarditis
Pulmonary
Pulmonary arteriovenous fistula
Lung infection
Lung abscess
Bronchiectasis
Esophageal strictures
Cerebral infarcts and tumors
Penetrating and nonpenetrating head injury
Postoperative neurosurgical procedure (trauma and nontrauma related)
Dermal sinus tracts
Sepsis
Immunosuppression
Unknown mechanism

PATHOBIOLOGY

Brain abscesses are collections of purulent material (neutrophils and necrotic tissue) caused by infection with a variety of bacterial, fungal, and parasitic organisms. Infection arising from other sites typically seeds the brain hematogenously. When contiguous to the brain, infection enters the brain by direct extension or by traveling along veins with associated thrombophlebitis of pial veins and sinuses. Within the brain, the infection begins as a cerebritis with perivascular infiltrates and infiltration of neutrophils into the brain parenchyma. With time, the developing abscess is characterized by a purulent exudate that includes necrotic brain tissue as well as viable and necrotic neutrophils. Granulation tissue develops at the interface between necrotic and viable tissue, and eventually, the abscess is walled off by a fibrous capsule. Formation of the capsule depends on the virulence of the organism and the immune status of the individual. More virulent organisms are associated with larger lesions, more necrosis, earlier ependymitis, and more frequent areas of inflammatory escaping outside the collagen capsule. Immunocompromised patients, such as human immunodeficiency virus (HIV)-infected patients with *Toxoplasma* species abscesses, are unable to mount an immune response to form a capsule and hence respond well to antibiotic therapy alone.

CLINICAL MANIFESTATIONS

The clinical picture reflects a triad of the infectious nature of the lesion, focal brain involvement, and an increasing intracranial mass effect (Table 421-2). One or two elements may be absent in a given case, particularly early in the course. Among infectious symptoms, fever is present at onset or early in the course in only about 60% of cases. Neck stiffness is an infrequent complaint, and meningeal signs are elicited in about 30% of cases.

Focal neurologic deficits depend on the site of the lesion, which in turn will be determined by the causal or predisposing condition. In some patients, seizures precede the diagnosis. The early deficits in patients with temporal lobe lesions, which are typically caused by spread of an otogenic abscess, are contralateral homonymous superior quadrantic visual field defects and, if in the dominant hemisphere, aphasia. Motor deficits eventually occur in 40 to 50% of supratentorial abscesses. Cerebellar abscesses, which are often caused

TABLE 421-2 BRAIN ABSCESS: INITIAL FEATURES IN 123 CASES

Headache	55%
Disturbed consciousness	48%
Fever	58%
Nuchal rigidity	29%
Nausea, vomiting	32%
Seizures	19%
Visual disturbance	15%
Dysarthria	20%
Hemiparesis	48%
Sepsis	17%

by aural-mastoid infections, are characterized by ipsilateral limb ataxia; there may also be abnormal head positioning, forward and away from the side of the lesion, and nystagmus that is slow and coarse on gaze to the side of the abscess and rapid in the opposite direction. Patients with multiple brain abscesses may have multifocal signs or encephalopathy. Patients with *Toxoplasma* species (Chapter 357) brain abscesses often have movement disorders because these abscesses frequently localize to the basal ganglia. In fact, nearly all patients with HIV infection in whom hemiballism or hemichorea is present have *Toxoplasma* species brain abscesses.

Headache is an important initial symptom in 80 to 90% of patients with bacterial abscess but is less frequent (approximately 20%) in patients with fungal abscesses. Symptoms of increased intracranial pressure, such as nausea, depressed level of consciousness, and papilledema, occur less often. The development of headache in a patient with a known chronic anaerobic infection, such as aural-mastoid, paranasal sinus, or pulmonary suppuration, suggests the possibility of brain abscess. Similarly, the development of headache in a child with cyanotic congenital heart disease is often related to a brain abscess. Tetralogy of Fallot (Chapter 69) is the most common congenital heart anomaly associated with brain abscess.

DIAGNOSIS

Examination of the cranium, ears, paranasal sinuses, oral cavity, heart, and lungs may provide important clues to the etiology, as may overt signs of infection at other sites. Cultures of blood and sputum may identify the organism and its antimicrobial sensitivity. In patients with signs of raised intracranial pressure, lumbar puncture may be contraindicated.

Magnetic resonance imaging (MRI) can detect early changes, such as brain edema, and is preferable to computed tomography (CT). In the early cerebritis stage, T2-weighted MRI shows abnormally high signal intensity corresponding to low signal intensity on the T1-weighted images. The fluid-attenuated inversion recovery (FLAIR) sequence provides superior visualization of brain edema. On T1-weighted images, the area of cerebritis that is seen initially as a low-signal-intensity, ill-defined area later progresses to a central cavity with slightly higher signal intensity than cerebrospinal fluid (CSF), surrounded by edema that is slightly hypointense in comparison to brain parenchyma. Later stages of infection show central necrosis and formation of a rim of slightly high signal intensity on T1-weighted images (Fig. 421-1). Gadolinium administration shows a ring-enhancing lesion. Diffusion-weighted imaging helps differentiate abscesses from brain tumors; an abscess cavity demonstrates high signal with decreased apparent diffusion coefficient values, whereas necrotic tumor cavities demonstrate the opposite.

Surgical aspiration or excision of the lesion may be necessary to establish a microbial diagnosis. Gram stain and culture from abscess fluid, with proper handling, have high yield, with or without previous antibiotic therapy. If immediate surgery is planned, antibiotics can be deferred until culture material has been acquired. Multiplex polymerase chain reaction testing is being developed for rapid identification of bacterial organisms and detection of antibiotic resistance genes.

TREATMENT

Rx

Brain abscess requires urgent intervention. Because of the risk for cerebral herniation with large lesions, treatment of cerebral edema (intravenous dexamethasone, 16 to 24 mg/day in four divided doses) may be needed even while initiating surgical intervention. Corticosteroids often decrease edema within 8 hours but may retard the formation of a capsule around the brain abscess, may suppress the immune response to the infection, and may decrease penetration of antibiotics; hence, they should be used for short periods, usually only until surgical decompression by needle drainage or surgical removal is possible. A trial of nonsurgical treatment may be considered in patients with (1) small lesion size; (2) an already identified pathogen; (3) no symptoms or signs of increased intracranial pressure requiring neurosurgical intervention; (4) a deep or inaccessible lesion; (5) multiple abscesses; (6) a contraindication to surgery (e.g., a bleeding diathesis); (7) a short duration of symptoms, which suggests that the lesion is in the cerebritis stage; and (8) availability of monitoring with MRI. Patients with acquired immunodeficiency syndrome and suspected cerebral toxoplasmosis (Chapter 357) should receive antimicrobial therapy initially. In patients who are suspected of having a brain stem abscess, the possibility of listerial infection (Chapter 301) should be considered (Fig. 421-2), even in the absence of a clear immunodeficiency. Empirical parenteral antibiotics to cover *Listeria* species should be started (Chapter 301).

Successful antibiotic management of brain abscess is based on knowledge of proved or suspected pathogens as well as familiarity with a drug's spectrum of activity and penetration into the central nervous system. When surgery cannot be performed, empirical antibiotic therapy must be initiated even if the organism cannot be isolated from the abscess (Table 421-3).

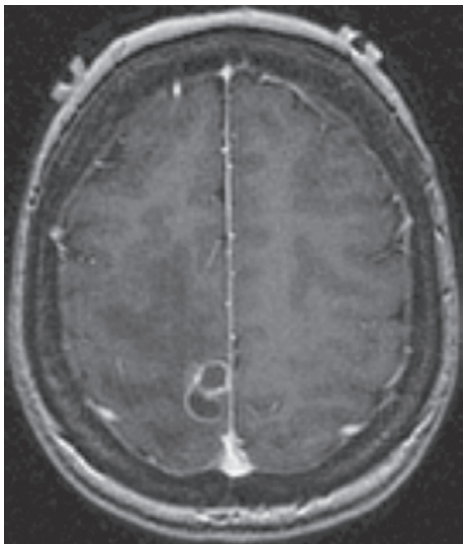


FIGURE 421-1. Brain abscess. Magnetic resonance imaging with gadolinium shows a multiloculated ring-enhancing lesion caused by *Nocardia* species infection.

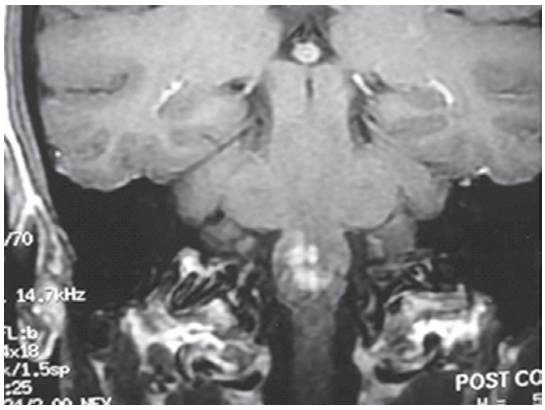


FIGURE 421-2. Brain stem abscess. Magnetic resonance imaging with gadolinium shows an enhancing lesion in the brain stem caused by *Listeria* species infection.

PROGNOSIS

Before the CT scan era, the mortality of brain abscesses ranged from 40 to 60%, and even with the drastic reduction in mortality in the era of modern neuroimaging, the mortality rate remains about 15%. In post-transplantation patients and those with deep hemispheric or brain stem abscesses, mortality

TABLE 421-3 COMMON PATHOGENS AND EMPIRICAL THERAPY FOR BRAIN ABSCESS

PREDISPOSING CONDITION	COMMON PATHOGENS	ANTIMICROBIAL AGENTS
Dental abscess	Streptococci, *Bacteroides fragilis*	Penicillin + metronidazole
Chronic otitis	*Bacteroides fragilis; Pseudomonas, Proteus, Klebsiella* species	Cefotaxime or ceftriaxone + metronidazole; ceftazidime or cefepime for *Pseudomonas* species
Sinusitis	Streptococci; *Haemophilus, Staphylococcus* species	Cefotaxime, ceftriaxone, or nafcillin + metronidazole
Penetrating trauma or postsurgical	*Staphylococcus, Pseudomonas, Enterobacter* species; streptococci	Nafcillin or vancomycin + ceftriaxone or cefotaxime + metronidazole
Bacterial endocarditis or drug use	Mixed flora, streptococci, *Staphylococcus* species	Nafcillin or vancomycin + ceftriaxone or cefotaxime + metronidazole
Congenital heart disease	Streptococci	Cefotaxime or ceftriaxone
Pulmonary infection	*Nocardia* species, *Bacteroides fragilis*, streptococci, mixed flora	Penicillin + metronidazole + trimethoprim-sulfamethoxazole
HIV infection	*Toxoplasma gondii*	Pyrimethamine + sulfadiazine + folinic acid

rates may exceed 80%. Other factors associated with a poor prognosis include extremes of age, multiple abscesses, and diagnostic delay in the absence of systemic signs of infection. Impaired level of consciousness is a poor prognostic sign even with early hospitalization and rapid diagnosis. Anaerobic and gram-negative organisms and culture-negative cases also have a poor prognosis. Seizure (Chapter 410) is a long-term risk that develops in up to 50% of patients, sometimes after latencies as long as 5 years.

SPINAL EPIDURAL ABSCESS

DEFINITION

Infection within the epidural space around the spinal cord is an uncommon but readily treatable potential cause of paralysis and death. The epidural space surrounds the dural sac and is limited by the posterior longitudinal ligament anteriorly, the ligamenta flava and the periosteum of the laminae posteriorly, and the pedicles of the spinal column and the intervertebral foramina containing their neural elements laterally. The space communicates with the paravertebral space through the intervertebral foramina. Superiorly, the space is closed at the foramen magnum. Caudally, the space is closed by the sacrococcygeal ligament. The epidural space contains loose areolar connective tissue, semiliquid fat, lymphatics, arteries, an extensive plexus of veins, and the spinal nerve roots.

EPIDEMIOLOGY

Spinal epidural abscesses can result from hematogenous spread of infection; risk factors include intravenous drug use, organ transplantation, chronic steroid use, malignancy, and diabetes. Local infection after acupuncture for back pain or epidural analgesia can also cause epidural abscesses. Cutaneous sites of infection are the most common remote sources, especially in intravenous drug users. Abdominal, respiratory tract, and urinary sources are also common. Osteomyelitis may be a cause of either direct extension or hematogenous spread, particularly when associated with sepsis. Contiguous spread may occur from epidurally placed catheters, psoas abscesses, decubitus ulceration, perinephric and retropharyngeal abscesses, or surgical sites. Minor back trauma has been implicated in causing a paraspinal hematoma, which may subsequently be seeded hematogenously. *Staphylococcus aureus* is the most common organism isolated from spinal epidural abscesses.

TABLE 421-4 INITIAL CHARACTERISTICS OF 915 SPINAL EPIDURAL ABSCESSES

STAGE 1	
Back pain	71%
Fever	66%
STAGE 2	
Radicular pain	20%
STAGE 3	
Muscle weakness	26%
Sphincter incontinence	24%
Sensory deficits	13%
STAGE 4	
Paralysis	31%
Quadriplegia	3%

From Reihsaus E, Waldbaur H, Seeling W. Spinal epidural abscess: a meta-analysis of 915 patients. *Neurosurg Rev*. 2000;23:175-204.

PATHOBIOLOGY

Because the dura mater around the cord is adherent to the vertebral column anteriorly, more epidural abscesses lie posteriorly, and because no anatomic barriers separate the spinal segments in the posterior epidural space, such abscesses usually extend over several vertebral segments. Spinal cord dysfunction probably reflects toxic processes secondary to inflammation, as well as venous thrombosis, thrombophlebitis, ischemia secondary to compression of the spinal arteries, and edema.

CLINICAL MANIFESTATIONS

The presence of a risk factor (>80% of patients) in the setting of neurologic deficits or back or radicular pain should suggest a spinal epidural abscess. The clinical manifestations can be divided into four stages (Table 421-4). Back pain (71%), fever (66%), tenderness of the spine with focal percussion (17%), spinal irritation (20%), and headache (3%) are common. Radicular pain can be mistaken for sciatica, a visceral abdominal process, chest wall pain, or cervical disc disease. Clinical signs are often substantially greater than would be predicted from the anatomic extent of pus or granulation tissue.

Unfortunately, the diagnosis often is missed initially. If the condition goes unrecognized at an early stage, the symptoms can evolve, over a period of hours to days, to paralysis below the spinal level of infection.

DIAGNOSIS

The differential diagnosis includes compressive and inflammatory processes involving the spinal cord: transverse myelitis (Chapter 419), herniation of an intervertebral disc (Chapter 407), epidural hemorrhage (Chapter 407), or metastatic tumor (Chapter 195), none of which are associated with evidence of systemic infection. Blood leukocytosis may not be present, but the sedimentation rate is often elevated. Other infectious processes that may produce back or neck pain or tenderness must be excluded: bacterial meningitis (Chapter 420), perinephric abscess, disc space infection (Chapter 407), and bacterial endocarditis (Chapter 76).

Lumbar puncture should be avoided in patients suspected of having a spinal epidural abscess for fear of spreading the infection to the subarachnoid space and causing meningitis. Gadolinium-enhanced MRI (Fig. 421-3) is the method of choice for diagnosis, but MRI findings in patients undergoing epidural analgesia can resemble those of epidural spinal abscess, even when no infection is present.

TREATMENT Rx

Patients with a progressing neurologic deficit should undergo urgent surgical drainage; CT-guided aspiration may be useful, and antibiotics plus percutaneously guided needle aspiration may be as therapeutically effective as antibiotics plus surgery. Unless culture results and sensitivities dictate otherwise, empirical therapy should cover *S. aureus* (nafcillin, 2 g every 6 hours; vancomycin, 1 g every 12 hours for methicillin-resistant strains). Additional gram-negative coverage with a third-generation cephalosporin (e.g.,

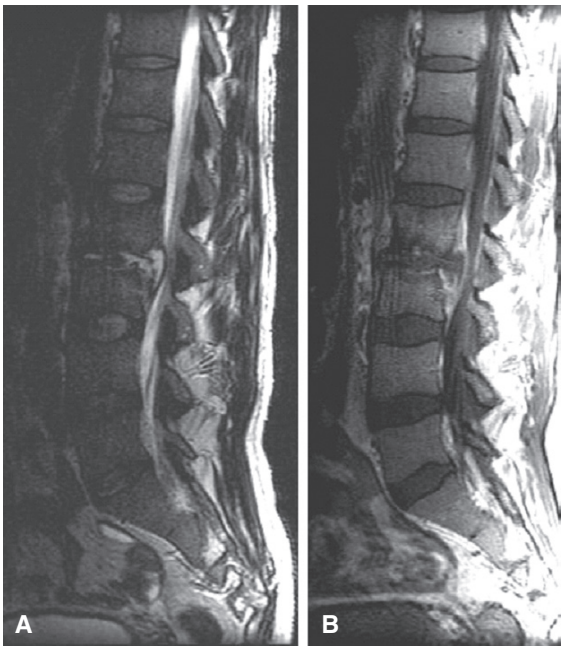


FIGURE 421-3. Epidural abscess. A and **B,** Magnetic resonance images of the lumbosacral spine show a lesion in the epidural space compressing the thecal sac. (Courtesy of Drs. Martin Pomper and Dima Hammoud, Johns Hopkins University.)

cefotaxime, 2 g every 6 hours, or ceftriaxone, 2 g every 12 hours) or a quinolone (e.g., ciprofloxacin, 400 mg every 12 hours) should be considered for severe disease. Rifampin (300 mg every 12 hours) may be added because of its ability to penetrate the abscess cavity. Intravenous therapy should be continued for 3 to 4 weeks, except in the presence of osteomyelitis (6 to 8 weeks).

PROGNOSIS

The mortality rate associated with spinal epidural abscess is about 15%. Approximately 50% of survivors have residual neurologic deficits. More severe preoperative neurologic deficits and deficits of longer duration are associated with a worse prognosis. In general, patients who develop paralysis that persists for longer than 36 hours do not recover function.

SUBDURAL EMPYEMA

Subdural empyema is an infection in the space between the dura and the arachnoid. It usually results from infected paranasal sinuses and rarely from infected mastoid sinuses by extension of thrombophlebitis from the sinuses into the subdural space. The infection is most commonly unilateral because bilateral spread is prevented by the falx. The empyema may evolve to cause cortical vein thrombosis, cerebral abscesses, or purulent meningitis.

CLINICAL FEATURES AND DIAGNOSIS

The most common symptoms are headache, fever, a neurologic deficit, and a stiff neck. However, subdural empyema may progress and cause signs of raised intracranial pressure, such as vomiting, altered level of consciousness, seizures, and papilledema. A high degree of suspicion is needed to establish the diagnosis early in the course of the illness. In patients with sinusitis (Chapter 434), the symptoms of subdural empyema may be incorrectly attributed to the sinusitis.

MRI with gadolinium enhancement and diffusion-weighted images is particularly useful in visualizing the subdural infection as a crescent-shaped mass with an enhancing rim over the cerebral convexities and below the inner table of the skull. CSF evaluation is useful only if there is accompanying meningitis. In a patient with signs of raised intracranial pressure, lumbar puncture should be avoided because of the risk for herniation.

TREATMENT Rx

Surgical drainage of the empyema is mandatory. Intravenous antibiotic therapy is also necessary and is based on the organisms isolated at the time of craniotomy.

PROGNOSIS

Mortality rates in most series are about 25%, with severe neurologic sequelae remaining in 20% of survivors. Accompanying venous sinus thrombosis or brain abscess carries a poor prognosis.

VENOUS SINUS THROMBOSIS SECONDARY TO INFECTION

The venous sinus system lacks valves, thereby permitting retrograde propagation of clots or infections that emanate from structures located in the central portion of the face or the middle ear.

Septic Cavernous Sinus Thrombosis

DEFINITION

The cavernous sinuses are the most caudal dural venous chambers at the base of the skull. The paired structures lie on either side of the pituitary fossa immediately above the midline sphenoid sinus. The cavernous sinus encloses the "cavernous portion" of the internal carotid artery as well as the third, fourth, and sixth cranial nerves en route to the apex of the orbit.

EPIDEMIOLOGY AND PATHOBIOLOGY

The infection usually spreads from the paranasal sinuses, dental abscesses, or other infections affecting the orbit or middle third of the face. *S. aureus* is the most common organism. Streptococci, pneumococci, and gram-negative bacilli are less common; anaerobic infection has also been reported. Many cases of idiopathic intracranial hypertension (Chapter 195) are due to thrombosis in the lateral sinuses.

CLINICAL MANIFESTATIONS

Cavernous sinus thrombosis may be manifested as an acute, fulminant disease or have an indolent, subacute manifestation. Fever and other systemic symptoms from sepsis may be present. Clinical symptoms and signs are related to anatomic structures within the cavernous sinuses or drained by them: unilateral periorbital edema, headache, photophobia, proptosis, ophthalmoplegia, pupillary dilation, decreased corneal reflex, and periorbital sensory loss. Obstruction of venous drainage from the retina can result in papilledema, retinal hemorrhages, and visual loss. The infection can spread rapidly (24 to 48 hours) through the intercavernous sinuses to the contralateral cavernous sinus. Thrombus can extend to other dural venous sinuses, adjacent vascular structures, or the brain parenchyma.

DIAGNOSIS

The diagnosis is made on clinical grounds and confirmed by radiographic studies. Radiologic evaluation includes sinus imaging, particularly the sphenoid and ethmoid sinuses. MRI using flow parameters and a magnetic resonance (MR) venogram is very sensitive and may reveal deformity of the cavernous portion of the internal carotid artery, a heterogeneous signal from the abnormal cavernous sinus, and an obvious hyperintense signal of thrombosed vascular sinuses. MRI with intravenous gadolinium can demonstrate venous thrombosis by illustrating a lack of the normal "flow void" within vascular structures. Cranial CT scans are less helpful but may show a subtle increase in the size and enhancement of the thrombosed sinus. MR angiography may demonstrate extrinsic narrowing of the intracavernous portion of the internal carotid artery.

TREATMENT AND PROGNOSIS Rx

Blood cultures are often negative, so delays in diagnosis are common. Even when the diagnosis is established, empirical antimicrobial treatment may not provide full coverage.

Treatment consists of prompt drainage of infected paranasal sinuses or other identifiable source of infection as well as specific antistaphylococcal agents (Chapter 296). Heparin anticoagulation without a loading dose is sometimes initiated to reduce morbidity from associated brain ischemia, but experience in septic venous thrombosis is limited compared with the more frequent use of anticoagulation in nonseptic venous thromboses. Hemorrhage caused by anticoagulation is rare in this setting. Despite modern therapy, mortality rates remains as high as 44%.

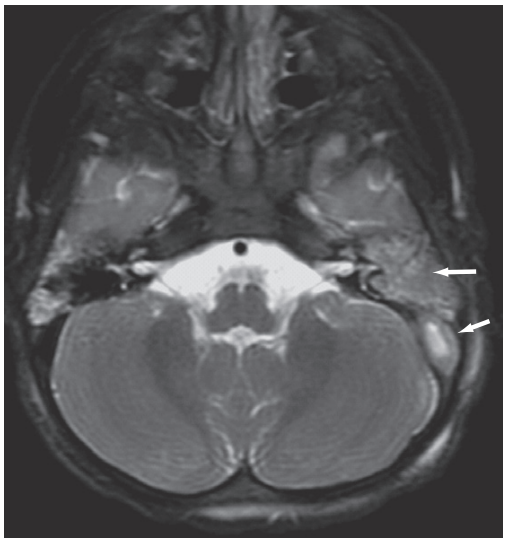


FIGURE 421-4. Lateral sinus thrombosis. Magnetic resonance imaging shows a thrombus in the lateral sinus *(short arrow)* with accompanying mastoiditis *(long arrow)*. (Courtesy of Drs. Martin Pomper and Dima Hammoud, Johns Hopkins University.)

Lateral Sinus Thrombosis

Septic thrombosis of the lateral sinus results from acute or chronic infections of the middle ear.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms consist of ear pain and fever followed by headache, nausea, vomiting, loss of hearing, and vertigo, usually evolving over a period of several weeks. Symptoms or signs suggestive of otitis media (Chapter 434), including mastoid swelling, may be seen. Sixth cranial nerve palsies can occur, but other focal neurologic signs are rare. In some patients with nonseptic lateral sinus thrombosis, headache may be the only symptom. Papilledema occurs in 50% of cases, and elevated CSF pressure is present in most, especially with occlusion of the right lateral sinus, which is the major venous conduit from the superior sagittal sinus (Fig. 421-4).

CSF is usually normal, although a parameningeal inflammatory profile (mild pleocytosis, slight elevation in protein level, and a normal glucose level) may be seen. The diagnosis is confirmed by MR venography.

TREATMENT Rx

Treatment includes intravenous antibiotics to cover staphylococci, anaerobes, and gram-negative bacilli such as *Proteus* species and *Escherichia coli* (nafcillin, 2 g every 6 hours, or vancomycin, 1 g every 12 hours; plus cefotaxime, 2 g every 6 hours, or ceftriaxone, 2 g every 12 hours; plus metronidazole, 7.5 mg/kg every 6 hours, or clindamycin, 300 mg every 6 hours; plus ciprofloxacin, 400 mg every 12 hours). Surgical drainage (mastoidectomy or tympanoplasty) may be required to eradicate the nidus of infection and to determine the antibiotic susceptibility of the organism. If the sinus contains pus, it must be opened so that the septic thrombus can be removed. Unless vision is compromised, increased intracranial pressure seldom requires specific treatment such as drainage or placement of a shunt.

PROGNOSIS

Broad intravenous antibiotic coverage and eradication of the perisinus infection, which may require surgical drainage, early in the course of the illness lead to a good prognosis. Neurologic sequelae may include a sixth nerve palsy, ataxia, and hearing loss.

Septic Sagittal Sinus Thrombosis

Although superior sagittal sinus thrombosis is the most common form of venous sinus thrombosis and is frequently associated with the use of oral contraceptives, septic sagittal sinus thrombosis is an uncommon condition that occurs as a consequence of purulent meningitis, infections of the ethmoid or maxillary sinuses spreading through venous channels, compound infected skull fractures, or rarely, neurosurgical wound infections.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms are primarily related to the elevated intracranial pressure and can evolve rapidly to stupor and coma. Seizures and hemiparesis may result from cortical infarction. Early recognition and treatment are necessary because septic sagittal sinus thrombosis carries a high mortality rate. The rate of progression, severity of symptoms, and prognosis are all related to the location of thrombosis. Obstruction of the anterior third of the sinus produces less intense symptoms and evolves more slowly.

CSF abnormalities are frequent, including enough red blood cells that the CSF can sometimes be mistaken for a subarachnoid hemorrhage; the opening pressure is increased in proportion to the extent of sagittal sinus involvement. A septic sagittal sinus is best visualized during the venous phase of cerebral angiography or MR venography. The diagnosis can also be made by MRI, which demonstrates an abnormal increase in signal intensity (absent flow void) within the affected venous sinus. Contrast-enhanced CT scanning may reveal a contrast void lying at the junction of the transverse and sagittal sinuses (the region of the torcular); this so-called delta sign is an intraluminal clot surrounded by contrast material.

TREATMENT Rx

Intravenous antibiotics should be directed at organisms recovered from the meningeal process or the meningeal site. *S. aureus* (Chapter 296), β-hemolytic streptococci (Chapter 298), pneumococci (Chapter 297), and gram-negative aerobes such as *Klebsiella* species (Chapter 314) are the most common organisms. Associated paranasal sinusitis should be drained surgically.

PROGNOSIS

If the thrombosis progresses to involve the middle and posterior thirds of the sinus, deterioration progresses rapidly. The prognosis is poor, with a mortality rate of nearly 30%.

NEUROLOGIC COMPLICATIONS OF INFECTIOUS ENDOCARDITIS

Neurologic complications develop in nearly one third of patients with infective endocarditis (Chapter 76), and neurologic manifestations are the initial symptom in 20% of patients with infective endocarditis. In nearly 30% of patients, the neurologic complications occur within 2 weeks after the initiation of treatment. Stroke is the most common manifestation; most strokes are due to cerebral emboli, and others are due to intracerebral hemorrhage. Infective endocarditis should always be considered in a patient with a fever and stroke.

PATHOBIOLOGY

Cerebral embolization occurs as a result of dislodgement or disruption of the cardiac vegetations that frequently cause occlusion of cerebral blood vessels. Emboli occurring before the initiation or completion of treatment with antibiotics may contain microorganisms capable of causing metastatic infections such as abscesses, arteritis, meningitis, or mycotic aneurysms. Most cerebral emboli involve small or moderate-sized blood vessels, and multiple cerebral emboli are common. Intracranial hemorrhage is usually due to rupture of a mycotic aneurysm (Chapter 415), septic erosion of the arterial wall without the formation of an aneurysm, or hemorrhagic transformation of a large cerebral infarct. About 20% of patients with mycotic aneurysms have multiple aneurysms; involvement of the middle cerebral artery and its branches occurs in more than 75% of patients, unlike congenital aneurysms, which occur predominantly in the circle of Willis. Mycotic aneurysms develop as a result of either septic embolization into the vasa vasorum or direct penetration of the microorganism into the wall of the artery. Streptococci and staphylococci account for nearly 90% of all mycotic aneurysms.

CLINICAL MANIFESTATIONS

The nature of the clinical manifestations depends on the underlying pathophysiology. Embolic stroke typically causes the acute onset of a focal neurologic deficit. Seizures may also occur. Multiple microemboli result in an altered or fluctuating level of consciousness not adequately explained by other abnormalities.

Most patients with mycotic aneurysms have a sudden, often fatal subarachnoid or intracerebral hemorrhage without warning signs. Warning signs, if present, include severe localized headache, ischemic events, seizures, and cranial nerve abnormalities. In some patients, mycotic aneurysms may be asymptomatic and resolve with antibiotic therapy. Clinical features of brain abscess and meningitis (Chapter 420) may also be observed in the setting of bacterial endocarditis.

DIAGNOSIS

MRI is the modality of choice for the diagnosis of cerebral infarcts and brain abscesses related to endocarditis, a CT scan is the best test for intracranial hemorrhage, and an MR angiogram is preferred for diagnosing an aneurysm. CSF evaluation is useful if accompanying meningitis or a slow leak from an aneurysm is suspected but not visualized with these imaging tests.

TREATMENT

Rx

Treatment of patients with infective endocarditis and cerebral emboli requires prevention of embolization with appropriate antibiotic therapy and sometimes cardiac surgery (Chapter 76). Anticoagulation is contraindicated in patients with cerebral infarcts and septic emboli because of the high risk for complications from intracerebral bleeding.

Patients with unruptured aneurysms smaller than 7 mm in diameter, proximal aneurysms, multiple aneurysms, ruptured aneurysms without an intracerebral hematoma, and aneurysms for which excision is likely to cause a neurologic deficit can be monitored conservatively with serial MRI and MR angiography. All other aneurysms require surgical excision of the aneurysm and the adjacent septic vessel wall. Patients who cannot undergo surgery may be candidates for endovascular embolization of the aneurysmal vessel.

PROGNOSIS

Mortality rates in patients with infective endocarditis and cerebral emboli range from 30 to 80%. Mortality is high if there is hemorrhagic transformation of the infarct. Mortality in patients with ruptured mycotic aneurysms is 80%, and even patients with unruptured aneurysms have a mortality rate of 30%.

SUGGESTED READINGS

Arlotti M, Grossi P, Pea F, et al. Consensus document on controversial issues for the treatment of infections of the central nervous system: bacterial brain abscesses. *Int J Infect Dis*. 2010;14:S79-S92. *A detailed review with consensus guidelines*.

Johnson MD, Johnson CD. Neurologic presentations of infective endocarditis. *Neurol Clin*. 2010;28:311-321. *Review*.

Tsou TP, Lee PI, Lu CY, et al. Microbiology and epidemiology of brain abscess and subdural empyema in a medical center: a 10 year experience. *J Microbiol Immunol Infect*. 2009;42:405-412. *Review of 151 brain abscesses and 10 subdural empyemas*.

TABLE 422-1 COMMON CAUSES OF ENCEPHALITIS IN THE UNITED STATES

I. Causes of viral encephalitis
- A. Nonseasonal
  - Herpes simplex virus type 1 (herpes simplex encephalitis)
  - Herpes simplex virus type 2 (neonatal encephalitis)
- B. Seasonal—summer and fall—arboviruses (arthropod borne)
  - West Nile virus
  - St. Louis encephalitis virus
  - Eastern equine encephalitis virus
  - Western equine encephalitis virus
  - LaCrosse/California encephalitis virus
- C. Seasonal—non–arthropod borne
  - Summer and fall: enteroviruses (including coxsackieviruses, ECHO viruses, polioviruses, and enterovirus 71)
  - Winter: influenza virus
- D. Immunosuppressed patients
  - Human immunodeficiency virus (chronic HIV encephalitis)
  - Varicella-zoster virus (subacute encephalitis)
  - JC virus (progressive multifocal leukoencephalopathy)
  - Cytomegalovirus (ventriculitis or encephalitis)
  - Human herpesvirus 6 (possible subacute encephalitis)
  - Epstein-Barr virus (subacute encephalitis)

II. Uncommon causes in the United States
- Lymphotrophic choriomeningitis virus
- Rabies
- Measles (subacute sclerosing panencephalitis)
- Mumps
- Adenovirus
- Herpes B virus (of monkeys)
- Rubella (progressive rubella panencephalitis)

III. Causes outside the United States
- Tick-borne encephalitis virus (Russia, Asia)
- Japanese encephalitis virus (Japan, Southeast Asia, Malaysia)
- Venezuelan equine encephalitis virus (Central and South America)
- Dengue virus (Southern Asia, Africa, South America)
- Rift Valley fever virus (east central Africa)
- Murray Valley encephalitis virus (Australia)
- Powassan fever encephalitis virus (Canada)
- Nipah virus (Malaysia and Bangladesh)

422

ACUTE VIRAL ENCEPHALITIS

ALLEN J. AKSAMIT, JR.

DEFINITION

Encephalitis is an inflammatory process that affects the parenchyma of the brain, usually in a diffuse manner. The term *encephalitis* indicates that the predominant clinical syndrome arises from infection and inflammatory reaction in the parenchyma of the brain rather than in the leptomeninges. When both the leptomeninges and brain parenchyma are involved, the term *meningoencephalitis* is used.

EPIDEMIOLOGY

Viral encephalitis has an estimated incidence of 7 per 100,000 per year. In general, a specific cause is identified in only 10 to 20% of patients in the United States. Many viruses (Table 422-1) are implicated, and testing by serologic or nucleic acid identification (by polymerase chain reaction [PCR]) is required to identify the specific virus. The epidemiology of each virus responsible for central nervous system infection is unique in terms of the types of patients who are at highest risk, geographic distribution, and seasonal occurrence, especially the arboviruses (Chapter 391) and enteroviruses (Chapter 387), which are covered in separate chapters.

In the United States, the most common cause of nonepidemic encephalitis is herpes simplex encephalitis, which is caused by herpes simplex virus type 1 (Chapter 382). The most common epidemic virus in the United States is now West Nile virus (Chapter 391), which is a Flavivirus related to St. Louis encephalitis virus and to its Asian counterpart Japanese encephalitis virus. There is serologic cross-reactivity between St. Louis encephalitis, Japanese encephalitis, and West Nile viruses.

PATHOBIOLOGY

In general, gross pathologic inspection of an encephalitic brain does not reveal purulence visible to the naked eye. If focal purulence is present, *cerebritis* is the more correct term. If frank necrosis and purulence are present, the correct pathologic term is *brain abscess* (Chapter 421). Encephalitis, however, can be associated with substantial necrosis, and patients with severe acute viral encephalitis frequently have microscopic evidence of necrosis. Certain viral encephalitides, such as herpes simplex encephalitis, can be frankly hemorrhagic. Viruses that cause acute encephalitis may often also cause meningitis (Chapter 420). Indeed, patients with encephalitis virtually always have some microscopic inflammatory changes in the leptomeninges. Conversely, patients with viral meningitis will inevitably have some component of microscopic encephalitis. The degree of inflammatory change present in the brain is determined by the individual viral pathogen and by host immune factors, which are responsible for the reaction to the invading virus.

CLINICAL MANIFESTATIONS

The clinical findings in patients with acute viral encephalitis start with a prodrome of fever, malaise, myalgia, and nonspecific symptoms. Nausea, vomiting, diarrhea, cough, sore throat, and rash can precede the neurologic symptoms. Invasion of the nervous system is typically accompanied by headache, photophobia, and altered consciousness, with symptoms progressing over a period of several days. Seizures are also a common heralding symptom. Meningeal signs are variably present and are an unreliable finding in encephalitis.

Focal brain dysfunction is seen with some viruses. For example, West Nile virus (Chapter 391) can cause a brain stem encephalitis with an early onset of coma. Herpes simplex virus (Chapter 382) tends to cause focal cortical neurologic deficits, including hemiparesis, aphasia, and seizures. Limbic system involvement in herpes simplex encephalitis or rabies can lead to prominent behavioral changes at the beginning of the illness before the patient's level of consciousness is depressed. Focal or generalized seizures, which suggest cortical involvement, are particularly common when herpes simplex encephalitis affects the hippocampus and limbic system. Rabies is typically associated with laryngospasm, hydrophobia, and depressed consciousness. Because of spinal cord involvement, West Nile virus, St. Louis encephalitis virus, poliovirus, and rabies virus infections can cause focal or asymmetrical weakness of the lower motor neuron type with areflexia.

DIAGNOSIS

In patients with coma or focal deficits, computed tomography (CT) of the head is typically performed before spinal fluid analysis to exclude a substantial mass effect and to avoid the risk for herniation during lumbar puncture. In patients without focal findings, however, lumbar puncture should be performed immediately to establish the diagnosis and allow early treatment. Opening pressures should be measured because increased intracranial pressure can occur with all forms of viral encephalitis.

Spinal fluid analysis, essential in suspected cases of viral encephalitis, typically reveals an elevated protein level, which usually is less than 120 mg/dL. The cerebrospinal fluid (CSF) glucose level is typically normal and greater than 40% of the coincident serum value, but some patients may rarely have a low CSF glucose level suggestive of a bacterial infection (Chapter 420). The white blood cell count is typically elevated, usually in the range of 10 to 500 cells/mm^3 and generally with a lymphocytic predominance. However, a polymorphonuclear predominance is seen in some cases of West Nile encephalitis and cytomegalovirus ventriculitis.

Serologic or PCR testing on spinal fluid is frequently helpful (Table 422-2). PCR testing has the added advantage of proving direct viral infection within the central nervous system, but serologic testing is more appropriate for West Nile virus encephalitis, which is best confirmed by an IgM antibody response in spinal fluid.

Magnetic resonance imaging (MRI) of the brain is the most sensitive technique for defining abnormalities in patients with viral encephalitis. However, frank viral encephalitis can occur with normal findings on MRI. The specific patterns can suggest the virus responsible; the best example is herpes simplex encephalitis, which has a characteristic pattern involving the mesiotemporal, inferofrontal, and insular cortices, usually unilateral or asymmetrically bilateral.

Differential Diagnosis

A number of nonviral pathogens can cause encephalitis that is clinically and pathologically indistinguishable from viral encephalitis. Examples include *Rickettsia* (Chapter 335), *Borrelia* (Chapter 329), Whipple's disease (Chapter 142), *Toxoplasma* (Chapter 357), and *Acanthamoeba* (Chapter 360). Additionally, autoimmune encephalitides that mimic viral encephalitis include limbic paraneoplastic encephalitis, Hashimoto's encephalopathy associated with autoimmune thyroiditis (Chapter 233), and encephalitis associated with anti–*N*-methyl-D-aspartate (NMDA) receptor antibodies. In parainfectious encephalitis, a systemic viral infection is associated with a febrile encephalopathy, sometimes with inflammatory spinal fluid but without direct evidence of brain invasion by the organism. Examples of parainfectious encephalitis include infection and encephalopathy associated with influenza virus (Chapter 372), varicella virus (Chapter 383), and Epstein-Barr virus (Chapter 385). Furthermore, manifestations of parainfectious effects by viruses may include severe brain white matter inflammation or demyelination referred to as acute disseminated encephalomyelitis.

TABLE 422-2 SELECTED TESTS FOR VIRAL ENCEPHALITIS

ORGANISM/ SYNDROME	TEST	COMMENT
WEST NILE VIRUS		
West Nile encephalitis	IgM in CSF	Diagnostic of CNS invasive disease or acute flaccid paralysis
HERPES SIMPLEX VIRUS TYPE 1		
Herpes simplex encephalitis	PCR in CSF	Sensitive and specific in the acute phase
	CSF–serum antibody ratio	Useful 2 weeks to 3 months after onset
HERPES SIMPLEX VIRUS TYPE 2		
Neonatal encephalitis	PCR in CSF	Confirmatory, high sensitivity
Relapsing meningitis	PCR in CSF	Sensitive and specific in first 3 days of illness
VARICELLA-ZOSTER VIRUS		
Meningoencephalitis	PCR in CSF	Confirmatory when used with clinical and spinal fluid findings; sensitivity unclear
EPSTEIN-BARR VIRUS		
EBV encephalitis	PCR in CSF	Suggests CNS invasion by virus
JC VIRUS		
Progressive multifocal leukoencephalopathy	PCR in CSF	Diagnostic but incompletely (70%) sensitive
CYTOMEGALOVIRUS		
CMV ventriculitis	PCR in CSF	Sensitive and specific

CNS = central nervous system; CSF = cerebrospinal fluid; PCR = polymerase chain reaction.

SELECTED SPECIFIC VIRUSES

Herpes Simplex Encephalitis

EPIDEMIOLOGY

Herpes simplex (Chapter 382) encephalitis, which is second only to West Nile encephalitis as the most common form of nonepidemic encephalitis in the United States, has an annual incidence of two to four cases per million people per year. There is no seasonal or gender predisposition. The encephalitis can strike older children as well as adults, although it is most commonly a disease of adults.

PATHOBIOLOGY

Herpes simplex encephalitis can occur in immunosuppressed or immunocompetent patients. Patients who are deficient in toll-like receptor 3 in the immune system may be selectively vulnerable to herpes simplex encephalitis.

Herpes simplex virus type 1 infects and establishes latency in the majority of the population. Whether herpes simplex encephalitis arises from reactivation of a latent viral infection in the trigeminal ganglion or is a primary nasopharyngeal infection that ascends into the olfactory nervous system is uncertain.

The pathology of herpes simplex encephalitis is a necrotizing, hemorrhagic, inflammatory encephalitis in the mesiotemporal, inferofrontal, and insular cortices, with gray matter being affected more than white matter. When the brain is affected bilaterally, the pathologic features are usually asymmetrical, a pattern that helps distinguish herpes simplex from other forms of limbic encephalitis.

CLINICAL MANIFESTATIONS

The clinical manifestations of herpes simplex encephalitis usually begin with a nonspecific febrile prodrome, which is followed within hours to days by the symptoms of headache, malaise, nausea, and vomiting. A reduced level of consciousness may occur early. Seizures may be the first manifestation of this encephalitis. Focal deficits, especially hemiparesis or aphasia, are common. More specific manifestations of herpes simplex encephalitis are symptoms of limbic system–associated behavioral changes, such as behavioral or emotional lability and inappropriateness. Memory is affected early if consciousness is preserved. As the encephalitis progresses, symptoms of increased

intracranial pressure, lethargy, and coma are usual. Focal findings alone in the context of encephalitis are not sufficient to confirm a diagnosis of herpes simplex encephalitis.

DIAGNOSIS

Spinal fluid analysis is a mainstay in the diagnosis of herpes simplex encephalitis. In a patient with focal encephalitis or coma, however, CT of the brain should be performed before spinal fluid analysis to avoid the risk for herniation. Elevation of the protein level and the white blood cell count, with a predominance of lymphocytes, is the most frequent pattern; red blood cells are also commonly seen. The CSF glucose level is usually normal, but it can be less than 50% of the blood glucose level in about 5% of patients.

The best and most accurate test for proof of herpes simplex encephalitis is the presence of herpes simplex virus type 1 DNA amplified by PCR in the spinal fluid. Herpes simplex virus type 1 can be distinguished from herpes simplex virus type 2 by specific primer amplification, applied as part of the PCR analysis. Because herpes simplex type 2 can cause encephalitis in neonates and meningitis in adults, this distinction may affect therapy.

MRI, which is the imaging technique of choice for this form of suspected encephalitis, typically shows characteristic focal involvement with increased T2 and fluid-attenuated inversion recovery (FLAIR) signal in the mesiotemporal lobes (including the amygdala, hippocampus, and uncus), the inferofrontal lobes (cingulate gyrus and orbital frontal cortex), and the insular cortex. The abnormalities seen on MRI are often unilateral but can be bilateral and asymmetrical. Focal MRI abnormalities must be distinguished from brain abscess (Chapter 421), cerebral infarction (Chapter 414), cerebral hemorrhage (Chapter 415), brain tumors (Chapter 195), and paraneoplastic limbic encephalitis(Chapter 197); radiographically detected involvement of the mesiotemporal rather than the lateral temporal areas and involvement of the gray matter rather than the white matter suggest herpes simplex encephalitis as the diagnosis. Early gadolinium contrast enhancement may occur but is not universal.

CT of the head is less sensitive than MRI for detecting mild cases of herpes encephalitis. However, because herpes simplex encephalitis can be hemorrhagic, CT may sometimes identify the hemorrhage more accurately than MRI can.

Electroencephalography is an adjunctive test that can show periodic lateralized epileptiform discharges ipsilateral to the involved temporal lobe. However, the findings are not specific for herpes simplex encephalitis and commonly occur in patients with cerebral infarction (Chapter 414) and occasionally other forms of viral encephalitis.

TREATMENT Rx

Multicenter prospective trials emphasize that early treatment affects outcome. When suspicion for herpes simplex encephalitis is raised in the acute setting by the presence of focal signs or symptoms, early empirical treatment is recommended even while the diagnostic evaluation is proceeding.

Intravenous acyclovir (30 mg/kg daily given three times per day in divided doses for 14 to 21 days) is the therapy of choice.■ Some experts have suggested treatment using the same doses for 21 days, but no prospective data show that a longer duration of therapy or higher doses of acyclovir affect neurologic outcomes.

Rabies

Human rabies, which is an encephalitic illness caused by the rabies virus, is usually transmitted by an animal bite. It produces a fatal encephalitis, although the latency between animal bite exposure and occurrence of neurologic symptoms may make the diagnosis unsuspected.

EPIDEMIOLOGY AND PATHOBIOLOGY

Rabies is a rare illness in the United States and developed world. However, initially unsuspected cases have been transmitted via trivial bites by infected bats, which are widely distributed in every state in the United States except Hawaii. Rabies virus variants in bats are now responsible for the majority of recent human cases in the United States and Canada. Raccoon rabies has extended from Florida into Georgia, Alabama, and South Carolina.

Canine rabies is still endemic in much of the developing world, including Africa, Latin America, Eastern Europe, and Asia, and the vast majority of human rabies cases occur as a result of untreated dog bites from endemic areas. Dog rabies came under control in the United States during the 1950s and was associated with a marked reduction in the number of human cases transmitted by dogs. Much of the dog-related clinical rabies seen in the United States is the result of dog bites that occurred in developing countries, before the patient migrated to the United States. Rare cases of transmission of rabies to transplant organ recipients have occurred recently in the United States.

The presence of Negri bodies (intracytoplasmic viral inclusions) in neurons of the brain stem, cerebellum (especially the Purkinje cells), or hippocampus defines rabies pathologically. These inclusions are often not present, but detection of antigen by immunohistochemical means can aid in the pathologic diagnosis. Because the disorder tends to be a brain stem encephalitis, the cardiovascular, bulbar, and respiratory centers are affected.

CLINICAL MANIFESTATIONS

Clinically, human rabies usually develops 20 to 90 days after a bite, although rarely disease develops after only a few days or after a year or more following bite exposure. Multiple bites and facial bites are associated with shorter incubation times.

Nonspecific prodromal symptoms include fever, chills, malaise, fatigue, insomnia, anorexia, headache, and irritability. In the majority of patients, pain or paresthesias will develop in the limb that was affected by the bite. Following the prodromal illness, an encephalitic form develops in about 80% of patients and causes varied behavior from episodes of agitated arousal to quiet lethargy. Fever is a common accompaniment but not universal at this phase. Disinhibition of brain stem reflexes leads to hydrophobia with laryngospasm and an inability to deal with salivation, swallowing of water, or other oral intake. When the brain stem encephalitis affects the bulbar, cardiovascular, and respiratory centers, autonomic dysfunction, cardiopulmonary complications, and respiratory failure may occur.

Another form of rabies that affects up to a third of patients is known as paralytic rabies. This form of rabies is manifested as acute flaccid paralysis, which may be multifocal and affect the limbs, as well as the bulbar musculature. The weakness can mimic poliomyelitis (Chapter 423) because of its multifocality, and it can be confused with Guillain-Barré syndrome (Chapter 428). Paralytic rabies typically occurs in conjunction with encephalitis.

DIAGNOSIS

Findings on spinal fluid analysis may be abnormal in human rabies. A pleocytosis, usually less than 100 white cells/μL, is found in more than 50% of patients in the first week of illness; the leukocytes are predominantly mononuclear. The protein concentration is commonly mildly elevated, and the glucose level is usually normal.

Imaging of patients with rabies is sometimes useful. MRI may show gray matter involvement and involvement of the brain stem in particular, with increased T2 signal, commonly without enhancement. Spinal cord MRI in patients with paralytic rabies may show increased T2 signal mimicking acute disseminated encephalomyelitis. Involvement of brain gray matter, including the hippocampus and basal ganglia structures, indicates the gray matter predilection and often bilateral involvement of supratentorial structures. However, imaging cannot be relied on to exclude rabies.

Serum antibodies against rabies virus are not usually present in unimmunized patients until the second week of illness, and patients can die before having a detectable serum antibody level. Serum antibodies may also be present in spinal fluid, but their absence is unreliable in excluding the diagnosis. Classically, staining a skin biopsy sample taken from an area near the nape of the neck for rabies antigen in the sensory nerves can confirm the diagnosis of rabies. Alternatively, small amounts of rabies RNA can be detected by PCR testing. Typical specimens to detect virus include saliva, brain tissue, or spinal fluid. A positive result confirms the diagnosis, but the exclusionary value of negative results is unknown.

TREATMENT Rx

After an animal bite, local treatment with antirabies immunoglobulin and systemic treatment with vaccination are typically offered. Rabies postexposure prophylaxis includes local wound cleansing, passive immunization with immunoglobulin, and active immunization with rabies vaccine. Inactivated cell culture rabies vaccines are used for active immunization, and the risk for vaccination-induced acute disseminated encephalomyelitis has been markedly reduced by the use of these vaccines. However, once rabies encephalitis is manifested, it is unclear whether vaccination, though regularly used, has any

role in improving outcome. Antiviral therapy and a variety of immunotherapies, including ribavirin and interferon alfa, have been tried in the treatment of rabies, usually without success. Although one patient was reputed to survive with the use of therapeutic coma without vaccination, subsequent reports of patients treated in similar fashion have been associated with a fatal outcome.

Rare Causes of Encephalitis

Lymphocytic choriomeningitis (Chapter 420) virus is a human infection acquired from mice. Typically, humans acquire the infection by contact with food or dust that is contaminated by excreta of the common house mouse. Most commonly, human disease occurs in winter, when the natural host tends to move indoors. It can also be acquired as a consequence of laboratory exposure by human caretakers.

Mumps virus (Chapter 377) is typically acquired by the respiratory route. Infection can occur throughout the year, but the incidence is higher during the spring. Although mumps virus infects both sexes equally, meningoencephalitis develops in males three times more frequently than in females. Vaccination programs in the United States have made mumps encephalitis rare.

TREATMENT

Rx

Effective antiviral therapy does not exist for viral encephalitis, except for herpes simplex encephalitis. However, because of the usual delay in establishing or excluding the diagnosis of herpes simplex encephalitis, patients suspected of having encephalitis should start acyclovir therapy (10 mg/kg intravenously every 8 hours for 2 weeks) even while specific serologic and spinal fluid analyses are being performed to make a specific diagnosis.

Supportive measures for patients with encephalitis typically include intensive care unit monitoring and treatment in the initial phases of the illness. Seizures are common and frequently refractory to antiepileptic drugs; however, the seizures themselves can increase morbidity and mortality, so vigorous treatment attempts are required (Chapter 410).

In patients who are immunosuppressed (see Table 422-1), the spectrum of possible infections is broader and potentially more treatable. Examples include varicella-zoster virus (Chapter 383), with acyclovir administered at doses similar to those used for herpes simplex virus, and cytomegalovirus (Chapter 384), with ganciclovir administered at 5 mg/kg intravenously every 12 hours for 2 weeks or cidofovir administered at 5 mg/kg intravenously weekly for 2 weeks, although some patients require long-term oral valganciclovir (900 mg every 24 hours) or intravenous cidofovir (5 mg/kg every 2 weeks). By comparison, no specific treatments are currently effective for Epstein-Barr virus (Chapter 385) and JC virus (progressive multifocal leukoencephalopathy, Chapter 378).

PROGNOSIS

The prognosis of encephalitis is dependent on the cause. Herpes simplex encephalitis, even with adequate treatment, has a 20% mortality, and the likelihood of major persistent morbidity with seizures or defects in memory and behavior is 35 to 40%. Each of the arboviruses has a different mortality rate, with eastern equine encephalitis virus associated with the highest mortality. LaCrosse encephalitis virus has the lowest mortality and is the most benign. Some forms of encephalitis have specific sequelae, such as sensorineural deafness or hydrocephalus associated with mumps encephalitis.

Grade A

1. Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med*. 1986;314:144-149.

SUGGESTED READINGS

Centers for Disease Control and Prevention (CDC). Surveillance for human West Nile virus disease—United States, 1999-2008. *MMWR Surveill Summ*. 2010;59(SS-2):1-17. *Review*.

Long SS. Encephalitis diagnosis and management in the real world. *Adv Exp Med Biol*. 2011;697:153-173. *Review of viral, other infectious, and noninfectious causes.*

423

POLIOMYELITIS

ALLEN J. AKSAMIT, JR.

DEFINITION

Poliomyelitis is an acute viral illness that is associated with encephalitic features and acute flaccid paralysis. Enterovirus 71 (Chapter 387) and West Nile virus (Chapter 391) can cause an identical clinical illness.

EPIDEMIOLOGY

The cause of poliomyelitis is the poliovirus, which is serotyped into three subtypes (types 1, 2, and 3) and belongs to the group of enteroviruses in the family Picornaviridae. Most clinical disease is caused by the type 1 strain. Vaccination eliminated polio epidemics in the United States and Europe in the 1960s. The last major polio epidemic in the United States occurred in 1960, with a steady decline in cases subsequently. The last case of wild-virus poliomyelitis in the United States was reported in 1979. However, polio continues to remain a significant illness in unvaccinated areas of the world, particularly in Nigeria, Pakistan, and Afghanistan. In temperate climates, poliovirus infections occur most often in the summer and fall months, but infection occurs throughout the year in tropical areas.

Because of its oral-fecal, host-to-host transmission, poliovirus infection is influenced by standards of hygiene. The greatest risk for transmission occurs in family members and other direct contacts, especially under crowded conditions. The incubation period is about 3 to 6 days, after which virus may be shed into the nasopharynx for 2 to 6 weeks and into feces for several months.

Although poliovirus infects many exposed individuals, the acute flaccid paralysis of poliomyelitis occurs in only 1 to 2% of infected persons. The precise factors that cause dissemination of virus to the nervous system and susceptibility to paralytic disease are unknown. Paralytic disease occurs more commonly in children and young adults.

Historically, in the United States, poliomyelitis occasionally resulted from the live attenuated poliovirus vaccine. The risk for *vaccine-associated poliomyelitis* was about 1 case in 2.4 million doses, with most of the risk occurring with the first dose. About 75% of cases were related to immunocompetent vaccine recipients; about half of these cases occurred in the vaccinated person, most of the remainder occurred in healthy close contacts of vaccine recipients, but about 5% occurred in healthy community contacts who had not been vaccinated recently and had not been in direct contact with vaccine recipients. The remaining 25% or so cases occurred in immunocompromised persons, in whom clinical disease is about 5000-fold more likely to develop than in immunocompetent persons, or in the direct contacts of immunocompromised persons. The live attenuated virus in the vaccine can also mutate to cause *vaccine-derived poliomyelitis*, which can infect unvaccinated persons and lead to clinical polio with an attack rate and severity similar to that of wild-type virus. The inactivated polio vaccine, which is the only vaccine currently in use in the United States since the year 2000, does not cause vaccine-induced polio.

PATHOBIOLOGY

Polioviruses are small (approximately 27 nm), roughly spherical particles with a single-stranded RNA core surrounded by a protein capsid. Poliovirus is an enterovirus that is ingested orally and replicates initially in the lymphatic system of the gastrointestinal tract, especially in Peyer's patches in the small intestine. Spread to the local gastrointestinal lymphatics is followed by systemic viremia, which seeds the nervous system, although the precise mechanism of entry into the nervous system is not well established. The virus can replicate in skeletal muscle, where it may cause the myalgias that often precede weakness. One hypothesis is that the virus is then spread via peripheral motor axons to the spinal cord by retrograde transport, where it selectively replicates in the anterior horn cells. Pathology indicates a disseminated asymmetrical pattern of infection of the anterior horn cells of the spinal cord. Death of anterior horn cells leads to permanent paralysis, but compensation by collateral sprouting from uninfected cells in the same segment of the cord can allow some improvement in functional status and motor recovery.

CLINICAL MANIFESTATIONS

Acute poliomyelitis has two phases. An initial phase coincides with viremia and is associated with fever and headache and sometimes with sore throat; it resolves in 1 to 4 days. The second phase of illness, which usually occurs 7 to 21 days (range, 4 to 30 days) after the initial infection, is associated with abrupt fever, headache, vomiting, and meningismus, presumably as a result of viral infection in the central nervous system. The meningitic symptoms of headache and stiff neck subsequently resolve but are rapidly followed by asymmetrical, multifocal muscle weakness of the lower motor neuron type, sometimes with severe myalgias.

Clinical examination shows weakness affecting muscles in an asymmetrical and multifocal fashion, with a corresponding reduction in muscle stretch reflexes. Sensation is normal, thereby attesting to the selective involvement of the anterior horns of the spinal cord. Neurogenic muscular atrophy rapidly follows in affected muscles. The extent of motor involvement is typically completed within 1 week.

The upper and lower limb, truncal, and respiratory muscles are affected. Muscles innervated by the bulbar (medullary) cranial nerves (9^{th}, 10^{th}, 11^{th}, or 12^{th}) are often involved. The facial nerve can be involved, but the eye muscles are usually spared. Rarely, direct involvement of the brain stem reticular formation can cause an encephalitic illness with coma or cause death by its effects on breathing and cardiovascular control.

DIAGNOSIS

In addition to the typical symptoms and signs, the diagnosis of poliomyelitis is aided by analysis of spinal fluid. Spinal fluid typically shows a pleocytosis with lymphocytic predominance. The spinal fluid protein level is elevated, but the glucose level is normal. Enteroviruses may be cultured from the spinal fluid, but specific viral studies identifying poliovirus and other enteroviruses are best accomplished by polymerase chain reaction (PCR) testing. More specific characterization of the individual virus type can be accomplished by direct sequencing of the genome.

Differential Diagnosis

Other viral causes of encephalomyelitis can mimic poliomyelitis. Enterovirus 71 (Chapter 387) can cause epidemics of fever and acute flaccid paralysis. Coxsackievirus 7 and enterovirus 70 can cause milder paralytic syndromes, usually without fever. West Nile virus (Chapter 391) infection of the central nervous system is also associated with fever and acute flaccid paralysis. Tick-borne encephalitis virus (Chapter 391), native to Russia, may behave similarly. A paralytic form of rabies encephalitis (Chapter 422) can lead to asymmetrical acute flaccid paralysis. Serologic and virologic testing can distinguish these other agents. Testing for West Nile virus detects IgM antibodies against the virus in spinal fluid. Rabies may be tested for by either serology or PCR testing for the rabies virus (Chapter 422).

Ascending or descending paralysis can also be seen in a variety of noninfectious or postinfectious illnesses, such as Guillain-Barré syndrome (Chapter 428) and acute inflammatory myelopathy (Chapter 407). Diphtheria (Chapter 300) can be associated with focal paralytic syndromes.

PREVENTION

Poliomyelitis can be prevented by lifelong immunity induced by either the live attenuated (oral) or killed (inactivated) polio vaccines, which are routinely given to children. Oral polio vaccine is relatively inexpensive, about $0.08 per dose. Short-term shedding of vaccine virus in the stools of recently immunized children leads to passive immunization of close contacts, thereby providing the ability of mass campaigns to interrupt the transmission of wild poliovirus. However, about 1 in every 2.5 million doses of the vaccine can cause *vaccine-associated* poliomyelitis with paralysis in the vaccinated child, in a close contact, or even in another person. Rarely, a strain of poliovirus in the oral polio vaccine may change genetically and circulate to cause *vaccine-derived* poliomyelitis. In endemic countries, this low risk for vaccine-associated polio and vaccine-derived polio is preferable to the much higher risk for polio from wild-type virus without vaccination.

In countries where the risk of disease from wild-type poliovirus is zero, however, programs have shifted to using inactivated polio vaccine. Inactivated polio vaccine, which is about five times as expensive as oral vaccine, produces protective antibodies that prevent the poliovirus from spreading from the intestinal tract to the central nervous system. Unlike oral polio vaccine, it does not prevent the spread of wild poliovirus and cannot contain an epidemic because virus can still multiply inside the intestines and be shed in stool.

In the United States, debate about the efficacy and risks of live attenuated versus killed vaccine ended in 2000 with a policy that exclusively uses the inactivated polio vaccine, which does not lead to vaccine-associated or vaccine-derived polio. Global eradication strategies using live attenuated vaccine now focus especially on Nigeria, India, Afghanistan, and Pakistan, where polio remains endemic.

TREATMENT AND PROGNOSIS

Rx

No specific treatment is available for patients affected by poliomyelitis caused by poliovirus. However, supportive therapy, including intensive care treatment to maintain respiratory function and provide cardiovascular support, can stabilize the patient and allow rehabilitation.

Death in patients with poliomyelitis is usually the result of bulbar muscle, respiratory, and cardiovascular impairment. With intensive treatment of respiratory insufficiency, patients can survive the acute paralytic illness. In general, motor improvement begins within a month after the onset of illness. On follow-up, many patients are left with profound neurologic deficits; others may return fully to activities of daily living, but some neurologic residua can usually be found on clinical or electrophysiologic examination.

Postpolio Syndromes

In patients who have had paralytic poliomyelitis, progressive atrophy and weakness can develop after more than 10 to 15 years of stable neurologic function. This syndrome, which is known as postpolio progressive muscular atrophy, is postulated to result from the normal age-related loss of motor neurons from a motor neuron pool already depleted by the viral illness. A second symptom complex in survivors of paralytic polio is characterized by progressive muscle pain, weakness, and fatigue; this "postpolio syndrome," which may affect up to 60% of patients infected during a polio epidemic, is not related to persistent viral infection and is of unknown cause.

SUGGESTED READINGS

Jenkins HE, Aylward RB, Gasasira A, et al. Implications of a circulating vaccine-derived poliovirus in Nigeria. *N Engl J Med*. 2010;362:2360-2369. *The attack rate and severity of disease with vaccine-derived poliovirus in Nigeria was similar to that of wild-type virus.*

Koopman FS, Uegaki K, Gilhus NE, et al. Treatment for postpolio syndrome. *Cochrane Database Syst Rev*. 2011;2:CD007818. *Review of pharmacological and rehabilitative treatments.*

Zangwill KM, Yeh SH, Wong EJ, et al. Paralytic syndromes in children: epidemiology and relationship to vaccination. *Pediatr Neurol*. 2010;42:206-212. *The incidence was 1.4 per 100,000 children per year in California, but no cases were related to polio vaccination.*

424

PRION DISEASES

PATRICK J. BOSQUE

DEFINITION

Prion diseases, which are a group of closely related neurodegenerative conditions of humans and other mammals, are caused by an accumulation of aggregated forms of the prion protein (PrP) in the central nervous system (CNS). These conditions can be transmitted by an infectious agent, the prion, that is composed of misfolded and aggregated PrP. The prion contains no specific nucleic acid. The name Creutzfeldt-Jakob disease (CJD) is applied to most human forms of prion disease, although other names are used for some forms.

EPIDEMIOLOGY

Prion diseases occur worldwide, with an incidence of about one case per million annually in most populations. These conditions can be acquired sporadically, genetically, or infectiously. Sporadic disease accounts for about 90% of cases, and genetic forms account for almost all the remainder. Cases acquired by infection are exceedingly rare in humans and account for less

than 1% of cases in most populations. Both dietary and iatrogenic exposure has transmitted prion disease to humans.

Kuru, the first human prion disease recognized to be transmissible, was caused by ceremonial cannibalism in tribes of the Fore language group in the highlands of New Guinea. The last episodes of exposure are thought to have occurred in the late 1950s, but the few cases that have occurred in the past decade indicate an incubation period that approaches 50 years.

Variant CJD is caused by exposure, presumably by the alimentary route, to prions from cattle with bovine spongiform encephalopathy. It first arose in Great Britain in 1994, about 10 years after the first cases of bovine spongiform encephalopathy there. Despite the exposure of millions of people to meat contaminated with bovine spongiform encephalopathy prions, fewer than 200 people worldwide have contracted variant CJD. The incidence of variant CJD has decreased in recent years as the bovine spongiform encephalopathy outbreak in cattle has been contained and the entry of contaminated meat into the food supply restricted.

Most cases of iatrogenic transmission of CJD have involved contaminated cadaveric dura mater allografts, and these have almost all been from a single product, Lyodura, manufactured before May 1987. The other large group of iatrogenic cases occurred in recipients of growth hormone derived from cadaveric pituitaries, before the availability of recombinant growth hormone. Blood and blood products derived from donors with variant CJD have transmitted the illness, but surprisingly, CJD appears not to be transmissible from the blood of persons with the sporadic form of the disease. Contaminated surgical instruments are persuasively documented to have transmitted CJD on only four occasions.

PATHOBIOLOGY

PrP is a cell surface glycoprotein normally produced in the brain and several other tissues in mammals. Its normal function is unknown, but it may play a role in copper metabolism. In prion diseases, an abnormal misfolded and aggregated isoform of PrP, termed PrP^{Sc}, accumulates. Remarkably, PrP^{Sc} is able to recruit the normal form of PrP into the pathologic aggregate. The precise structure of PrP^{Sc} aggregates and the mechanism of prion propagation are incompletely understood, but a basic conceptual model proposes that the normally α-helical regions of PrP directly interact with the β-sheets of PrP^{Sc}, lose their normal structure, and then join the aggregate. At some point, the growing aggregate fractures, thereby creating additional aggregate particles. In this way, aggregates of PrP^{Sc} can propagate as infectious agents.

What precisely initiates sporadic or genetic prion diseases is not known. In infectious forms of prion disease that are transmitted by the alimentary route, prions first replicate in the enteric lymphatic system, including Peyer's patches. From the lymphatic system, prions spread to the CNS via sympathetic nerves in lymphatic tissue. Once in the CNS, prions appear to spread trans-synaptically. As with other neurodegenerative diseases associated with accumulations of aggregated proteins (e.g., β-amyloid in Alzheimer's disease), the mechanism by which the formation PrP^{Sc} causes neuronal dysfunction and death is unknown.

Pathology

Traditionally, prion diseases are recognized by a combination of vacuolization or "spongiosus" of the gray matter, astrocytic gliosis, and loss of neurons. In modern practice, the presence of PrP^{Sc}, demonstrated by immunohistochemical or biochemical techniques, is the pathologic hallmark of these conditions. In some forms of prion disease, PrP^{Sc} will form amyloid plaques, which are dense aggregates of protein linked by intermolecular β-sheets that bind Congo red. However, most commonly the PrP^{Sc} aggregates are smaller and more diffuse.

Genetics

All inherited forms of prion disease are caused by mutations in the PrP coding sequence of the gene *PRNP*. Mutations associated with familial forms of prion disease include more than 20 missense mutations, 2 premature stop mutations, and a series of insertions that code for an additional series of eight amino acids in a region where five of these octapeptide repeats normally occur. Genetic forms of prion disease are transmitted in an autosomal dominant pattern, usually with high but incomplete penetrance. Certain genotypes affect susceptibility to prion disease. Codon 129 of *PRNP* is polymorphic in most populations, with alleles coding for either valine or methionine. Persons who are homozygous (129VV or 129MM) at this allele are overrepresented among victims of sporadic CJD, and all victims of variant CJD (see later) carry 129M on both *PRNP* alleles.

Three distinctive forms of prion disease are associated with certain *PRNP* mutations: Gerstmann-Straüssler-Scheinker syndrome, fatal familial insomnia, and slowly progressive forms of CJD. Gerstmann-Straüssler-Scheinker syndrome is caused by any of several mutations in *PRNP*, the most common of which codes for a substitution of leucine for proline at codon 102 (P102L). Pathologically, there are accumulations of plaques of PrP amyloid in the brain, especially in the cerebellum.

Fatal familial insomnia is caused by a D178N mutation on the same allele as a methionine at the polymorphic codon 129 of *PRNP*. Pathologically, there is neuronal loss and accumulation of PrP^{Sc} in the thalamus. In contrast, the D178N mutation on an allele with valine at codon 129 causes a disease that is indistinguishable from sporadic CJD.

Some *PRNP* mutations cause a slowly progressive dementia. The most common of these mutations are large expansions of the octapeptide repeat region.

CLINICAL MANIFESTATIONS

Sporadic

The most common form of human prion disease is sporadic CJD. Onset is typically in later midlife at an average of about 60 years of age, although onset as young as 17 years and as old as 80 years has been reported. In about 25% of cases, patients or their families report a prodrome of a psychiatric disturbance, such as anxiety, depression, or altered sleep. Cognitive dysfunction is usually the most prominent neurologic sign. Unlike Alzheimer's disease, however, prion disease typically involves other brain systems and causes motor signs (such as ataxia, bradykinesia, or spasticity), vague somatic sensory disturbances, or alterations in visual perception. Myoclonus is a characteristic but not pathognomonic sign. Perhaps the most distinctive feature of prion disease is the pace of its progression. Typically, clear decrements in neurologic function can be observed over a period of weeks.

Genetic

Most genetic forms of prion disease are accompanied by symptoms indistinguishable from the those of the common sporadic syndrome just described. However, the mean age at onset may be somewhat younger.

In Gerstmann-Straüssler-Scheinker syndrome, the clinical signs are prominent ataxia, a slower rate of progression than occurs with sporadic CJD (typically 5 to 6 years from onset to death), and late dementia. Fatal familial insomnia begins with anxiety, depression, and sleep disturbance. Ataxia or other motor signs may also develop early in the disease course. Dementia occurs relatively late in the condition. Very rarely, a sporadic form of CJD will be manifested as a clinical syndrome of sporadic fatal insomnia that is indistinguishable from fatal familial insomnia.

Slowly progressive CJD may have clinical manifestations similar to those of familial Alzheimer's disease (Chapter 409) or resemble Huntington's disease (Chapter 417).

Infectiously Acquired

The extremely rare infectiously acquired forms of prion disease have features that are different from the common sporadic manifestation. The three infectiously transmitted forms of prion disease are variant CJD, kuru, and iatrogenic CJD.

Variant CJD is distinguished clinically from sporadic CJD by a much younger mean age at onset (mean, 26 years; range, 12 to 74 years), the prominence of psychiatric and sensory signs early in the disease, and the later emergence of dementia and motor signs, typically more than 6 months after the first symptoms. Iatrogenic CJD usually resembles sporadic CJD, but a subset of patients may have an ataxic form that clinically and pathologically shares some features with Gerstmann-Straüssler-Scheinker syndrome.

Kuru begins with limb pain followed by cerebellar ataxia and tremor ("kuru" means "shiver" in the Fore language). Overt dementia occurs late in the disease course.

DIAGNOSIS

The diagnosis of prion disease should be considered in patients with relatively rapidly progressive dementia, especially when structural, inflammatory, and more common metabolic, endocrine, and deficiency diseases have been excluded (Table 424-1). If the initial evaluation fails to yield an alternative diagnosis, a number of available tests further support the diagnosis of prion disease. However, prion diseases are rare, and ancillary tests have less than perfect specificity and sensitivity; if they are applied indiscriminately, these

TABLE 424-1 EVALUATION OF RAPIDLY PROGRESSIVE DEMENTIA

Initial screening	**Serum tests:** glucose, sodium, calcium, blood urea nitrogen, creatinine, hepatic aminotransferases, albumin, prothrombin time, TSH, antinuclear antigen, vitamin B_{12}, HIV and syphilis serology **Imaging:** brain MRI **CSF:** glucose, protein, cell counts, VDRL
Test findings supporting a diagnosis of prion disease	**MRI:** T2 hyperintensity in the basal ganglia, sometimes in the cortex **CSF 14-3-3 protein:** elevated levels fairly specific for CJD **EEG:** Periodic sharp wave complexes

CJD = Creutzfeldt-Jakob disease; CSF = cerebrospinal fluid ; EEG = electroencephalography; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone; VDRL = Venereal Disease Research Laboratory test.

TABLE 424-2 DIFFERENTIAL DIAGNOSIS OF RAPIDLY PROGRESSIVE DEMENTIA

Neurodegenerative diseases that may mimic CJD	Alzheimer's disease, diffuse Lewy body disease, frontotemporal dementia, corticobasal ganglion degeneration, progressive supranuclear palsy
Some less common treatable diseases that mimic CJD	**Autoimmune:** central nervous system vasculitis, limbic encephalitis, Hashimoto's encephalopathy, anti–voltage-gated potassium channel encephalopathy **Infections:** viral encephalitis, chronic meningitis **Toxicities:** lithium, bismuth, methotrexate **Neoplasms:** primary central nervous system lymphoma, intravascular lymphoma **Structural:** Normal-pressure hydrocephalus

CJD = Creutzfeldt-Jakob disease.

tests will frequently yield false-positive results. The presence of elevated cerebrospinal fluid levels of a protein called 14-3-3 is relatively specific for CJD if inflammatory and ischemic causes of dementia are excluded. An unusual hyperintensity of the deep gray matter (basal ganglia and thalamus) and sometimes the cortical gray matter on certain magnetic resonance imaging sequences (T2-weighted, fluid-attenuated inversion recovery, and diffusion-weighted weighting) occurs in about two thirds of CJD cases. The electroencephalogram in patients with CJD may show a pattern of periodic large-amplitude triphasic complexes.

Most diseases that cause rapidly progressive dementia are, like prion disease, untreatable and relentlessly progressive, for example, atypical Alzheimer's disease and diffuse Lewy body dementia (Table 424-2). However, it is important to exclude rare and at least partially treatable entities that can mimic prion disease, including autoimmune, infectious, toxic, malignant, and structural causes.

Certain diagnosis of prion disease can be made by brain biopsy. Tissue is examined immunohistochemically for the presence of abnormal aggregates of PrP. National or regional specialized prion disease centers, such as the National Prion Disorders Pathology Service Center (available at *http://www.cjdsurveillance.com*) in the United States, can assist pathologists in tissue analysis. In patients with a family history of neurodegenerative disease consistent with prion disease, determining the sequence of the protein-coding region of the prion protein gene can be diagnostic if a mutation is found.

TREATMENT AND PROGNOSIS

Rx

Prion diseases are incurable, and no treatment significantly improves the course of disease. Most patients with sporadic CJD die within a year of the onset of symptoms. Patients with Gerstmann-Straüssler-Scheinker syndrome and certain other genetic or variant forms of prion disease may live longer. Excellent animal models of prion disease exist, and a number of novel therapeutic approaches are under active investigation. It is worthwhile to consider enrollment in experimental clinical trials if they are available (*http://clinicaltrials.gov*).

PREVENTION

Most cases of prion disease occur sporadically and cannot be prevented. Genetic cases can potentially be prevented through genetic counseling and prenatal testing, although whether such measures are warranted to prevent a disease that may not be manifested until midlife or later is an ethically complex question. Infectiously transmitted cases are currently amenable to preventive measures, including avoidance of surgical transmission as a result of contaminated instruments or tissue grafts and protection of the human food supply from meat products contaminated with bovine spongiform encephalopathy or other ruminant prions. Chronic wasting disease is epidemic among deer and elk in certain regions of the United States, and scrapie, which affects sheep and goats, is endemic at low levels in the United States and many other countries. Neither of these prion diseases has been convincingly linked to human illness, but prudence dictates that humans should avoid eating any prion-infected animal.

SUGGESTED READINGS

Frost B, Diamond MI. Prion-like mechanisms in neurodegenerative diseases. *Nat Rev Neurosci*. 2010;11:155-159. *Propagation of protein misfolding may be a common pathogenetic mechanism in neurodegenerative diseases.*

Geschwind MD, Shu H, Haman A, et al. Rapidly progressive dementia. *Ann Neurol*. 2008;64:97-108. *Summarizes alternative diagnoses found in patients referred to a large center with an initial diagnosis of CJD.*

Mastrianni JA. The genetics of prion diseases. *Genet Med*. 2010;12:187-195. *Review.*

Samson AO, Levitt M. Normal modes of prion proteins: from native to infectious particle. *Biochemistry*. 2011;50:2243-2248. *Review of the conformational biology.*

425

NUTRITIONAL AND ALCOHOL-RELATED NEUROLOGIC DISORDERS

BARBARA S. KOPPEL

An adequate supply of vitamins and minerals is necessary for development and metabolic function of both the central and peripheral nervous systems. Deficiencies of vitamins and minerals can cause a variety of neurologic syndromes (Table 425-1).

Vitamin deficiency (Chapter 225) can be caused by either malnutrition (Chapter 222) or malabsorption (Chapter 142). In malnutrition, it may be difficult to determine the specific vitamin responsible for particular neurologic symptoms and signs because multiple deficiencies are likely to coexist. Malnutrition is the most common cause of vitamin deficiency in economically disadvantaged countries. When adequate food supplies are readily available, malnutrition may be caused by surgery for obesity, unbalanced ("fad") diets, prolonged vomiting or anorexia, excess alcohol consumption, incomplete parenteral nutrition, or a genetic predisposition to malabsorption or dysfunction of transport proteins.

DEFICIENCY OF WATER-SOLUBLE VITAMINS

Thiamine (Vitamin B_1) Deficiency

Thiamine is converted to thiamine pyrophosphate, which serves as a coenzyme in glucose and lipid metabolism and in the synthesis of neurotransmitters from branched-chain amino acids. To avoid deficiency, thiamine must be consumed regularly in adequate amounts.

BERIBERI

In developing countries, the most common manifestation of thiamine deficiency is beriberi, which results in a painful sensorimotor peripheral neuropathy and heart failure ("wet beriberi"). Other causes of thiamine deficiency include consumption of foods in which the vitamin has been inactivated by processing or overcooking or foods that contain thiaminase-producing bacteria (e.g., raw fish). Headache, vomiting, seizures, and cranial nerve dysfunction can develop in babies born to malnourished mothers or fed thiamine-deficient formula.

TABLE 425-1 SUMMARY OF VITAMIN AND MINERAL DEFICIENCIES

VITAMIN AND MINERAL DEFICIENCIES	NEUROLOGIC SYNDROME OR SYNDROMES	SUPPORTING TESTS	TREATMENT	CAUSES (OTHER THAN MALNUTRITION)
A (Retinol)	Blindness from retinal or corneal damage	Visual fields, visual acuity Serum level <30-65 µg/dL	30,000 IU vitamin A daily × 1 wk	Hypothyroidism, diabetes, renal or liver failure
B_1 (thiamine)	Wernicke's encephalopathy: ataxia, nystagmus, ophthalmoparesis, confusion, delirium Korsakoff's syndrome: amnesia, confabulation Beriberi: axonal neuropathy	MRI: symmetrical lesions of midbrain (periaqueductal area), pons, hypothalamus, thalamus, cerebellum MRI: necrosis of mamillary bodies, dorsomedial and anterior thalamus Nerve conduction tests: decreased amplitude Serum thiamine level <20 ng/dL Erythrocyte transketolase	Prevent by 100 mg PO daily before and 1 year after bariatric surgery, 100 mg IV before glucose administration or refeeding Treat Wernicke's encephalopathy with 5 days of thiamine, 100-500 mg IV or IM daily, then PO 100 mg daily Antioxidants (*N*-acetylcysteine)	Alcoholism, bariatric or other major GI surgery, prolonged vomiting, hemodialysis, diuretic treatment of heart failure, cachexia, 5-fluorouracil, other blockers of thiamine phosphate production
B_3 (niacin)	Pellagra: confusion, dementia, weakness, ataxia, spasticity, myoclonus, glossitis, dermatitis, photosensitivity	Erythrocyte NAD, plasma niacin, urinary N1-methylnicotinamide	Nicotinic acid, 50 mg PO tid or 25 mg IV tid; nicotinamide, 50-100 mg IM or PO tid	Alcoholism, corn- or cereal-based diet, Hartnup's syndrome, carcinoid syndrome
B_5 (pantothenic acid)	Dysesthesias, foot paresthesias	Deficient coenzyme A	5 mg PO daily	Severe malnutrition
B_6 (pyridoxine)	Neuropathy, sensory ataxia, depression Infantile pyridoxine-deficient epilepsy	Plasma PLP <27 nmol/L; urinary 4-pyridoxic acid, <3 nmol ↑ Homocysteine after methionine loading challenge ↑ α-AASA in urine, plasma, CSF	50-100 mg PO daily for neuropathy (preventive use if taking B_6 antagonist) 100-200 mg daily for adult epilepsy	Diverticulosis, isoniazid, cycloserine, other antagonists Genetic defects in antiquitin (aldehyde dehydrogenase), pyridoxal synthesis
B_{12} (cobalamin)	Myelopathy with spastic paraparesis and sensory ataxia, peripheral neuropathy, optic neuropathy, memory loss, dementia; indirect contributor to stroke	Blood level <200 pg/mL ↑ Methylmalonic acid >145 nmol/L Intrinsic factor antibodies Schilling test, megaloblastic anemia Delayed somatosensory evoked potentials ↑ Homocysteine, total >12.5 µmol/L	IM B_{12}, 1000 µg daily for 1 week, then weekly for 1 month, then monthly or oral B_{12}, 1000 µg daily, or nasal B_{12}, 500 µg weekly for lifetime if abnormal absorption, 50-100 µg daily if normal absorption	Achlorhydria, gastric or ileal resection, blind loop syndrome, sprue, HIV infection, nitrous oxide anesthesia (especially abuse), fish tapeworm, vegan diet
D (calciferol)	Proximal myopathy, often painful; cognitive impairment Secondary compression of spinal cord, plexus, or peripheral nerves from rickets or osteomalacia	25-(OH) vitamin D_3 level <10 ng/mL in urine Serum calcium ↑ PTH >54 pg/mL Osteopenia/porosis on bone densitometry	Daily supplementation with 400 IU, >50,000 IU 3 times per wk if malabsorption; use blood level or urine calcium excretion to guide (should be >100 mg/day)	Lack of exposure to sunlight, including sunblock protection; chronic antiepileptic drug use
E (tocopherol)	Spinal and cerebellar ataxia, Babinski's sign, ophthalmoplegia, peripheral neuropathy, retinitis pigmentosa	Vitamin E level <2.5 mg/L (normal, 6-15 with normal lipid level) ↑ A-β-lipoprotein levels, antigliadin antibodies Genetic analysis to rule out other spinocerebellar ataxias such as Friedreich's ataxia	Supplement with 6-800 IU, 5-10 mg/kg twice daily, for ataxia of genetic causes, water-soluble 200 mg/kg/day or IM α-tocopherol for malabsorption	Biliary atresia, celiac sprue, Genetic: ↓ α-tocopherol transport protein (8q13), microsomal triglyceride transfer protein
Folate	Dementia, B_{12} deficiency, stroke	↑ Homocysteine, plasma level <2.5 µg/L	1 mg 3 times per day until normal level, then maintenance of 1 mg/day Pregnancy: additional 0.4 mg/day if taking a folate antagonist	Malabsorption or use of antagonist (methotrexate) or antiepileptic medication
K (phytonadione)	Intracranial hemorrhage	INR or PT elevation	IM phytonadione at birth, maternal vitamin K for last month of pregnancy	Medication use that increases metabolism, such as phenytoin
Copper	Myelopathy, neuropathy	Serum Cu <75 µg/dL, ↓ urinary Cu, ceruloplasmin <23 mg/dL MRI: ↑ T2 signal in cervical cord, dorsal column Mutation in *ATP7A* gene (Menkes' disease)	Elemental Cu, 8 mg/day PO week 1, 6 mg/day week 2, 4 mg/day week 3, 2 mg/day ongoing malabsorption Menkes' disease: 250 mg SC bid	Wilson's disease, Menkes' disease, alcoholism, malabsorption, gastric bypass, zinc toxicity
Magnesium	Seizures, encephalopathy	Serum magnesium <1.5 mg/dL, correct for low albumin	Magnesium sulfate IV or PO Avoid magnesium-wasting drugs	Alcoholism, especially beer
Potassium	Muscle weakness, chronic, acute	Serum potassium <3.5 mEq/L, ECG	IV or PO KCl until normalized	Diuretic use, bulimia

AASA = aminoadipic semialdehyde; CSF = cerebrospinal fluid; ECG, electrocardiography; GI = gastrointestinal; INR = international normalized ratio; MRI = magnetic resonance imaging; NAD = nicotinamide adenine dinucleotide; PLP = pyridoxal-5-phosphate (active coenzyme of pyridoxine); PT = prothrombin time; PTH = parathyroid hormone.

WERNICKE'S ENCEPHALOPATHY

Severe short-term thiamine deficiency results in Wernicke's encephalopathy, a syndrome characterized by confusion and other changes in mental status, abnormal eye movements, and ataxia. Wernicke's encephalopathy occurs most commonly in the setting of chronic alcohol abuse, but it can also be seen following bariatric surgery, refeeding after a period of starvation, or after the intravenous administration of glucose without thiamine. The symptoms and signs of Wernicke's encephalopathy reflect dysfunction of brain regions that are dependent on thiamine or have high rates of energy metabolism, where lactate production from anaerobic metabolism causes damage to astrocytes or the blood-brain barrier. These regions include the periaqueductal gray matter of the midbrain, pons, and medulla, as well as the cerebellum,

anterior thalamus, mamillary bodies, and rarely, the cerebral cortex and hypothalamus.

The classic triad of mental status changes, ocular abnormalities, and ataxia is present in less than 50% of patients. Changes in mental status range from mild memory impairment or inattention to delirium. Eye movement abnormalities include nystagmus, dysconjugate gaze, and gaze palsies. Ataxia can affect the limbs, trunk, and gait. Patients with Wernicke's encephalopathy can also have autonomic and hypothalamic dysfunction, such as bradycardia and hypothermia, as well as papilledema, optic neuropathy, seizures, and myoclonus. In symptomatic patients, T2-weighted magnetic resonance imaging (MRI) demonstrates increased signal from edema or hemorrhage in affected areas, most often the thalamus.

KORSAKOFF'S SYNDROME

Korsakoff's syndrome becomes apparent in 80% of patients with Wernicke's encephalopathy as the ataxia and eye movement abnormalities improve. Korsakoff's syndrome is characterized by disproportionate retrograde and anterograde episodic amnesia, confabulation or hallucinations, and sometimes apathy. The primary pathologic findings occur in the limbic system, especially the mamillary bodies, amygdala, and anterior thalamus.

The memory deficit, which prevents the learning of new information or the acquisition of new memories, is disproportionately severe in relation to other aspects of the cognitive function. For example, alertness, attention, social interactions, and motor learning are generally well preserved. There may be mild disorientation with respect to time and place, and sometimes apathy and other emotional changes are present. Confabulation, in which the intrusion of errors in response to questions leads to fabrication without the intention of deceiving, is often present spontaneously in the first weeks. Confabulation may be a compensatory mechanism, and it usually lessens over time. Neuropsychological testing often demonstrates emotional changes and mild problems in executive function, which are suggestive of frontal lobe involvement.

TREATMENT Rx

Treatment with thiamine (see Table 425-1) can prevent or treat beriberi and Wernicke's encephalopathy. Korsakoff's syndrome, however, does not respond to replacement of thiamine and must be prevented by timely recognition and treatment of Wernicke's encephalopathy.

Cobalamin (Vitamin B_{12}) Deficiency

Cobalamin deficiency results in combined system disease or subacute combined degeneration, which is a spinal cord syndrome (myelopathy) in which damage to the dorsal (sensory) and lateral (motor) tracts results in impaired position and vibratory sensation and spastic paraparesis.

EPIDEMIOLOGY AND PATHOBIOLOGY

Cobalamin deficiency (Chapters 167 and 225) is most common in individuals older than 60 years because the incidence of atrophic gastritis (Chapter 141) and achlorhydria rises in older individuals who lack the gastric intrinsic factor needed for absorption of vitamin B_{12}. Cobalamin deficiency is rarely due to inadequate dietary intake (e.g., a vegan diet for several years). Nitrous oxide toxicity, from illicit use but not from administration for anesthesia, can cause cobalamin deficiency by inactivating the cobalamin-dependent enzyme methionine synthase, so this anesthetic should be avoided in people with known or suspected cobalamin deficiency. Low vitamin B_{12} levels have been associated with increased homocysteine levels, but a relationship to vascular disease or vascular-related dementia has not been established.

CLINICAL MANIFESTATIONS

The proprioceptive loss results in sensory ataxia with Romberg's sign (failure to maintain balance with the eyes closed). A peripheral neuropathy with numbness and tingling in the hands and feet is almost always present. Cerebral involvement includes memory loss, changes in personality, and occasional psychosis. Symptoms generally progress slowly, but they may appear especially rapidly after exposure to nitrous oxide anesthesia by individuals with preexisting subclinical cobalamin deficiency.

DIAGNOSIS

Serum vitamin B_{12} levels are almost always low but can rarely be normal in symptomatic patients. In such cases, serum levels of methylmalonic acid and homocysteine are useful ancillary tests because these levels are increased in persons with vitamin B_{12} deficiency as a result of impaired cobalamin-dependent reactions (Chapter 167). Pernicious anemia (Chapter 167) is severe in about 20% of patients. However, both the hematocrit and mean corpuscular volume can be normal because the hematologic effects of cobalamin deficiency can be partially masked by folate supplementation.

Low levels of cobalamin can also be present in many normal people, especially the elderly. Because of the increasing frequency of dementia, peripheral polyneuropathy, and myelopathy with age, a low cobalamin level does not necessarily imply cause and effect. Nonetheless, the triad of dementia, polyneuropathy, and myelopathy is rare. The definitive definition of causality is clinical improvement after cobalamin replacement.

TREATMENT Rx

Treatment usually begins with a subcutaneous or intramuscular injection of 500 to 1000 µg of cobalamin daily for 1 week and then weekly for 1 month. After that time, oral supplementation with 50 to 100 µg daily of cyanocobalamin usually suffices in patients with achlorhydria or other causes of malabsorption; 1000 µg daily should be used in patients with intrinsic factor antibodies. A nasal gel form (500 µg weekly) may also be effective.

PROGNOSIS

Neurologic symptoms, especially paresthesias, typically improve to some extent within 3 months of achieving adequate serum levels. Numbness and areflexia often persist, especially if treatment is delayed. If there is no improvement whatsoever, vitamin B_{12} deficiency is most likely not responsible for the condition. For example, human immunodeficiency virus–associated myelopathy, which can have a similar clinical manifestation, does not reverse with supplemental vitamin B_{12} because it is caused by disruption of transmethylation pathways, not low cobalamin levels (see Table 425-1).

Folate Deficiency

Folate is an important coenzyme in the metabolism of nucleic and amino acids. Inborn errors of folate metabolism cause mental retardation and seizures. Although folate deficiency is more likely to produce hematologic abnormalities than neurologic deficits, it is an important risk factor for neural tube defects in babies born to mothers who have insufficient folate intake or use anticonvulsant drugs such as valproate, antituberculosis medications, or folate antagonists such as methotrexate. Women of childbearing age who are taking these medications are now routinely given 0.4 mg of folate daily in addition to the 1 mg contained in prenatal vitamins. Vitamin B_{12} levels should be checked to avoid ongoing neurologic damage as a result of unrecognized cobalamin deficiency when anemia is treated with folate alone. Folate deficiency is treated with 1 mg three times daily for 1 month followed by 1 mg each day.

Folate deficiency results in increased levels of homocysteine, which is associated with an increased risk for ischemic heart disease and stroke. However, multiple trials of supplementation of folate and B vitamins in patients with elevated homocysteine levels but not with classic homocysteinemia have been uniformly unsuccessful in reducing adverse clinical events.

Pyridoxine (Vitamin B_6) Deficiency

Pyridoxine is a coenzyme in multiple reactions that involve gluconeogenesis, biosynthesis of neurotransmitters, and the metabolism of amino acids, nucleic acids, and lipids. Pyridoxine deficiency can be caused by genetic defects, such as defective antiquitin, that lead to increased utilization of pyridoxine. In adults, low levels of pyridoxine are well tolerated, so symptomatic deficiency is rare. However, symptomatic deficiency can occur in the setting of renal failure or dialysis; cirrhosis; the use of medications such as isoniazid for antitubercular therapy or hydralazine for hypertension without concurrent supplementation; or extreme malnutrition, especially diets consisting predominantly of white rice.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Prolonged pyridoxine deficiency causes a painful axonal peripheral neuropathy that leads to weakness and sensory ataxia. Some patients may have skin thickening, seborrheic dermatitis, or glossitis, which suggest pellagra. Serum levels of the active form of pyridoxine, pyridoxal 5′-phosphate, and urine levels of the metabolite 4-pyridoxic acid are low. Ancillary tests include nerve

conduction studies, which show decreased amplitude, typical of axonal neuropathy. In inherited forms of pyridoxine deficiency, electroencephalography shows generalized 1- to 4-Hz spiked wave discharges and slowing.

Toxicity from excess intake of pyridoxine (>100 mg daily), usually from vitamin supplements, causes a ganglionopathy that is characterized by impaired sensation, sensory ataxia with Romberg's sign, and areflexia.

TREATMENT Rx

Patients in whom symptoms of pyridoxine deficiency develop or who take pyridoxine antagonists should receive supplemental pyridoxine (50 to 100 mg daily). Children with pyridoxine-dependent epilepsy require lifelong supplementation with 100 mg of pyridoxine daily. For pyridoxine toxicity, simply stopping vitamin intake will usually reverse the damage.

DEFICIENCY OF FAT-SOLUBLE VITAMINS

Vitamin E (Tocopherol) Deficiency

Although vitamin E is composed of several tocopherols, it is the α form that is biologically active in humans and contained in most foods. Because it is so widely available, deficiency is almost never due to inadequate dietary consumption. Rather, vitamin E deficiency is almost always the result of malabsorption because of such conditions as biliary and pancreatic disease (Chapters 158 and 146), cystic fibrosis (Chapter 89), celiac disease (Chapter 142), Crohn's disease (Chapter 143), extensive small bowel resection, and blind loop syndrome (Chapter 142). In addition, vitamin E deficiency is associated with genetic defects such as those causing hypolipoproteinemia and abetalipoproteinemia, chylomicron retention disease, and ataxia with vitamin E deficiency.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome with ataxia, loss of vibration and position senses, hyporeflexia, and extensor plantar responses. Other findings can include ophthalmoplegia, retinopathy, ptosis, and rarely, myopathy.

Serum levels of vitamin E can vary with the serum lipid levels. In extreme hyperlipidemia, such as cholestasis, the ratio of vitamin E to cholesterol will be more reliable than the absolute vitamin E level, which can be normal despite a low ratio.

TREATMENT Rx

The amount of vitamin E replacement depends on the cause. Malabsorption syndromes require 1000 to 2000 mg daily for infants and 10 to 20 g for adults. Genetic causes can be treated with 5 to 10 g/day. After bariatric surgery, 300 mg daily is recommended. For vitamin E, 1 mg is equivalent to 1.49 IU. Although vitamin E has been advocated to forestall neurodegenerative diseases such as Alzheimer's disease, this role has not been established.[Z]

Vitamin D (Calciferol) Deficiency

Vitamin D deficiency results from inadequate exposure to sunlight, dietary insufficiency, or malabsorption because of celiac disease, inflammatory bowel disease, or extensive small bowel resection. The most important consequences of vitamin D deficiency are rickets in children, osteomalacia in adults, and hypocalcemia with secondary hyperparathyroidism. Hypocalcemia, in turn, can cause tetany, encephalopathy, and seizures. A proximal myopathy, worse in the legs than the arms, and cutaneous hyperalgesia have been reported. Inadequate vitamin D levels, present in 44% of Americans older than 65 years, are associated with cognitive dysfunction or dementia. Lower levels of vitamin D are also correlated with the risk for multiple sclerosis (Chapter 419). Individuals who can absorb vitamin D normally require 400 to 600 IU of vitamin D_3 (cholecalciferol) (10 to 15 μg), but persons with malabsorption may need more than twice that amount. The eventual dose should be titrated to produce a serum 25-hydroxyvitamin D level of at least 30 ng/mL.

Vitamin A Deficiency

Vitamin A deficiency, which is most often associated with night blindness, can also impair taste and has rarely been associated with raised intracranial pressure in children. Malabsorption rarely leads to vitamin A deficiency. Vitamin A toxicity, which is occasionally a complication of the use of isotretinoin for acne or excessive consumption of liver in the diet, can cause pseudotumor cerebri with headache and papilledema.

Vitamin K Deficiency

Vitamin K deficiency, which is a rare consequence of malabsorption, is seen more commonly in patients who have compromised liver synthesis or who are receiving warfarin therapy. Vitamin K deficiency causes excessive bleeding and increases the risk for intracerebral hemorrhage (Chapter 415), especially in newborns whose mothers are taking antagonists such as phenytoin. Five milligrams daily is usually adequate supplementation, but the dose may need to be adjusted based on the prothrombin time.

DEFICIENCY OF MISCELLANEOUS ELEMENTS AND NUTRIENTS

Copper Deficiency

Acquired copper deficiency is rare but may occur in premature or malnourished infants and in patients with malabsorption from celiac disease, cystic fibrosis, or Crohn's disease. It can also occur in patients with nephrotic syndrome and following gastric surgery, especially bariatric surgery. Copper deficiency is also a well-recognized consequence of excessive intake of zinc, usually as a result of the overuse of zinc-containing products, such as denture cream or herbal preparations to treat rhinitis and sinusitis, or because of parenteral overload during hemodialysis.

The most common neurologic complication in persons with copper deficiency is a myelopathy that is clinically very similar to that seen with cobalamin deficiency. The most prominent features are spastic paraparesis and sensory ataxia. A peripheral polyneuropathy of the axonal type is usually present as well. Copper levels, including excreted urinary copper, should be measured in patients who are suspected of having vitamin B_{12} deficiency but fail to respond to treatment with cyanocobalamin. Optic neuropathy, wrist-drop, and footdrop have also been reported. Menkes' disease, an X-linked recessive copper deficiency caused by mutations in the *ATP7A* gene needed for absorption, is characterized by severe mental retardation and kinky hair. The diagnosis is made by finding low serum copper levels or changes in the ratio of dopamine to norepinephrine. Large doses of copper histidine (250 mg twice daily until age 1, then daily until age 3) must be delivered subcutaneously, but improvement is variable. Patients survive to adulthood only if copper injections start neonatally.

Wilson's disease (Chapter 218) is an autosomal recessive disorder that results from excessive copper accumulation, primarily in the liver and brain, as a result of failed transport and impaired copper excretion. Ceruloplasmin, the transport protein for copper, is deficient. Neurologic manifestations can include depression, psychosis, dementia, dysarthria, tremor, chorea, and other movement disorders. Accumulation of copper in the liver leads to chronic liver failure. Wilson's disease is treated by copper chelation (Chapter 218) and by minimizing dietary intake.

Other Nutritional Disorders

Biotin deficiency is caused by an autosomal recessive disorder affecting biotinidase. It results in developmental delay, seizures, ataxia, and deafness.

Some epidemics that are manifested as peripheral neuropathy or optic neuropathy, such as Strachan's Jamaican neuropathy and Cuban tobacco-alcohol amblyopia, occur in the setting of malnutrition and respond to replacement of B vitamins or folate. Toxicity from foods should always be suspected in populations that are reliant on a single main source of nutrition, even when the exact cause is not known. Examples include spastic paraparesis or muscle atrophy from overconsumption of legumes in the *Lathyrus* genus, such as chick peas, which contain the neurotoxic glutamate agonist oxalyldiaminoproprionic acid; konzo, probably from cyanide poisoning (Chapter 110), which is related to improperly prepared cassava in Africa; and amyotrophic lateral sclerosis and Parkinson-dementia complex in Guam, probably caused by cycad toxins in flour.

ALCOHOL-RELATED DISORDERS

Alcohol (Chapter 32) is responsible for a wide spectrum of neurologic disorders. At one extreme, it can cause irreversible dementia, cerebellar degeneration, optic neuropathy, and peripheral polyneuropathy. Alcohol also causes transient neurologic syndromes such as seizures, tremors, hallucinosis, and delirium tremens. Acute intoxication can range from mild euphoria,

to vestibular and cerebellar dysfunction, to coma and death. When alcohol is the main source of calories, it contributes to nutritional deficiency syndromes such as Wernicke-Korsakoff syndrome, beriberi, and pellagra. Alcohol-induced liver toxicity results in hepatic encephalopathy and non-wilsonian hepatolenticular degeneration. Coagulopathy caused by liver disease or suppressed platelet production raises the risk for subdural or intracranial hematoma. Fetal alcohol syndrome reflects the vulnerability of the developing nervous system to the toxic effects of alcohol.

Signs of intoxication correlate with blood alcohol levels: from 50 mg/dL for personality changes; 150 mg/dL for ataxia, vestibular dysfunction, and nystagmus; 300 mg/dL for stupor; 400 mg/dL for coma; and up to 500 mg/dL for respiratory depression or apnea. However, the effects vary greatly, depending on the chronicity of intake and the rate at which high levels develop. Intoxication alone should never be assumed to be the sole cause of a depressed mental state because alcoholics are at increased risk for other causes of coma (Chapter 411).

Specific Clinical Syndromes

Seizures and status epilepticus (Chapter 410) can be a direct consequence of intoxication, withdrawal, hyponatremia (Chapter 118), and hypomagnesemia (Chapter 121) or result from epileptogenic foci from previous head trauma or stroke.

Hepatic encephalopathy can be the result of alcoholic cirrhosis (Chapter 156), especially in patients who have bleeding esophageal varices, and is characterized by irritability alternating with depressed mental status, seizures, tremor, and asterixis.

Dementia develops even when nutrition is well maintained because of alcohol's direct neurotoxic effects. Contributing factors include head injury, status epilepticus, and cerebrovascular disease. Further evidence of alcohol's deleterious effect is cerebral atrophy involving both gray and white matter. The dementia is probably not reversible.

Wernicke's encephalopathy and *Korsakoff syndrome* are described in the section on thiamine.

Marchiafava-Bignami syndrome was first described in postmortem studies of Italian chianti drinkers but can occur in persons who consume any type of alcohol. Acute signs include coma, seizures, hemiparesis, rigidity, and sometimes death. The most severe pathology involves demyelination and necrosis of the corpus callosum. Findings on MRI include increased T2- and diffusion-weighted signals in the corpus callosum, especially the splenium.

Cerebellar degeneration and ataxia result from the alcohol-induced loss of Purkinje cells, mainly in the anterior superior parts of the cerebellar vermis; the cerebellar hemispheres are less affected. As a result, the clinical picture is mainly truncal and gait ataxia, with a wide-based unsteady gait and inability to walk tandem. The arms are much less involved, if affected at all. Intention tremor, nystagmus, and dysarthria are rare. Findings are exacerbated by concurrent thiamine deficiency and Wernicke's encephalopathy.

Optic neuropathy, which occurs with severe chronic alcohol abuse, is manifested as progressive, painless visual loss as a result of damage to the optic nerve fibers. The macular region is most affected. Similar findings, first described in Cuban men who were heavy cigar smokers, have also been attributed to tobacco. However, neither alcohol nor tobacco is apparently directly responsible for the optic nerve damage, so it is more likely that the syndrome results from malnutrition and deficiencies of multiple vitamins, including vitamins A and B.

Peripheral neuropathy (Chapter 428) ("alcoholic neuropathy") is the most common neurologic complication of chronic alcoholism. It is an axonal sensorimotor neuropathy that causes dysfunction of small nerve fibers, thereby leading to distal sensory symptoms such as burning dysesthesias and paresthesias of the soles of the feet. The typical numbness develops in a stocking-glove distribution, with loss of ankle reflexes. Mild distal weakness eventually occurs in some patients. Involvement of the autonomic nervous system frequently causes impotence, as well as urinary or bowel complaints. Although vitamin supplements, especially thiamine and pyridoxine, may lead to some improvement, especially in the painful paresthesias, complete resolution is rare. If abstinence from alcohol is not also achieved, the symptoms persist, thereby implying that a direct toxic effect of alcohol is likely.

Compressive neuropathies, especially of the radial nerve ("Saturday night palsy") and peroneal nerve, occur in individuals who injure peripheral nerves during periods of prolonged pressure on a nerve while obtunded from heavy alcohol consumption. Recovery takes several weeks but is generally complete.

Myopathy occurs in binge drinkers, in whom severe muscle injury with rhabdomyolysis (Chapter 115) can develop, especially in the setting of fasting and prolonged absence of movement. Myoglobinuria can result in kidney damage. Heavy alcohol consumption is also associated with cardiomyopathy (Chapter 60), which can lead to arrhythmias even in the absence of hypokalemia. Chronic alcohol abuse causes a symmetrical proximal weakness (Chapter 429), but it is rarely the only neurologic finding; although weakness can be demonstrated in up to 50% of chronic alcoholics, it is not usually severe enough to prevent walking or standing.

Fetal alcohol syndrome is recognized at birth in infants whose mothers consumed significant amounts of alcohol, especially in the early stages of pregnancy. The characteristic findings are growth retardation, microcephaly, hypotonia, skeletal and cardiac anomalies, and characteristic facial features (micrognathia, small palpebral fissures). Recently, migration defects have been demonstrated by diffusion-weighted MRI and tractography. Exposure of the developing brain to alcohol can also lead to subtle or severe neurocognitive defects and attention deficit disorder, which may not be detected until later in childhood. The teratogenic effects of alcohol are not prevented by adequate amounts of thiamine, folate, and other vitamins.

Grade A

1. Andrès E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B_{12}) therapy. *Expert Opin Pharmacother*. 2010;11:249-256.
2. Isaac MG, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev*. 2008;3:CD002854.

SUGGESTED READINGS

Kopelman MD, Thomson AD, Guerrini I, et al. The Korsakoff syndrome: clinical aspects, psychology and treatment. *Alcohol Alcohol*. 2009;44:148-154. *About 75% of abstinent patients have some recovery*.

Kumar N: Neurologic presentation of nutritional deficiencies. *Neurol Clin*. 2010;28:107-170. *Review*.

Mellion M, Gilchrist JM, De La Monte S. Alcohol-related peripheral neuropathy: nutritional, toxic, or both? *Muscle Nerve*. 2011;43:309-316. *Review suggesting that it is mostly toxic*.

Rudnicki SA. Prevention and treatment of peripheral neuropathy after bariatric surgery. *Curr Treat Options Neurol*. 2010;12:29-36. *Review of vitamin deficiencies, with specific recommendations for testing for and supplementation with vitamins A, C, D, K, E; iron; zinc; selenium; magnesium; and copper*.

426

CONGENITAL, DEVELOPMENTAL, AND NEUROCUTANEOUS DISORDERS

JONATHAN W. MINK

CONGENITAL DISORDERS

Malformations of Cerebral Cortex

Developmental malformations of the cerebral cortex arise from a wide variety of etiologies, including genetic mutations, intrauterine infections, intrauterine ischemia, and toxic exposures. These malformations are heterogeneous and can result from disrupted neuronal proliferation, migration, or cortical organization. In general, disorders that arise early in development are more severe than those that arise after the basic architecture of the brain has developed. When small areas of the brain are involved, the patient may have minor impairment of neurologic function. When larger areas of the brain are involved, patients often have cognitive deficits and more severe neurologic dysfunction. Epilepsy (Chapter 410), which is the most common manifestation of abnormal cortical development, may occur with or without other neurologic signs or symptoms.

Disorders of Neuronal Proliferation

Neuronal proliferation can be abnormally increased or decreased owing to a variety of mechanisms. These disorders can manifest with megalencephaly or

microcephaly, or head size can be normal. Abnormal proliferation can involve specific cell types, thereby resulting in focal or multifocal areas of dysplasia or in the formation of hamartomas (see Tuberous Sclerosis, later).

FOCAL CORTICAL DYSPLASIA WITH BALLOON CELLS

Focal cortical dysplasia is caused by abnormal proliferation of both neurons and glia. Its neuropathology is characterized by the presence of giant dysmorphic neurons and "balloon cells" associated with altered cortical lamination, but some lesions have abnormal cortical layering with ectopic neurons in white matter. Affected patients typically present with partial seizures that are often intractable to medical therapy. These seizures can begin at any age but most commonly present during childhood or adolescence. The type of seizure depends on the anatomic location of the dysplasia. Other neurologic manifestations, such a sensory, motor, or cognitive impairments, depend on the extent of the dysplasia and whether multiple brain regions are affected. The diagnosis of focal cortical dysplasia is usually made with brain magnetic resonance imaging (MRI), which demonstrates focal thickening of a gyrus or alteration of the gray-white matter junction. Management includes medical treatment of seizures, but surgical resection of the epileptic focus may be required for complete remission (Chapter 410).

Disorders of Neuronal Migration

Disorders of neuronal migration typically result in disruption of the normal laminar organization of the cerebral cortex. Defects include impaired initiation of neuronal migration, impaired orderly migration, and impaired termination of migration. All result in abnormal cortical organization and function.

LISSENCEPHALY AND BAND HETEROTOPIA

The lissencephalies (smooth brain) are a group of disorders that are caused by arrested migration of neurons to the cerebral cortex. Lissencephaly genes include *LIS1* (chromosome 17p13.3) and *DCX* (chromosome Xq22), both of which are thought to be involved in the regulation of microtubule organization and function. Individuals with mutations of *LIS1* typically have severe malformations that are most prominent in the posterior cerebrum. More extensive mutations in the region of *LIS1* result in Miller-Dieker syndrome, a condition characterized by lissencephaly and distinctive facial features that include a prominent forehead, midface hypoplasia, low-set and abnormally shaped ears, and a small jaw. Males with *DCX* mutations typically have a severe lissencephaly that is most prominent in the anterior cerebrum. Lissencephaly is typically diagnosed in infancy or early childhood, usually accompanied by microcephaly, severe global developmental delay, cerebral palsy, and intractable epilepsy. Diagnosis of lissencephaly is made by brain MRI that shows a smooth cortex with minimal sulcation. Genetic testing for *LIS1* and *DCX* is available. Management consists of seizure control, genetic counseling, and supportive care.

Band heterotopia (double cortex) is a less severe form of lissencephaly that is usually seen in women with *DCX* mutation. Clinical manifestations of band heterotopia range from mild to severe and include seizures, intellectual disability, and developmental delay. Women with a *DCX* mutation are at risk of having male children with severe lissencephaly. Brain MRI demonstrates a band of gray matter underlying a nearly normal-appearing cerebral cortex. Management consists of seizure control and genetic counseling.

NODULAR HETEROTOPIA

Nodular heterotopias are characterized by nodular ectopic collections of neurons and glia in the subependyma or in the subcortical white matter. The most important form is subependymal nodular heterotopia, a condition characterized by multiple gray matter nodules in the walls of the lateral ventricles bilaterally. This X-linked condition is due to a mutation in *FLNA* (chromosome Xq28), which codes for filamin A, an actin-cross-linking phosphoprotein that is critical for the initiation of migration. As a result of this mutation, many neurons do not migrate out of the subventricular zone. Most affected individuals are heterozygous females. Males are severely affected and often die in infancy. Most affected females present with seizures during childhood or adolescence. Females may be intellectually normal or have mild disability. Individuals with subependymal nodular heterotopia appear to be at increased risk for aortic or carotid dissection and for cardiac valvular abnormalities.

The diagnosis is based on brain MRI, which shows gray matter nodules along the walls of the lateral ventricles. Genetic testing for FLNA is available. Management consists of seizure control and genetic counseling.

Disorders of Cortical Organization

Disorders of cortical organization include conditions such as polymicrogyria and schizencephaly. These disorders are not due to abnormal numbers of neurons or impaired migration but instead include abnormalities of gyration, sulcation, connectivity, or synaptogenesis. The best understood of these disorders are polymicrogyria and schizencephaly.

POLYMICROGYRIA

Polymicrogyria is characterized by regions of complex cortical convolutions with miniature gyri that are fused and superimposed together. Polymicrogyria is caused by failure of cortical organization as a result of in utero injury or genetic mutation; it has been associated with prenatal infections, such as cytomegalovirus, and possible vascular abnormalities, but often it is idiopathic. A single gene, *GPR56* (chromosome 16q13), has been associated with bilateral frontoparietal polymicrogyria. *GPR56* codes for a G protein–coupled receptor that appears to be important for human cerebral cortical development. Clinical manifestations include epilepsy, developmental delay, cerebral palsy, and intellectual disability, depending on the location and extent of the abnormality. The diagnosis of polymicrogyria is made by brain MRI. Clinical management consists of seizure management and supportive therapies.

SCHIZENCEPHALY

Schizencephaly is characterized by infolding of cortical gray matter along a hemispheric cleft near the primary cerebral fissures. It is thought to represent a more extensive injury than what leads to polymicrogyria. In most cases, the cause cannot be determined, but it has been associated with in utero insult. A rare familial form has been described, but no gene has been identified. Clinical features include developmental delay, cerebral palsy, dysarthria, and epilepsy. The clinical abnormalities are more severe with large open-lip schizencephaly and with bilateral lesions than with small unilateral closed-lip schizencephaly. Diagnosis is made by brain MRI. Management consists of seizure control and supportive therapies when indicated.

Malformations of Cerebellum and Brain Stem

Developmental abnormalities of the hindbrain are less well understood than are abnormalities of cerebral cortical development. Two of the better known and important syndromes are Joubert's syndrome and Dandy-Walker malformation.

JOUBERT'S SYNDROME

Joubert's syndrome is characterized by a distinctive pattern of cerebellar and brain stem developmental malformation. Four causative genes (*NPHP1*, *CEP290*, *AHI1*, and *TMEM67* [*MKS3*]) together account for approximately 30% of cases. Clinical features include hypotonia, truncal ataxia, developmental delay, abnormal eye movements, and disordered breathing. The combination of signs and severity can be variable. Some individuals with Joubert's syndrome also have retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, or hepatic fibrosis. No formal diagnostic criteria exist. The diagnosis is usually based on the combination of hypotonia in infancy with later development of ataxia, intellectual impairment, and abnormal breathing pattern, or abnormal eye movements in combination with a characteristic MRI finding known as the molar tooth sign. The molar tooth sign results from hypoplasia of the cerebellar vermis and accompanying brain stem abnormalities on axial imaging through the junction of the midbrain and pons. Genetic testing is available for the four identified genes. Management is supportive. Caffeine can be helpful for periodic hypoventilation, but some patients require tracheostomy.

DANDY-WALKER MALFORMATION

Dandy-Walker malformation is characterized by cerebellar vermis hypoplasia and cystic dilation of the fourth ventricle. Rare familial cases have been reported, but a genetic basis has not been identified. This heterogeneous disorder is usually accompanied by hypotonia, delayed motor development, and ataxia. Intellectual disability is present in about 50% of affected individuals. In some cases, hydrocephalus requires shunting. Diagnosis is based on characteristic findings on brain MRI. Treatment is supportive, with cerebrospinal fluid (CSF) shunting when indicated.

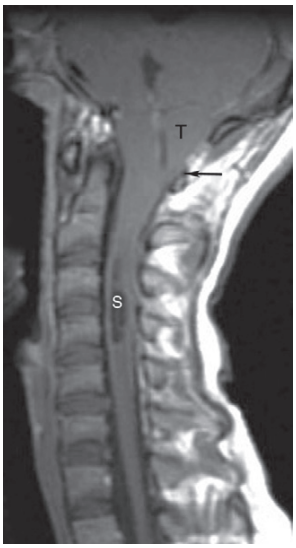


FIGURE 426-1. Chiari I malformation. A sagittal magnetic resonance image shows low, pointed cerebellar tonsils (i.e., Chiari I malformation, T) that extend to the level of C1 (*black arrow*) and a dilated central canal of the spinal cord (i.e., syringohydromyelia, S). (From Barkovich AJ, Kuzniecky RI. Congenital, Developmental, and Neurocutaneous Disorders. In Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine,* 23rd ed. Philadelphia: Saunders Elsevier; 2008:2790.)

CHIARI MALFORMATIONS

Four types of Chiari malformation have been described. The most common of these are Chiari types I and II. Chiari I malformations are most often diagnosed in adulthood, whereas Chiari II malformations are associated with spina bifida and are usually diagnosed in childhood.

Chiari I malformations are characterized by downward displacement of the cerebellar tonsils through the foramen magnum, often first accompanied by compression of the tonsils. Chiari I is a developmental abnormality that is thought to be congenital in most cases, even though symptoms may not present until adulthood, typically in the third or fourth decade of life. The abnormality is often asymptomatic and discovered only as an incidental finding. However, clinical manifestations can result from compression of neural structures at the cranial-cervical junction or obstruction of CSF flow. Signs and symptoms include headaches that worsen with straining or coughing, lower cranial nerve findings, downbeat nystagmus, ataxia, or long-tract signs. Chiari I malformations are accompanied by syringomyelia (see later) in up to 80% of cases. Diagnosis is made with brain MRI, which shows the cerebellar tonsils extending through the foramen magnum 5 mm or more (Fig. 426-1). Surgical treatment with craniocervical decompression is recommended for symptomatic patients but usually not for asymptomatic individuals or patients whose only symptom is headache.

Chiari II malformations, commonly called Arnold-Chiari malformations, are characterized by descent of the cerebellar tonsils, the inferior vermis, and portions of the cerebellar hemispheres into the spinal canal along with elongation and displacement of the brain stem and fourth ventricle. Chiari II malformations are almost always associated with meningomyelocele and spina bifida. Hydrocephalus requiring shunting occurs in most cases. Brain stem dysfunction may result from intrinsic malformation or from compression of neural structures at the craniocervical junction. Treatment is surgical repair of the myelomeningocele, relief of hydrocephalus, and occasionally, cervical bone decompression. The prognosis depends on the level and extent of the myelomeningocele and on the severity of brain anomalies.

Malformations of Spinal Cord

Tethered Spinal Cord

Tethered spinal cord syndrome is a disorder caused by an anomalous filum terminale that restricts the normal ascent of the conus medullaris and limits the movement of the spinal cord within the spinal column. The result is an abnormal stretching of the spinal cord with neurologic symptoms referable to the lower spinal cord. Tethering may also develop after spinal cord injury. Associated spinal anomalies are common and may include diastematomyelia, spinal lipomas, dermal sinuses, and fibrolipomas of the filum terminale. Symptoms can occur at any age but usually develop during periods of rapid growth in childhood or adolescence. However, tethered spinal cord syndrome may go undiagnosed until adulthood, when sensory and motor problems and loss of bowel and bladder control emerge. Erectile dysfunction may occur in males. Symptoms are typically progressive. Diagnosis is made with MRI, which shows a low conus medullaris (i.e., below the bottom of the L2 vertebral body) or a thickened or fat-containing filum terminale. Diminished pulsations of the spinal cord may also be seen. Treatment consists of surgical release of the tethered cord. With successful surgery, symptoms typically do not progress and may improve.

SYRINGOHYDROMYELIA

Syringohydromyelia is a condition in which the central canal of the spinal cord (hydromyelia) or the substance of the spinal cord (syringomyelia) is expanded by the accumulation of CSF. In many cases, both hydromyelia and syringomyelia are present (syringohydromyelia). The proximate cause of syringes probably is altered flow of CSF with variations in pressure in different parts of the subarachnoid space. The pressure variations create forces that drive CSF into the spinal cord. Possible causes include narrowing of the foramen magnum, Chiari I and II malformations, intramedullary and extramedullary spinal cord tumors, and subarachnoid scarring. Subsequent extension of the cyst may result from rapid changes in intraspinal pressure owing to such events as coughing or sneezing. Symptoms of syringohydromyelia most commonly begin in late adolescence or early adulthood and progress irregularly, with long periods of stability. The classic presentation is asymmetrical weakness and atrophy in the upper extremities, loss of upper limb deep tendon reflexes, and loss of pain and temperature sensation (with preservation of vibration and proprioception) in the neck, arms, and upper part of the trunk. With progression, spasticity and hyperreflexia develop in the lower extremities. Progressive ascending and descending levels of weakness and sensory impairment typically occur over time. The diagnosis is made by spinal MRI (see Fig. 426-1). If syringohydromyelia is identified, it is important to perform a brain MRI to look for associated abnormalities of the craniocervical junction. Occasionally, mild central canal dilation is discovered incidentally in patients without spinal cord symptoms or signs. If no associated cause is found, the prognosis of such incidentally discovered anomalies is generally good. Treatment is directed at the cause, if one can be identified. Syringopleural or syringoperitoneal shunting is sometimes performed with variable benefit.

DEVELOPMENTAL DISORDERS

Disorders that result from impaired postnatal neurodevelopmental function range from specific disorders such as fragile X syndrome and Rett's syndrome, to complex syndromes such as autism, to nonspecific developmental delay and learning disabilities.

Fragile X Syndrome

Fragile X syndrome is an X-linked trinucleotide repeat disorder that is characterized by nonsyndromic mental retardation in most affected males. The pathogenesis of fragile X syndrome is not well understood. The classic disorder is seen in males with full mutations (>200 repeats) in the *FMR1* gene. Fragile X syndrome may present as only moderate to severe mental retardation, but it is often associated with a prominent forehead, large ears, prominent jaw, and macro-orchidism. Postpubertal males often have poor impulse control, perseveration, and poor eye contact. Up to 25% of affected males have autism. Heterozygous females may be asymptomatic or may have a syndrome similar to what is seen in males, depending on repeat size and random X-inactivation.

Other disorders associated with *FMR1* include the fragile X ataxia syndrome, which is characterized by the late onset, usually after age 50 years, of progressive cerebellar ataxia and intention tremor in individuals who have an *FMR1* premutation (60 to 200 repeats). It occurs equally in males and females. Diagnosis is by molecular genetic testing. Cytogenetic testing for fragile sites is no longer recommended because it is less sensitive and more expensive than molecular testing. Treatment is symptomatic and supportive. Genetic counseling is recommended for affected individuals and their families.

Rett's Syndrome

Rett's syndrome is a neurodevelopmental disorder that occurs in females with mutations in the *MECP2* gene. *MECP2* mutations are generally lethal in male embryos, but Rett's syndrome has been reported in males with XXY karyotype or with somatic mosaicism. *MECP2* is thought to mediate

transcriptional silencing of methylated DNA. Most mutations are probably de novo or may reflect germline mosaicism; 99% of cases represent a single occurrence within a family. Affected girls are usually normal at birth and have apparently normal development for the first 6 to 18 months of life. Brain growth decelerates, and development stagnates, followed by rapid regression of language and motor skills. A classic feature of Rett's syndrome is the loss of purposeful hand use and the development of repetitive stereotyped hand movements that usually have the appearance of wringing or clapping. Other features present to variable degree are bruxism, episodic apnea and hyperpnea, seizures, gait disorders, and tremor. Non-neurologic features include growth failure and wasting, bowel dysmotility, scoliosis, osteopenia, and vasomotor changes in the limbs. Diagnosis is by molecular genetic methods. Treatment is symptomatic.

Autism

Autism is a neurodevelopmental syndrome characterized by impaired communication, impaired social interaction, and restricted interests or repetitive behaviors. Fragile X syndrome and tuberous sclerosis are two important entities in which an autistic phenotype can occur and in which autism may be the most prominent feature. Symptoms typically present before 3 years of age and persist into adulthood. Autism is a spectrum ranging from severe, with impairment in all domains, to mild with normal intellect and language but with impaired social interactions and repetitive behaviors or restricted interests. Autism has many causes but in most cases is idiopathic. Epilepsy is common in autism. Diagnosis is based on careful diagnostic interview and examination. When epilepsy is present, treatment with antiepileptic medications is indicated. Behavioral therapy can help individuals learn rules for social interaction and can improve communication. It can also help with problematic behavior. Educational support is important. Medications such as atypical antipsychotics, selective serotonin reuptake inhibitors, and anxiolytics (Chapter 404) can help with aggressive behavior, repetitive behaviors, and anxiety.

NEUROCUTANEOUS DISORDERS

Neurocutaneous disorders are congenital syndromes characterized by dysplastic and neoplastic lesions primarily involving the nervous system and skin. The more than 40 described syndromes include neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, and von Hippel-Lindau disease.

Neurofibromatosis

Neurofibromatosis encompasses a spectrum of syndromes with distinctive neural and cutaneous lesions. The two major forms of neurofibromatosis are genetically and clinically distinct.

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1, which is the classic disorder described by von Recklinghausen, is an autosomal dominant condition with an incidence of 1 per 2500 to 3000 births. Although it is an autosomal dominant disease, approximately 50% of cases are due to new mutations. Most mutations in *NF1* occur in the parental germline. The *NF1* gene, which is located on chromosome 17q11.2, codes a protein called neurofibromin, which is thought to function as a tumor suppressor by acting as a negative regulator of the Ras signaling pathway. Neurofibromatosis type 1 is characterized by multiple cafe au lait spots, axillary and inguinal freckling, multiple discrete cutaneous neurofibromas (Fig. 426-2), and Lisch nodules (Table 426-1). Subcutaneous neurofibromas may be painful or disfiguring. Learning disabilities are present in at least 50% of individuals. Other manifestations include plexiform neurofibromas, optic nerve and other central nervous system (CNS) gliomas, malignant peripheral nerve sheath tumors, tibial dysplasia, and vasculopathy.

Management of patients depends on the specific manifestations and often requires multidisciplinary collaboration. Most patients with neurofibromatosis type 1 do not require treatment, but all require surveillance (Table 426-2). Subcutaneous, intraspinal, and intracranial tumors can be treated surgically. Optic nerve gliomas may be treated with chemotherapy; both cisplatin and temozolomide have shown some benefit. Radiation is not recommended. Genetic counseling should be provided to all patients and their families.

NEUROFIBROMATOSIS TYPE 2

Neurofibromatosis type 2, which is often referred to as central neurofibromatosis, is an autosomal dominant condition with an incidence of approximately 1 in 25,000 individuals. The *NF2* gene is located on chromosome 22q12.2. Its gene product, merlin, is cytoskeletal protein that is thought to act as a membrane-stabilizing protein. The specific function of merlin is unknown. Neurofibromatosis type 2 is characterized by bilateral vestibular schwannomas, which usually present with symptoms of tinnitus, hearing loss, and imbalance. The age at onset is usually in young adulthood, but some individuals may develop posterior subcapsular lens opacities or mono-neuropathy in childhood. Almost all affected individuals develop bilateral vestibular schwannomas by age 30 years (Table 426-3). Affected individuals may also develop schwannomas of other cranial and peripheral nerves, meningiomas, and, rarely, ependymomas or astrocytomas. Posterior subcapsular lens opacities are the most common ocular abnormality.

Management is dependent on the specific manifestations and complications. In individuals who either have tested positive for known *NF2* mutations or have a family history of neurofibromatosis type 2 and whose genetic status cannot be determined with genetic testing, annual brain MRI is recommended starting between ages 10 and 12 years and continuing until at least age 40 years. Hearing evaluations may be useful in detecting changes in auditory nerve function before changes can be visualized by MRI. Routine complete eye examinations should be part of the care of all individuals.

Bevacizumab, a vascular endothelial growth factor inhibitor (5 mg/kg intravenously every 2 weeks), can improve hearing in some patients with neurofibromatosis type 2 and vestibular schwannomas. Surgical treatment of schwannomas and meningiomas may be indicated to preserve function or to relieve compression of adjacent structures, especially in patients with intramedullary spinal tumors. Genetic counseling should be provided to affected individuals and their families.

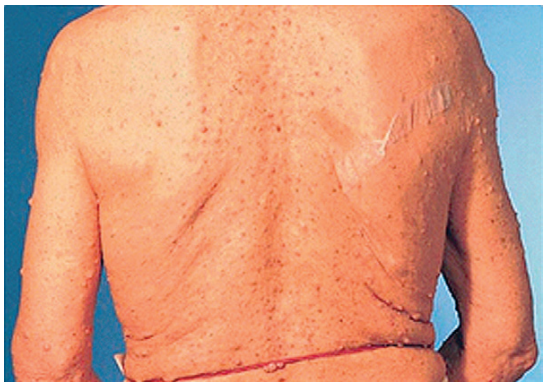


FIGURE 426-2. Multiple neurofibromas covering the back of a patient with neurofibromatosis type 1.

TABLE 426-1 DIAGNOSTIC CRITERIA FOR NEUROFIBROMATOSIS TYPE 1

Two or more of the following clinical features signify the presence of neurofibromatosis type 1:
Six or more cafe au lait macules (>0.5 cm at largest diameter in prepubertal individuals or >1.5 cm in individuals past puberty)
Axillary freckling or freckling in inguinal regions
Two or more neurofibromas of any type or ≥1 plexiform neurofibroma
Two or more Lisch nodules (iris hamartomas)
A distinctive osseous lesion
A first-degree relative with neurofibromatosis type 1 diagnosed by using the above-listed criteria

TABLE 426-2 RECOMMENDED SURVEILLANCE IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 1

Annual physical examination by a physician who is familiar with the individual and with the disease
Annual ophthalmologic examination in early childhood, less frequent examination in older children and adults
Regular developmental assessment by screening questionnaire (in childhood)
Regular blood pressure monitoring
Other studies only as indicated on the basis of clinically apparent signs or symptoms
Monitoring of those who have abnormalities of the central nervous system, skeletal system, or cardiovascular system by an appropriate specialist

TABLE 426-3 DIAGNOSTIC CRITERIA FOR NEUROFIBROMATOSIS TYPE 2

Presence of one or more of the following makes the diagnosis of neurofibromatosis type 2:

- Bilateral vestibular schwannomas
- A first-degree relative with neurofibromatosis type 2, *and*
  - Unilateral vestibular schwannoma, *or*
  - Any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities*
- Unilateral vestibular schwannoma, *and*
  - Any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities*
- Multiple meningiomas, *and*
  - Unilateral vestibular schwannoma, *or*
  - Any two of: schwannoma, glioma, neurofibroma, cataract*

*"Any two of" refers to two individual tumors or cataracts.

TABLE 426-4 DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX

Definite—Two major features or one major feature plus two minor features
Probable—One major feature plus one minor feature
Possible—One major feature or two or more minor features

Major features
- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual fibromas
- More than three hypomelanotic macules (ash leaf spots)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor features
- Multiple dental enamel pits
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts

Tuberous Sclerosis

Tuberous sclerosis complex is characterized by abnormalities of the brain, kidney, and heart. Tuberous sclerosis may occur as an autosomal dominant syndrome or result from spontaneous mutation. Two tuberous sclerosis genes have been identified. *TSC1* (chromosome 9q34) codes for a protein called hamartin, a protein that interacts with the product of the *TSC2* gene to inhibit the mammalian target of rapamycin (mTOR). *TSC2* (chromosome 16p13) codes for tuberin, which interacts with hamartin. *TSC2* mutations account for about 60% of individuals with clinical tuberous sclerosis.

The specific findings vary across individuals, and severity ranges from minimal to severe. Skin lesions are seen in almost 100% of affected individuals, but CNS lesions are the leading cause of morbidity and mortality. Epilepsy is seen in as many as 80% of patients with CNS lesions. Intellectual impairment and developmental delay are common, and up to 40% of patients have an autism spectrum disorder. Giant cell astrocytoma is the leading cause of death. Up to 80% of children with tuberous sclerosis have an identifiable renal lesion (Chapter 203) by 10.5 years of age, and renal disease is the second leading cause of early death in individuals with tuberous sclerosis. Cardiac rhabdomyomas, which can occur in up to 50% of patients, are usually present at birth and typically regress over time. Diagnosis of tuberous sclerosis (Table 426-4) is usually clinical and confirmed by identification of calcified or uncalcified hamartomas on imaging studies (Fig. 426-3).

Treatment is directed at complications of the disease, particularly epilepsy (Chapter 410). Neurosurgical intervention may sometimes be indicated for epilepsy and for symptomatic treatment of complications, such as hydrocephalus, which results from midline giant cell tumors. In a small, nonrandomized study, treatment with sirolimus (dosed to achieve blood levels of 1 to 5 ng/mL) for 1 year reduced the size of the angiomyolipomas during the year of treatment. Rapamycin has shown promise in early investigations for treatment of giant cell astrocytomas. Serial brain MRI and renal ultrasound screening may be indicated in some patients because benign tumors of these organs may enlarge rapidly. Genetic counseling is an important part of management.

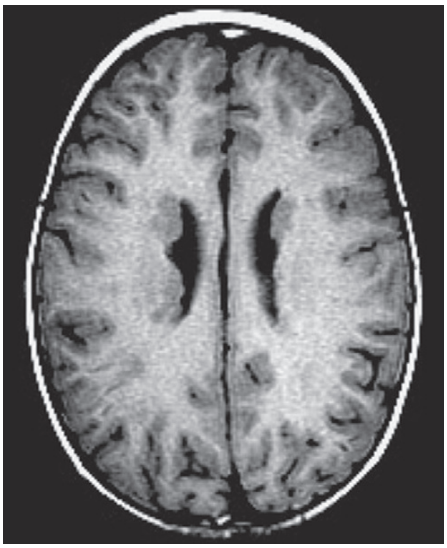


FIGURE 426-3. Subependymal nodules and multiple cortical tubers in a patient with tuberous sclerosis.

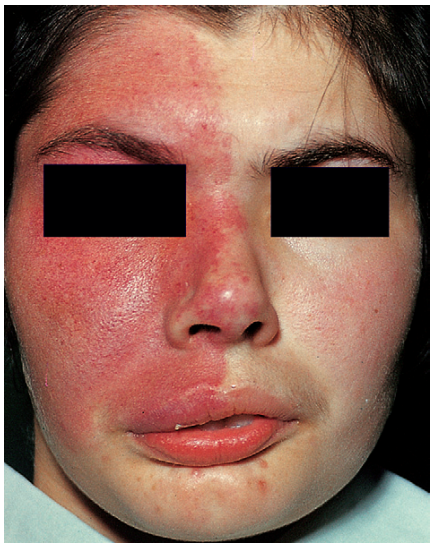


FIGURE 426-4. Sturge-Weber syndrome. This patient has a classic diffuse capillary hemangioma in the distribution of the ophthalmic, nasociliary, and maxillary branches of the trigeminal nerve. The lesion extends backward over the anterior two thirds of the crown of the head. (From Forbes CD, Jackson WD. *Color Atlas and Text of Clinical Medicine*, 2nd ed. London: Mosby; 1996.)

Sturge-Weber Syndrome

Sturge-Weber syndrome is a sporadic disorder characterized by facial vascular nevi, epilepsy, cognitive impairment, and sometimes hemiparesis, hemianopsia, or glaucoma. The characteristic CNS feature of this disorder is capillary angiomatosis of the pia mater. Cerebral cortical calcifications are generally seen in a pericapillary distribution and are progressive. Most patients with Sturge-Weber syndrome have epilepsy. The diagnosis is usually based on the presence of a facial nevus (Fig. 426-4), which is manifested as a typical port-wine stain, and confirmatory imaging on a contrast brain MRI showing leptomeningeal enhancement.

Regular ophthalmologic examination is warranted because of the risk for glaucoma. Treatment is usually aimed at the epilepsy, which can be medically

intractable. In patients with intractable epilepsy and infantile-onset hemiplegia, hemispherectomy can improve the seizures and the neurodevelopmental outcome.

Von Hippel-Lindau Disease

Von Hippel-Lindau disease (i.e., CNS angiomatosis) is an autosomal dominant disorder caused by a defective tumor suppressor gene at chromosome 3p25-p26. It is characterized by retinal angiomas, brain (usually cerebellar) and spinal cord hemangioblastomas, renal cell carcinomas, endolymphatic sac tumors, pheochromocytomas, papillary cystadenomas of the epididymis, angiomas of the liver and kidney, and cysts of the pancreas, kidney, liver, and epididymis. Both sexes are affected equally.

Symptoms typically begin during the third or fourth decade. Retinal inflammation with exudate, hemorrhage, and retinal detachment from the retinal angiomas typically precedes the cerebellar complaints, but the order is not constant. The ocular findings are nonspecific, and the retinal detachment may mask the underlying lesion. Headache, vertigo, and vomiting result from cerebellar tumors. Cerebellar signs such as ataxia, dysdiadochokinesis, and dysmetria are common. Rare patients present with symptoms of spinal cord or visceral lesions, or may have hearing loss from tumors of the endolymphatic sac.

Clinical diagnosis is established if the patient has more than one CNS hemangioblastoma, one hemangioblastoma with a visceral manifestation of the disease, or one manifestation of the disease and a known family history. Molecular genetic testing detects mutations in the *VHL* gene in nearly 100% of affected individuals.

For patients with von Hippel-Lindau disease and for those with a disease-causing VHL mutation, surveillance is recommended with annual ophthalmologic examination, annual blood pressure monitoring, measurement of urinary catecholamine metabolites beginning at age 5 years in families with pheochromocytoma, and annual abdominal ultrasound examination beginning at age 16 years with evaluation of suspicious lesions by computed tomography or MRI. Treatment is symptomatic. Retinal detachments and tumors are treated by laser therapy. Large brain tumors (Chapter 195), renal cell carcinomas (Chapter 203), pheochromocytomas (Chapter 235), epididymal tumors (Chapter 206), and endolymphatic sac tumors are treated surgically; smaller CNS tumors may be treated by gamma knife.

1. Plotkin SR, Stemmer-Rachamimov AO, Barker FG 2nd, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. *N Engl J Med*. 2009;361:358-367.

SUGGESTED READINGS

Evans GR, Lloyd SK, Ramsden RT. Neurofibromatosis type 2. *Adv Otorhinolaryngol*. 2011;70:91-98. *Review emphasizing the role of surgery*.

Ferner RE. The neurofibromatoses. *Pract Neurol*. 2010;10:82-93. *Review*.

Krueger DA, Care MM, Holland K, et al. Everolimus for subependymal giant-call astrocytomas in tuberous sclerosis. *N Eng J Med*. 2010;363:1801-1811. *In a nonrandomized study, oral everolimus decreased the volume of subependymal giant-cell astrocytomas and the frequency of seizures in patients with tuberous sclerosis*.

Nordstrom-O'Brien M, van der Luijt RB, van Rooijen E, et al. Genetic analysis of von Hippel-Lindau disease. *Hum Mutat*. 2010;31:521-537. *Review of mutations and their clinical manifestations*.

427

AUTONOMIC DISORDERS AND THEIR MANAGEMENT

WILLIAM P. CHESHIRE, JR.

The peripheral autonomic nervous system and the central integration of autonomic reflexes maintain homeostasis and modulate the complex physiologic responses at the interface between the internal milieu and the external world. Autonomic activity, which generally occurs below the level of conscious control, regulates cardiovascular, thermal, metabolic, gastrointestinal, urinary, and reproductive functions and coordinates the adaptive response to stress.

Many diseases can involve the autonomic nervous system, which in turn can involve all organ systems. Examples include brain lesions that affect any part of the central autonomic network, disorders that damage peripheral nerve function, and systemic illnesses that impair autonomic responses.

EPIDEMIOLOGY

The most frequently disabling manifestation of autonomic failure is orthostatic hypotension, which increases in prevalence with aging and is associated with a two-fold increased risk for falls, fractures, syncope, transient ischemic attacks, and decreased functional capacity in elderly individuals. The prevalence of orthostatic hypotension is 5 to 20% among all elderly persons, but it rises to 30% in persons older than 75 years and to greater than 50% in frail individuals who live in nursing homes. Neurally mediated syncope (vasodepressor, vasovagal), as well as various situational syncopes that occur in response to emotional distress, micturition, defecation, coughing, carotid sinus stimulation, and other factors, accounts for 1 to 3% of all emergency room visits. The lifetime prevalence of syncope is about 20%. Another common autonomic syndrome is postprandial hypotension, which occurs in 20 to 60% of elderly individuals and increases the risk for mortality by 80%.

Diabetes mellitus (Chapter 236) is the most common cause of autonomic neuropathy in the developed world. Within 10 to 15 years of the onset of diabetes, laboratory evidence of autonomic neuropathy can be detected in about 30% of patients, and symptomatic autonomic failure with orthostatic hypotension can be detected in about 5% of patients. Other autonomic symptoms in diabetics include constipation in 40 to 60% of patients, gastroparesis in 20 to 40%, bladder dysfunction in 30 to 80%, erectile impotence in more than 30% of males, and occasionally, intermittent diarrhea.

Hyperhidrosis involving the palms and soles represents the most common form of essential hyperhidrosis and affects about 1% of the population. Although excessive sweating is usually symptomatic, anhidrosis may go unnoticed unless it interferes with the thermoregulatory response to heat stress. Impaired thermoregulation can cause increased mortality rates during heat waves or in times of heat stress (Chapter 109).

PATHOBIOLOGY

The peripheral autonomic nervous system comprises three main divisions: (1) *sympathetic*, or outflow from the thoracolumbar segments of the spinal cord; (2) *parasympathetic*, or outflow from cranial nerves III, VII, IX, and X and from the sacral spinal segments; and (3) *enteric*, or the ganglionated plexuses intrinsic to the wall of the gut. Disorders of the autonomic nervous system may occur suddenly or evolve gradually. They may affect specific or multiple autonomic pathways depending on their pathogenesis and localization. Orthostatic hypotension, a hallmark of autonomic disorders, results from sympathetic vasomotor denervation, which renders a standing patient unable to constrict the splanchnic and other peripheral vascular beds in response to the pooling of blood volume (500 to 1000 mL) secondary to gravity.

Physiologic effects of sympathetic activation include pupillary dilation, increased heart rate and contractility, increased peripheral vascular resistance, bronchodilation, increased glandular secretions, decreased gastrointestinal motility, increased sweating, decreased function of reproductive organs, and mobilization of energy substrates. The effects of parasympathetic activation include pupillary constriction, lacrimal and salivary secretion, decreased heart rate and contractility, bronchoconstriction, increased gastrointestinal motility, and contraction of the detrusor muscle of the bladder. Sympathetic and parasympathetic responses, though generally antagonistic, are not always equally counterbalanced.

Sympathetic preganglionic neurons, which use acetylcholine as their primary neurotransmitter, originate in the segmentally organized intermediolateral column of the spinal cord and exit via the ventral roots to pass through the white rami communicans and reach the paravertebral sympathetic chain ganglia, which innervate all organs and tissues except those of the abdomen and pelvis. The superior cervical ganglion, for example, innervates cranial structures, and the stellate ganglion innervates the upper limb. Sympathetic preganglionic axons also form the splanchnic nerves, which innervate the celiac, superior mesenteric, and hypogastric ganglia, as well as the adrenal medulla. With the exception of neurons that innervate the sweat glands, which are cholinergic, all other sympathetic postganglionic neurons are adrenergic and use norepinephrine as their primary transmitter.

Preganglionic innervation of parasympathetic neurons is also cholinergic; however, in contrast to their sympathetic counterparts, the major postganglionic parasympathetic neurotransmitter is acetylcholine. Parasympathetic preganglionic fibers originate in the Edinger-Westphal, salivatory, and vagal dorsal motor nuclei in the brain stem. The ciliary, sphenopalatine, otic, submandibular, sublingual, and pelvic ganglia send postganglionic parasympathetic fibers to their target organs. Cranial nerves IX and X, which constitute the afferent limbs of the baroreceptor reflex, relay beat-to-beat information about systemic arterial pressure to the nucleus of the solitary tract.

The gastrointestinal tract contains neural plexuses, the most prominent of which are the myenteric (Auerbach) plexus found between the two layers of the muscularis externa and the submucosal (Meissner) plexus. Disorders of the enteric nervous system mainly affect gastrointestinal motility or sphincter control rather than absorptive or secretory functions.

BRAIN DISORDERS

Important disease targets involved in central autonomic regulation include the interrelated neuronal cell groups of the hypothalamus, as well as the ventrolateral medulla, nucleus of the solitary tract, parabrachial nucleus, periaqueductal gray matter, amygdala, and insular and prefrontal cortices. Together, these relay systems and integrative centers compose the central autonomic network, which when impaired, fails to activate or modulate sympathetic and parasympathetic tone and neurohumoral responses.

A number of neurodegenerative disorders disrupt the central pathways of autonomic regulation. The most severe form is multiple system atrophy, a sporadic, adult-onset disease in which severe autonomic failure accompanies and occasionally precedes parkinsonism (Shy-Drager syndrome; Chapter 416) or cerebellar ataxia (Chapter 417). In multiple system atrophy, there is degeneration of the striatum, pigmented nuclei, pontine nuclei, inferior olives, cerebellar Purkinje cells, and dorsal vagal and vestibular nuclei. Autonomic dysfunction also occurs in dementia with Lewy bodies (Chapter 409) and, to a lesser degree, in Parkinson's disease, both of which also involve abnormal neuronal accumulation of α-synuclein.

Essential to the integration of behavioral, autonomic, and neuroendocrine responses is the tightly packed, interwoven group of cells that constitute the hypothalamus. Lesions of the anterior hypothalamus may alter thirst perception and sodium regulation. Dysfunction of the magnocellular arginine vasopressin neurons of the supraoptic and supraventricular nuclei can be manifested as decreased secretion of antidiuretic hormone, thereby resulting in diabetes insipidus (Chapter 232) with hypovolemia, or as inappropriately increased secretion of antidiuretic hormone, thereby resulting in hyponatremia. Medial preoptic–anterior hypothalamic dysfunction associated with dysgenesis of the corpus callosum (Shapiro's syndrome) is characterized by episodic hyperhidrosis and hypothermia. Lesions of the posterior hypothalamus can result from hypothermia, Wernicke-Korsakoff syndrome (Chapter 425), acute traumatic brain injury (Chapter 406), multiple sclerosis (Chapter 419), mesodiencephalic hematoma, and toluene toxicity.

Catastrophic neurologic conditions such as subarachnoid hemorrhage, head trauma, status epilepticus, and acute hydrocephalus with increased intracranial pressure can profoundly stimulate sympathetic responses with cardiovascular consequence. Release of the hypothalamus as a result of cortical inhibition is the presumed mechanism. These paroxysmal sympathetic storms (diencephalic syndrome) are characterized by episodic sympathetic hyperactivity with hypertension, tachycardia, hyperventilation, pupillary dilation, flushing, and diaphoresis. Communicating hydrocephalus, structural lesions affecting the medial frontal cortex, and degenerative conditions affecting the frontobasal ganglia can cause urinary incontinence with uninhibited bladder contractions.

Autonomic responses are closely linked to emotional states. Portions of the insular and anterior cingulate cortices mediate the autonomic responses to emotional stress. Because cardioregulatory function is represented within the insular cortex, insular strokes have been associated with destabilization of sympathoregulatory balance and occasional adverse cardiac events. Correlations of electroencephalography and electrocardiography have shown that seizures arising from the mesial temporal lobe may induce ictal tachycardia or, more rarely, bradycardia or asystole.

Lesions of the brain stem may also be manifested as autonomic dysfunction. Damage to the medulla oblongata may give rise to hypertension, orthostatic hypotension, or syncope. Medullary ischemia or compression can cause acute neurogenic hypertension (Cushing's response). Lateral medullary infarction (Wallenberg's syndrome) typically produces ipsilateral Horner's syndrome and occasionally more extensive dysautonomia, including bradycardia, acute hypertension, supine hypotension, or central hypoventilation.

TABLE 427-1 SOME CAUSES OF PERIPHERAL AUTONOMIC NEUROPATHY

Metabolic	Diabetes mellitus Alcohol Acute intermittent porphyria Uremia
Autoimmune	Autoimmune autonomic ganglionopathy Guillain-Barré syndrome Morvan's syndrome Lambert-Eaton myasthenic syndrome Chronic inflammatory demyelinating polyradiculoneuropathy Sjögren's syndrome Systemic lupus erythematosus Mixed connective tissue diseases
Paraproteinemic	Amyloidosis
Nutritional	Cyanocobalamin deficiency Thiamine deficiency Gluten-sensitive neuropathy
Toxic	Heavy metals Organic solvents Organophosphates Vacor Acrylamide
Drug induced	Cisplatin Vincristine Amiodarone Metronidazole Perhexiline Paclitaxel
Infectious	Human immunodeficiency virus Leprosy Chagas' disease Botulism Diphtheria Lyme disease
Genetic	Hereditary sensory and autonomic neuropathies Types I and II Type III (familial dysautonomia) Type IV (congenital insensitivity to pain) Type V Fabry's disease
Idiopathic	Adie's syndrome Ross' syndrome Acute cholinergic neuropathy Chronic idiopathic anhidrosis Amyotrophic lateral sclerosis

SPINAL CORD DISORDERS

Lesions of the spinal cord, whether compressive, demyelinating, vascular, or neoplastic, commonly result in an overactive bladder (Chapter 25) with symptoms of frequency, urgency, and sometimes incontinence. Lesions that involve the sacral cord segments or cauda equina result in an underactive bladder with incomplete emptying, overflow incontinence, sphincter atonia, and sexual dysfunction.

After spinal cord injuries above the level of T5, sprouting of afferent fibers in the thoracolumbar dorsal horns and necrosis of the descending white matter connections to sympathetic preganglionic neurons result in autonomic dysreflexia. In these patients, peripheral sensory stimuli such as bladder distention can induce a reversible state of sympathetic hyperresponsiveness, including hypertension, diaphoresis, flushing, and headache.

PERIPHERAL GANGLIONOPATHIES AND NEUROPATHIES

Autonomic dysfunction can arise at the level of the autonomic ganglia or peripheral nerves (Table 427-1). Peripheral autonomic nerves are generally small in caliber and unmyelinated or thinly myelinated. Peripheral neuropathies selectively involve small nerve fibers and cause various combinations of sensory, sympathetic, or parasympathetic signs and symptoms.

TABLE 427-2 AUTOIMMUNE AUTONOMIC NEUROPATHIES

CLINICAL SYNDROME	ASSOCIATED AUTOANTIBODY
Autoimmune autonomic ganglionopathy	Anti-GAChR
Guillain-Barré syndrome	Anti-GM_1, anti-GM_3
Paraneoplastic autonomic neuropathy	ANNA-1 (anti-Hu), PCA-2, CRMP-5
Lambert-Eaton myasthenic syndrome	Anti-VGCC
Morvan's syndrome	Anti-VGKC
Sjögren's syndrome	SSA (anti-Ro), SSB (anti-La)

ANNA-1 = antineuronal nuclear antibody; anti-GAChR = nicotinic ganglionic acetylcholine receptor antibody; anti-GM_1, anti-GM_3 = antiganglioside antibody; anti-VGCC = P/Q-type voltage-gated calcium-channel antibody; anti-VGKC = voltage-gated potassium-channel antibody; CRMP-5 = collapsin response mediator protein 5; PCA-2 = Purkinje cell cytoplasmic antibody type 2.

Among the peripheral dysautonomias is the syndrome of pure autonomic failure, which is defined as the insidious onset of severe, generalized autonomic failure as the sole clinical feature in the absence of any signs of extrapyramidal, cerebellar, or sensory or motor peripheral nerve dysfunction. Pathologic studies have found Lewy body accumulation in autonomic ganglia, peripheral autonomic nerves, the substantia nigra, and the locus ceruleus.

Diabetic neuropathy involves autonomic nerves early in its course but advances to clinically apparent autonomic neuropathy only in about 14% of patients. The incidence increases with the duration of diabetes and advancing age. In diabetic patients, microvascular ischemia causes progressive peripheral nerve damage, although an autoimmune mechanism may also play a role in a subset of patients. Some patients with otherwise unexplained distal small fiber autonomic neuropathy have impaired fasting glucose. Whether this association reflects an early stage of diabetic neuropathy or a chance association, given the prevalence of glucose intolerance, remains to be determined.

Other syndromes of neurologic autoimmunity (Table 427-2) include Guillain-Barré syndrome, in which antiganglioside antibodies mediate an acute inflammatory demyelinating polyradiculoneuropathy that may be associated with tachycardia, blood pressure lability, and pupillomotor, sudomotor, and vasomotor disturbances (Chapter 428). The syndrome of acute pandysautonomia is typically manifested dramatically over a period of days to weeks as combined sympathetic and parasympathetic failure with gastrointestinal dysmotility and, in contrast to Guillain-Barré syndrome, sparing of the somatic nerves. An antecedent, presumably viral infection is reported in about 50% of cases. The finding of antibodies against the nicotinic acetylcholine receptor in the autonomic ganglia in many of these patients has led to the clinical designation autoimmune autonomic ganglionopathy. Ganglionic acetylcholine receptor antibodies occur in some patients with lung cancer or thymoma. Low levels of these antibodies have also been found in a subset of patients with isolated gastrointestinal dysmotility.

Autoimmune neuromyotonia is characterized by peripheral nerve hyperexcitability, insomnia, fluctuating delirium, and prominent dysautonomia with hyperhidrosis and orthostatic intolerance. Most patients have antibodies to voltage-gated potassium channels.

Paraneoplastic autonomic neuropathies (Chapter 187), which can predate the diagnosis of malignancy, are a rare epiphenomenon of malignancy, most frequently small cell lung carcinoma (Chapter 197), and can also occur in association with ovarian carcinoma (Chapter 205), breast carcinoma (Chapter 204), thymoma, lymphoma (Chapter 191), and other cancers. The most commonly encountered paraneoplastic antibody is antineuronal nuclear antibody type 1 (ANNA-1 or anti-Hu), which binds to a 35- to 40-kD family of neuronal nuclear RNA-binding proteins, including those in autonomic and enteric ganglia. Antibodies against collapsing response mediator proteins (CRMP-5 or anti-CV2) have also been associated with paraneoplastic autonomic neuropathy. Dysautonomia occurs in approximately 10 to 30% of patients with ANNA-1 and in 30% of patients with CRMP-5 seropositivity. Small cell lung cancer (Chapter 197) has been found in more than 80% of patients seropositive for ANNA-1 or CRMP-5.

Hereditary sensory and autonomic neuropathy (HSAN) type I, which is due to a mutation of the gene for serine palmitoyltransferase long-chain base subunit 1, is inherited in an autosomal dominant pattern and is characterized by distal anhidrosis with loss of nociceptive and thermal perception. Mutations in *HSN2* have been linked to HSAN type II, an autosomal recessive neuropathy that causes distal anhidrosis and sensory loss. Sural nerve biopsy specimens disclose virtual absence of myelinated fibers and decreased numbers of unmyelinated fibers. Autonomic involvement is most prominent in HSAN type III, commonly known as familial dysautonomia, or Riley-Day syndrome. This autosomal recessive disorder, which affects 1 in 3600 live births in parents of Ashkenazi Jewish descent, has been linked to mutations in the I-κB kinase–associated protein gene (*IKBKAP*). Pathologic studies disclose severely depleted sympathetic preganglionic and postganglionic neuronal populations with preservation of parasympathetic neurons. Affected children cry without tears, feed poorly, lack fungiform papillae, have depressed patellar reflexes, and are subject to orthostatic hypotension and autonomic storms.

HSAN type IV, or congenital insensitivity to pain with anhidrosis, is an autosomal recessive disorder that is associated with mental retardation and repeated episodes of fever. HSAN type IV results from mutations in the gene for neurotrophic tyrosine kinase receptor type 1 (*NTRK1*), which is important for inducing neurite outgrowth in embryonic sensory and sympathetic neurons. Peripheral nerve biopsy discloses virtual absence of unmyelinated fibers.

HSAN type V is an autosomal recessive disorder characterized by loss of pain sensation and sudomotor abnormalities.

The age-related decline in baroreflex sensitivity, adrenergic responses to sympathetic activation, parasympathetic control of heart rate, esophageal and gastrointestinal motility, and efficient thermoregulation predisposes the elderly to orthostatic, postprandial, and drug-induced hypotension. Pheochromocytomas (Chapter 235) and carcinoid syndrome (Chapter 240) can also be accompanied by autonomic symptoms, including blood pressure lability.

CLINICAL MANIFESTATIONS

Several common patterns of autonomic dysfunction may be distinguished.

Generalized Autonomic Failure

Early symptoms of adrenergic failure typically include lightheadedness on arising in the morning or following a warm shower, physical exercise, or a large meal. Other common symptoms include male erectile dysfunction, decreased sweating, dry mouth, constipation, and bladder dysfunction. Severe orthostatic hypotension without pulse acceleration, which is the hallmark of severe generalized autonomic failure, may be accompanied by supine and nocturnal hypertension, thus reversing the normal diurnal decrease in blood pressure during sleep.

Acute Autonomic Syndromes

Acute or subacute manifestations of autonomic dysfunction may result from rapidly developing disease or from decompensation of chronic autonomic disease. An abrupt onset of new focal autonomic signs, particularly when accompanied by headache or motor or sensory deficits, should prompt a detailed neurologic assessment for an acute cerebral or spinal syndrome, which may be caused by vascular, traumatic, inflammatory, neoplastic, or infectious diseases.

Chronic Autonomic Syndromes

The clinical spectrum of chronic autonomic neuropathies includes distal small fiber neuropathies with a stocking-and-glove distribution of anhidrosis, often combined with loss of pain and temperature sensibility. Other patients may have orthostatic hypotension and impaired exercise tolerance, with either an increased resting heart rate because of a parasympathetic cardiovagal neuropathy or a fixed heart rate that does not increase adequately in response to physiologic demands as a result of the involvement of sympathetic fibers. Some patients with distal sudomotor neuropathy will complain of spontaneous or gustatory proximal hyperhidrosis with episodic sweating involving the face, head, and upper part of the trunk.

Gastroparesis, which is a common feature of autonomic neuropathies, is characterized by delayed gastric emptying, which may be manifested as early satiety, nausea, anorexia, bloating, and sometimes pain and weight loss. Intestinal dysmotility may cause severe constipation (Chapter 138). In advanced peripheral neuropathies, in ganglionopathies in which involvement is not length dependent, and in central degenerative disorders, the loss of sweating may extend to proximal body regions or globally. Widespread anhidrosis may result in impaired thermoregulatory sweating and the potential for hyperthermia in conditions of heat stress (Chapter 109).

Paroxysmal Dysautonomias

Paroxysmal and episodic autonomic symptoms include postprandial hypotension, which is a reduction in systolic blood pressure of at least 20 mm Hg within 2 hours of the start of a meal, typically one high in carbohydrate content. Postprandial hypotension may occur in elderly individuals with or without orthostatic hypotension.

Dysfunction of the afferent limb of the baroreflex system leads to volatile blood pressure in patients with acute inflammatory demyelinating polyneuropathy and syndromes of baroreflex failure. Additional causes of aberrant activation of autonomic reflexes include epilepsy, diencephalic syndrome, subarachnoid hemorrhage, acute head trauma, pheochromocytoma, intoxication, drug withdrawal, neurally mediated syncope, and panic disorder.

Selective Autonomic Syndromes

Regional autonomic disorders are characterized by focal or system-selective autonomic dysfunction. An example is harlequin syndrome, in which heat stress, exercise, or sudden emotion in a patient with hemifacial cutaneous sympathetic denervation evokes a dramatic facial division in which the denervated half remains pale and dry and the intact half flushes red. Oculosympathetic paresis or Horner's syndrome may also be present. Harlequin syndrome may occur in patients with Holmes-Adie syndrome, which consists of tonic pupils with asymmetrical or absent tendon reflexes, and has been described in patients with Ross' syndrome, a partial dysautonomia consisting of the clinical triad of unilateral or bilateral tonic pupils, tendon hyporeflexia, and segmental body anhidrosis.

Other Specific Syndromes

Baroreflex failure is commonly the result of damage to the carotid sinus baroreceptors or the glossopharyngeal nerves. Similarly, interruption of vagal input from the aortic arch baroreceptors to the nucleus of the solitary tract can impair baroreflex responses. Baroreflex failure also occurs in patients who have undergone surgery or irradiation of the neck. These patients will exhibit severe and labile hypertension with concomitant tachycardia, palpitations, headache, diaphoresis, and emotional lability.

Serotonin syndrome develops within hours or days of the addition of a new serotonergic agent to a drug regimen that already enhances serotonergic neurotransmission, on overdose with a selective serotonin reuptake inhibitor, or from abuse of psychostimulants such as amphetamine, methamphetamine, and 3,4-methylenedioxymetamphetamine (MDMA or "ecstasy"). Manifestations include agitation, hypervigilance, confusion, hyperthermia, increased sweating, fluctuating blood pressure, hyperreflexia, and myoclonus.

Neuroleptic malignant syndrome (Chapters 440 and 442) is a potentially life-threatening hypermetabolic condition that develops within days to weeks in 0.2% of patients who receive drugs that block dopamine 2 receptors. The clinical findings consist of hyperthermia, profuse sweating, muscle rigidity, bradykinesia, and delirium. If the offending medication is not withheld, the syndrome may progress to tachycardia, tachypnea, labile blood pressure, myoclonus, obtundation, and catatonia.

Among the infectious neuropathies, tetanus infection (Chapter 304) causes sympathetic overactivity in a third of patients because of the exotoxin tetanospasmin, which is taken up by peripheral nerve terminals and transported across synaptic junctions to reach the central nervous system. There it binds to gangliosides at presynaptic junctions to disinhibit preganglionic neurons and damages autonomic brain stem nuclei. Sympathetic hyperactivity results in labile or persistent hypertension or hypotension, tachyarrhythmias, peripheral vasoconstriction, fever, and profuse sweating. Diphtheritic neuropathy (Chapter 300) causes bulbar weakness and may be associated with cardiovagal impairment but not usually with orthostatic hypotension.

The acute cholinergic neuropathy of botulism (Chapter 304) occurs along with bulbar and generalized neuromuscular paralysis 12 to 36 hours after the ingestion of food contaminated with the gram-positive anaerobic bacterium *Clostridium botulinum*. Botulinum toxin binds with high affinity to presynaptic receptors of cholinergic nerve terminals and inhibits the release of acetylcholine, thereby blocking neuromuscular and cholinergic autonomic transmission. Autonomic manifestations include anhidrosis, dry eyes, dry mouth, paralytic ileus, gastric dilation, urinary retention, and sometimes orthostatic hypotension with fluctuating blood pressure and vasomotor tone.

Human immunodeficiency virus infection commonly causes autonomic disturbances, particularly in its advanced stages. Manifestations can include orthostatic hypotension, tachycardia, urinary dysfunction, impotency, diarrhea, and cardiac conduction defects. Perivascular mononuclear inflammatory infiltrates and neuronal degeneration in biopsy specimens of sympathetic ganglia suggest an autoimmune pathogenesis.

TABLE 427-3 SOME COMMONLY PRESCRIBED DRUGS THAT AFFECT SWEATING

Drugs that increase sweating
Opioids
Serotonin re-uptake inhibitors
Anticholinesterases
Cholinergic agonists
Drugs that decrease sweating
M_3 anticholinergics
Carbonic anhydrase inhibitors
Tricyclic antidepressants
Neuroleptics
Antihistamines
Central α-adrenergic agonists
Botulinum toxin

Chagas' disease (Chapter 355) causes a predominantly parasympathetic neuropathy characterized by megaesophagus, megaduodenum, and megacolon, as well as sympathetic cardiovascular failure with cardiomegaly and conduction defects. The autonomic neuropathy has an autoimmune basis and develops years to decades following primary infection with *Trypanosoma cruzi*.

Leprosy (Chapter 334), one of the most common causes of neuropathy worldwide, frequently causes peripheral autonomic neuropathy as a result of an immune reaction against *Mycobacterium leprae*. Focal anhidrosis occurs in areas of hypopigmented and hypoesthetic skin. Cardiac denervation and orthostatic hypotension have been described.

Toxins known to cause autonomic neuropathy include the rodenticide Vacor, as well as thallium, arsenic, mercury, acrylamide, and organic solvents such as carbon disulfide and hexacarbon. Organophosphate poisoning (Chapter 110) induces miosis and copious secretions. Ergot poisoning from rye contaminated with the fungus *Claviceps purpurea* results in intense vasoconstriction, paresthesia, seizures, and diarrhea. Poisoning with muscarine, which is present in certain poisonous mushrooms (Chapter 110), results in increased salivation, sweating, and lacrimation followed by nausea, abdominal pain, and diarrhea.

Medicinal drugs that may induce an autonomic peripheral neuropathy include cisplatin, vincristine, amiodarone, metronidazole, perhexiline maleate, and paclitaxel. Many drugs are capable of increasing or decreasing sweating (Table 427-3).

Nutritional deficiencies that lead to autonomic dysfunction include alcoholic neuropathy, which is a dying-back neuropathy identical to that of beriberi that is caused by thiamine deficiency (Chapter 425). Distal parts of the vagus nerve are affected early, and orthostatic hypotension may occur in more advanced stages. Subacute combined degeneration from vitamin B_{12} deficiency (Chapter 225) results in axonal degeneration and is occasionally manifested as orthostatic hypotension. Autonomic neuropathy has been described in some cases of celiac disease (Chapter 142).

Amyloidosis (Chapter 194) results from the focal deposition of insoluble fibrillary proteins arranged in β-pleated sheet configurations within the extracellular space of various tissues, which may include the vasculature of peripheral autonomic nerves and sympathetic ganglia. Amyloid neuropathy is typically manifested as a painful distal small fiber sensory and severe autonomic neuropathy. Autonomic dysfunction frequently occurs in primary AL, immunoglobulin light chain–associated disease, and hereditary amyloidosis, but only rarely in reactive or AA amyloidosis.

DIAGNOSIS

Clinical evaluation of autonomic dysfunction begins with a careful history. It is important to distinguish chronic and stable conditions from progressive and episodic phenomena and to recognize the circumstances that provoke or modify symptoms. Orthostatic hypotension, for example, is typically worse in the morning and may be aggravated by prolonged standing, physical exertion, heat, carbohydrate ingestion, or menstruation (Table 427-4).

Bedside Evaluation

The skin examination should assess turgor, pallor, flushing, and acral cyanosis, as well as any asymmetry of sweating, which may be more palpable than

TABLE 427-4 GRADING OF ORTHOSTATIC INTOLERANCE

	SYMPTOM FREQUENCY	ACTIVITIES OF DAILY LIVING IN THE UPRIGHT POSTURE	STANDING TIME (ON MOST OCCASIONS)	ORTHOSTATIC BLOOD PRESSURE
Grade I	Infrequent orthostatic symptoms developing only under conditions of increased stress*	Unrestricted	>15 min	May or may not be abnormal
Grade II	Intermittent orthostatic symptoms occurring at least weekly	Some limitation	>5 min	Some changes in cardiovascular indices, e.g., oscillations, or decrease in pulse pressure by >50%
Grade III	Frequent orthostatic symptoms occurring on most occasions	Marked limitation	>1 min	Orthostatic hypotension is present >50% of the time, recorded on different days
Grade IV	Orthostatic symptoms are consistently present	Incapacitated and unable to stand without presyncope or syncope developing	<1 min	Orthostatic hypotension is severe and consistently present

*Conditions that increase orthostatic stress include dehydration, deconditioning from prolonged bedrest, physical exertion, heat stress, and medications that lower blood pressure or impair adrenergic function.
Adapted from Low PA, Singer W. Update on management of neurogenic orthostatic hypotension. *Lancet Neurol.* 2008;7:451-458.

visible. Signs of pupillary asymmetry, ptosis, mucosal dryness, distal sensory or reflex changes, bradykinesia, or rigidity should be noted.

Blood pressure and heart rate should be measured with the patient supine and again after standing for 1 to 3 minutes and correlated with symptoms. Orthostatic hypotension is defined as a reduction in systolic blood pressure of at least 20 mm Hg or a reduction in diastolic blood pressure of at least 10 mm Hg, with or without symptoms, within 1 to 3 minutes of assuming an erect posture. Neurogenic orthostatic hypotension is typically sustained with continued standing. Measurements taken immediately on standing can be misleading because some healthy young persons without orthostatic hypotension will exhibit transient hypotension within 30 seconds of standing but then recover. Except in patients treated with β-blockers, orthostatic hypotension without reflex tachycardia is evidence of generalized adrenergic failure. If reflex tachycardia occurs, dehydration or excessive venous pooling should be considered.

Some patients with orthostatic intolerance experience an abnormal increase in heart rate rather than a drop in blood pressure on standing. Postural tachycardia syndrome is defined as an increase in heart rate by more than 30 beats per minute or to consistently greater than 120 beats per minute when standing.

Laboratory Evaluation

Laboratory testing depends on the type and distribution of autonomic dysfunction. Investigations may include a complete blood count, fasting glucose, electrolytes, morning cortisol, thyroid function testing, vitamin B_{12} level, and when appropriate, autoimmune markers. Creatine kinase should be checked in patients with hyperthermia.

In a patient with an autonomic neuropathy, seropositivity for any of the characterized paraneoplastic autoantibodies should prompt a careful search for an underlying malignancy, even if the results of routine imaging studies are normal. Positron emission tomography is more sensitive than computed tomography in detecting small tumor foci. In patients with suspected pheochromocytoma, the most sensitive screening test is the free metanephrine level (Chapter 235).

Pupillary responses to the instillation of dilute pilocarpine, epinephrine, and cocaine can assist in the localization of oculosympathetic and oculoparasympathetic deficits. Lacrimal secretion may be quantified by the Schirmer and rose bengal tests (Chapter 276). Sialography may be useful to quantify salivary flow. Salivary gland biopsy may be necessary to diagnose Sjögren's syndrome, particularly the seronegative form.

Manometry and scintigraphic studies are useful in the diagnosis of disorders of gastrointestinal motility. Urodynamic studies can elaborate patterns of urinary bladder dysfunction. Suspected amyloid may require biopsy (Chapter 193).

Ambulatory blood pressure testing (Chapter 67), usually over a period of 24 hours, is useful to detect patterns of nocturnal hypertension, postprandial hypotension, and the labile hypertension of baroreflex failure. Adrenergic function can be assessed noninvasively by tilt table testing (Chapter 62). Adrenergic failure can also be defined by deficient recovery and overshoot of arterial pressure following 15 seconds of expiration at 40 mm Hg. The Valsalva ratio, defined as the maximum heart rate generated by the Valsalva maneuver divided by the lowest heart rate within 30 seconds of the peak, is a measure of parasympathetic cardiovagal function. A sensitive index of cardiovagal function is the heart rate response to sinusoidal deep breathing, which quantifies respiratory sinus arrhythmia.

TREATMENT Rx

Treatment begins with educating patients about the underlying physiology, helping them avoid exacerbations, and managing their symptoms. In cases of mild dysautonomia, medications may not be needed. Elderly patients may be able to compensate for some of the age-associated decline in autonomic function through regular exercise.

Efforts at treating the underlying cause of an autonomic neuropathy should be pursued. Good control of glucose in patients with diabetes mellitus (Chapters 236 and 237) reduces the rate of complications, including neuropathy. Meticulous foot care can prevent cutaneous and joint trauma, ulceration, and infection of desensitized skin.

Orthostatic Intolerance

The goals of treatment are to increase the time that the patient is able to stand without orthostatic symptoms developing while simultaneously avoiding excessive recumbent hypertension. Mild orthostatic hypotension may respond to conservative measures such as increasing oral hydration (2 to 2.5 L/day), drinking sports beverages, and adding dietary salt or sodium tablets to increase daily salt intake to 10 to 20 g. Prolonged bedrest and medications that could potentially exacerbate orthostatic hypotension should be avoided if possible. Elevating the head of the bed by inserting 4- to 6-inch blocks under the head posts can improve orthostatic tolerance by reducing nocturnal natriuresis and stimulating release of renin.

Water bolus treatment (drinking 16 oz of water) can increase systolic blood pressure by 20 mm Hg for about 2 hours by a sympathetic reflex. Lower extremity resistance strength training combined with education about physical countermaneuvers (leg crossing, squatting, bending forward, or placing one foot on a chair) can help patients increase venous return to the heart and improve orthostatic tolerance by activating leg muscles. Compressive stockings are effective if they are tightly fitting, especially if they provide abdominal compression in addition to leg compression. However, they may be poorly tolerated in warm climates and are cumbersome to apply.

Pharmacologic measures include fludrocortisone (0.1 to 0.4 mg/day) to expand plasma volume, midodrine (5 to 10 mg three times daily) to constrict capacitance vessels, and pyridostigmine (30 to 60 mg two or three times daily) to enhance ganglionic transmission during orthostatic stress. Pyridostigmine has a more modest pressor effect but has the advantage of inducing less supine hypertension. Yohombine (5.4 mg three times daily) improves orthostatic hypotension by engaging residual sympathetic tone. Droxidopa (100 to 600 mg three times daily), an orally active synthetic precursor of norepinephrine, is approved in Japan for the treatment of orthostatic hypotension and is under study in the United States. Nocturnal hypertension may be minimized by avoiding pressor agents within several hours of bedtime, elevating the head of the bed, or having a nighttime snack. In severe cases, bedtime hydralazine (25 mg), nifedipine (10 mg), amlodipine (2.5 to 5 mg), or a nitroglycerin patch (0.1 mg/hr) may be needed.

Postprandial hypotension may be managed by dividing meals to avoid large carbohydrate loads. Caffeine or midodrine with breakfast may be helpful.

Sweating Disorders

Initial therapy for palmar hyperhidrosis begins with tap water iontophoresis, in which a low-level electric current applied to the skin surface blocks sweat ducts at the level of the stratum corneum; for severe cases, endoscopic thoracic sympathotomy is effective. Focal hyperhidrosis, such as gustatory sweating caused by aberrant innervation of the facial sweat glands

by regenerating parasympathetic fibers of the facial nerve, responds well to botulinum toxin injections. Generalized hyperhidrosis can be suppressed by oral anticholinergic drugs (e.g., glycopyrrolate, 1 to 2 mg one to three times daily), which tend to be well tolerated because very little crosses the blood-brain barrier; dry mouth is an invariable side effect. Aluminum chloride hexahydrate (20%) in anhydrous ethyl alcohol applied topically to dry skin at bedtime), oral belladonna (0.2 mg 1 to 2 times daily), propantheline (15 mg three times daily), topiramate (beginning at 25 mg twice daily), and clonidine (0.1 mg three times daily orally or by transdermal patch) may also be helpful for hyperhidrosis. Botulinum toxin types A and B, injected intradermally, are effective for axillary hyperhidrosis.

In a patient who is unable to sweat, hyperthermia cannot be prevented by drinking more water. Seeking shade, avoidance of exertion in hot weather, moistening the skin with a wet washcloth, and the use of portable fans can be quite effective. Carbonic acid inhibitors such as topiramate and zonisamide, which can inhibit thermoregulatory sweating, should be avoided if patients experience heat intolerance.

PROGNOSIS

The prognosis depends on the nature of the autonomic disorder. In general, the development of orthostatic hypotension worsens the prognosis.

A diagnosis of multiple system atrophy carries an estimated life expectancy of 7 to 9 years. A patient with pure autonomic failure may have a prolonged and stable clinical course, but it is not unusual for this syndrome to progress years later to a phenotype of multiple system atrophy or dementia with Lewy bodies. Amyloid neuropathy portends a median survival of less than 1 year if orthostatic hypotension is present. Diabetic autonomic neuropathy is associated with an approximately two-fold increased risk for silent myocardial ischemia and overall mortality.

Regional Sympathetic Dysfunction

Regional sympathetic dysfunction may accompany the pain that sometimes follows peripheral nerve injuries. For example, sympathetic activation can occur as a normal physiologic response to any painful state.

Complex regional pain syndrome is characterized by severe, ongoing neuropathic pain that is disproportionate in intensity, duration, and distribution to the expected sequela of limb trauma. In this syndrome, allodynia (pain in response to normally nonpainful stimuli, such as light touch or cold) or hyperalgesia (increased sensitivity to painful stimuli) accompany cutaneous vasomotor or sudomotor abnormalities. The vasomotor changes are manifested as vasodilation with a warm, red or swollen limb or, alternatively, as vasoconstriction with a cold, pale limb. The sudomotor findings range from regional hyperhidrosis to anhidrosis. Regional dystrophic changes, such as dry atrophic skin, sparse or coarse hair, brittle nails, and osteopenia, may also develop. Although sympathetic dysfunction may be pronounced, it does not appear to cause the pain. The mechanisms of pain and sympathetic dysfunction in this condition are incompletely understood and may result from crosstalk among aberrantly regenerated peripheral nerve fibers, expression of new α-adrenergic receptors on sensory nerve fibers and sweat glands, release of substance P and pro-inflammatory peptides at the site of injury, and sensitization of pain-mediating structures at multiple levels within the central nervous system.

Mobilization of the affected limb is of paramount importance in the early treatment of complex regional pain syndrome. A primary goal of analgesic medication or regional anesthesia in early treatment is to facilitate participation in physical therapy. Randomized controlled trials report improvement with the use of bisphosphonates (e.g., alendronate, 40 mg orally or 7.5 mg intravenously daily), steroids (e.g., prednisone, 40 mg daily, or methylprednisolone, 8 mg four times daily initially and then tapered), dimethyl sulfoxide (50% cream one to four times daily), epidural clonidine (300 to 700 μg daily), intrathecal baclofen (25 to 75 μg daily), and epidural spinal cord stimulation. One randomized trial of intravenous immunoglobulin, 0.5 g/kg, found that pain was reduced.■

Grade A

1. Winker R, Barth A, Bidmon D, et al. Endurance exercise training in orthostatic intolerance: a randomized, controlled trial. *Hypertension*. 2005;45:291-298.
2. Podoleanu C, Maggi R, Brignole M, et al. Lower limb and abdominal compression bandages prevent progressive orthostatic hypotension in elderly persons: a randomized single-blind controlled study. *J Am Coll Cardiol*. 2006;58:1425-1432.
3. Kaufmann H, Saadia D, Voustianiouk A. Midodrine in neurally mediated syncope: a double-blind, randomized, crossover study. *Ann Neurol*. 2002;52:342-345.
4. Singer W, Sandroni P, Opfer-Gehrking TL, et al. Pyridostigmine treatment trial in neurogenic orthostatic hypotension. *Arch Neurol*. 2006;63:513-518.
5. Shibao C, Okamoto LE, Gamboa A, et al. Comparative efficacy of yohimbine against pyridostigmine for the treatment of orthostatic hypotension in autonomic failure. *Hypertension*. 2010;56:847-851.
6. Goebel A, Baranowski A, Maurer K, et al. Intravenous immunoglobulin treatment of the complex regional pain syndrome. *Ann Intern Med*. 2010;152:152-158.

SUGGESTED READINGS

Frasson E, Brigo F, Acler M, et al. Botulinum toxin type A vs type B for axillary hyperhidrosis in a case series of patients observed for 6 months. *Arch Dermatol*. 2011;147:122-123. *Data suggesting a benefit*.

Tran de QH, Duong S, Bertini P, et al. Treatment of complex regional pain syndrome: a review of the evidence. *Can J Anaesth*. 2010;57:149-166. *Review of evidence from randomized controlled trials*.

428 PERIPHERAL NEUROPATHIES

MICHAEL E. SHY

APPROACH TO PERIPHERAL NEUROPATHIES

DEFINITION AND PATHOBIOLOGY

Peripheral neuropathy is a general term for disorders affecting peripheral nerves. The peripheral nervous system consists of motor, sensory, and autonomic neurons that extend outside the central nervous system (CNS) and are ensheathed by Schwann cells or ganglionic satellite cells. The peripheral nervous system includes the dorsal and ventral spinal roots, spinal and cranial nerves, sensory and motor terminals, and part of the autonomic nervous system. Motor neurons extend from their cell body in the ventral horn of the spinal cord to the neuromuscular junctions at the muscle that they innervate. The cell bodies of primary sensory neurons lie outside the spinal cord in the dorsal root ganglia, where they extend peripherally to specialized sensory end organs, including nociceptors, thermoreceptors, and mechanoreceptors. Central projections from dorsal root ganglia enter the spinal cord through the dorsal roots. At each spinal segment, the ventral roots, which carry motor axons, and the dorsal roots, which carry sensory axons, join to form mixed sensorimotor nerves. In the cervical, brachial, and lumbosacral areas, the mixed spinal nerves form plexuses from which arise the major anatomically defined limb nerves. Each mixed nerve is composed of large numbers of myelinated and nonmyelinated nerve fibers of varying diameter. The large myelinated axons include motor neurons and large fiber sensory nerves that mediate position and vibration sense. Small, thinly myelinated and nonmyelinated axons primarily provide nociception and autonomic functions. Preganglionic sympathetic autonomic fibers begin in the intermediolateral column of the spinal cord and synapse in ganglia of the sympathetic trunk. Preganglionic parasympathetic fibers travel long distances from their cell bodies in the brain stem or sacral spinal cord to reach terminal ganglia near the organs that the parasympathetic fibers innervate.

CLINICAL MANIFESTATIONS

Symptoms of peripheral neuropathy include weakness, sensory loss, abnormal balance, and autonomic dysfunction. Weakness is often distal and more severe in the legs than the arms. Deep and superficial muscles that are innervated by the peroneal nerve, such as the tibialis anterior and peroneus brevis and longus muscles, often cause more symptoms than do the plantar flexion muscles innervated by the tibial nerve, such as the gastrocnemius. As a result, tripping on a carpet or curb and ankle sprains are frequent symptoms. In the hands, symptoms typically involve fine movements, such as using buttons or zippers and inserting and turning keys in locks. Cramps, the painful knotting of a muscle, frequently occur with motor or sensorimotor neuropathies.

The sensory symptoms of neuropathy reflect disease of small, thinly myelinated or nonmyelinated fibers subserving pain and temperature, as well as large myelinated fibers subserving position sense. Common symptoms of small fiber sensory neuropathy include feeling as though the feet are "walking on pebbles" or "ice cold" and difficulty determining whether bath water is hot or cold with the foot. Painful dysesthesias, such as feeling as though the feet

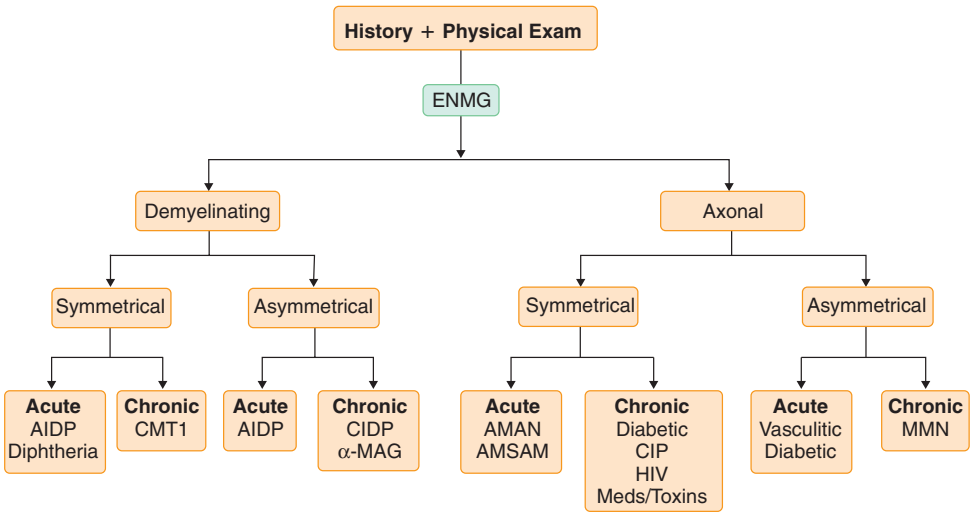


FIGURE 428-1. A systematic approach to evaluate neuropathy. The diseases listed are examples of neuropathies associated with specific neurophysiologic and clinical findings. Diabetic distal, predominantly sensory neuropathies are manifested as chronic axonal neuropathies; acute asymmetrical neuropathies can also occur with diabetes. Most neuropathies caused by toxins or by side effects of medication are chronic, symmetrical axonal neuropathies. AIDP, AMAN, and AMSAN are subtypes of Guillain-Barré syndrome. These and other examples are discussed in more detail in the text. AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy; CIDP = chronic inflammatory polyradiculoneuropathy; CIP = chronic illness polyneuropathy; CMT1 = Charcot-Marie-Tooth disease type 1, a genetic disorder; ENMG = electroneuromyography; HIV = human immunodeficiency virus–related neuropathy; α-MAG = anti-myelin-associated glycoprotein; MMN = multifocal motor neuropathy.

are "on fire," "on hot coals," or "stuck with pins," are also associated with small fiber abnormalities. Similar symptoms occur less frequently in the hands because most neuropathies are dependent on the length of the nerves; as a general rule, sensory symptoms begin in the hands when sensory symptoms in the legs have progressed up to the knee. An exception is when the patient also has carpal tunnel syndrome, which is often manifested as pain and tingling in the hands and can awaken patients from sleep. Large fiber sensory loss usually impairs balance, which may be worse at night when vision cannot overcome the loss of proprioception. Loss of proprioception is also frequently length dependent, so a patient may improve balance by lightly touching a wall with the hand to improve proprioceptive input to the brain.

Autonomic symptoms are frequent in neuropathies associated with diabetes or amyloidosis and include urinary retention or incontinence, abnormalities of sweating, constipation alternating with diarrhea, and lightheadedness when standing. Impotence is frequent.

DIAGNOSIS

Systematic Approach to Patients with Peripheral Neuropathy

Evaluation begins with the history and physical examination to demonstrate peripheral nerve disease and proceeds to neurophysiologic testing to characterize whether the process is demyelinating or axonal. Other specific tests are then ordered (Fig. 428-1).

Peripheral neuropathies usually affect both motor and sensory nerves, thereby causing both weakness and sensory loss. However, certain neuropathies are predominantly sensory, such as diabetes, or motor, such as multifocal motor neuropathy (Tables 428-1 and 428-2). Most neuropathies are symmetrical and length dependent. Pronounced asymmetries in symptoms suggest specific disorders, such as mononeuritis multiplex or hereditary neuropathy with liability to pressure palsies. It is also useful to know whether symptoms are acute (<1 month), subacute (<6 months), or chronic (>6 months). For example, Guillain-Barré syndrome develops over a period of days to weeks, whereas chronic inflammatory demyelinating polyneuropathy (CIDP) evolves over months, and inherited neuropathies may develop over years.

Neurologic Examination

Wasting of muscle is prominent in many sensorimotor or motor neuropathies, regardless of whether they are primary axonal or primary demyelinating disorders, because even demyelinating neuropathies are associated with secondary axonal degeneration. Atrophy frequently occurs in muscles of dorsiflexion, such as the tibialis anterior, and in intrinsic hand muscles, such as the first dorsal interosseus. Fasciculations, which appear as small twitches of the muscle, are sometimes present, particularly in axonal neuropathies.

Weakness is often most pronounced in foot dorsiflexion and eversion and in the intrinsic hand muscles. In the lower extremities, weakness usually progresses to the muscles of plantar flexion before more proximal muscles become involved.

TABLE 428-1 PREDOMINANTLY SENSORY NEUROPATHIES

CLASSIFICATION	SUBGROUP	TYPE	FIBERS
Genetic		HSAN	Large, small
Inflammatory, immune	Monoclonal gammopathy	Anti-MAG (early on)	Mainly large
	Vasculitis	Sjögren's syndrome	Large, small
	Paraneoplastic	Anti-Hu	Large
Metabolic	Diabetic	Distal symmetrical polyneuropathy	Large, small
Infectious	HIV	HIV neuropathy	Small
	Herpes zoster	Focal radiculoneuropathy	Small
	Leprosy	Tuberculoid	Small
Toxic, deficiency	Medications	Vincristine	Small
		Paclitaxel	Large
		Cisplatin	Large
		Thalidomide	Large
		NRTIs	Small
	Toxins	Thallium	Small
		Acrylamide	Large
		Pyridoxine (B_6)	Large, small
	Deficiency states	Vitamin B_1	Large, small
		Vitamin B_{12}	Large
		Vitamin E	Large
Idiopathic	Frequent		Large, small

HIV = human immunodeficiency virus; HSAN = hereditary sensory and autonomic neuropathy; MAG = myelin-associated glycoprotein; NRTIs = nucleoside reverse transcriptase inhibitors.

TABLE 428-2 PREDOMINANTLY MOTOR NEUROPATHIES

CLASSIFICATION	SUBGROUP	TYPE
Genetic		HMN
Inflammatory, immune	Guillain-Barré	AMAN
	Multifocal motor neuropathy	MMN
	Critical illness myopathy	CIM
Toxic, deficiency	Medications	Dapsone
	Toxins	Lead (adults)

AMAN = acute motor axonal neuropathy; CIM = critical illness myopathy; HMN = hereditary motor neuropathy; MMN = multifocal motor neuropathy.

Sensory loss is usually in a stocking-glove distribution in both large and small fiber neuropathy. Cold, erythematous, or bluish discolored feet suggest loss of small fiber function. Large fiber sensory loss, or *sensory ataxia*, in the upper extremities can often be detected by an inability of the patient to locate the thumb accurately with the opposite index finger while the eyes are closed or by the presence of a characteristic irregular tremor (pseudoathetosis) of the fingers.

The sensory examination should include vibration, position, and light touch as well as pain and temperature. It is important to determine the degree and extent of sensory loss in addition to the pattern of deficits (symmetrical or asymmetrical; distal or generalized; focal, multifocal, or diffuse).

The complete absence of reflexes early in the course of a neuropathy suggests a demyelinating neuropathy ; for example, the absence of reflexes in early childhood is often the first detectable abnormality in children with inherited demyelinating neuropathies. Alternatively, the absence of ankle reflexes but the presence of normal patellar or upper extremity reflexes is common in "dying back" (length-dependent) axonal neuropathies, both acquired and inherited. Reflexes may be present in small fiber neuropathies.

On gait testing, subtle weakness in the feet can be detected by an inability of the patient to heel walk. Sensory ataxia can be appreciated by a wide-based gait or inability to tandem walk.

Neurologic Testing

Neurophysiology

Electromyography (EMG) and nerve conduction studies can determine whether a neuropathy is primarily demyelinating or axonal and can confirm whether the process is symmetrical or asymmetrical (Chapter 403).

Motor nerve conduction velocities measure conduction over the main body of nerves but not their proximal or distal portion. Distal motor latencies and F wave latencies measure velocities over the distal and proximal portions of the nerves. When slowing is roughly the same over the proximal, distal, and main portion of the nerve, the slowing is said to be uniform. When the slowing is multifocal or asymmetrical, either along the same nerve or between different nerves, the slowing is said to be nonuniform. Slowed conduction velocities (to less than 70% of normal) suggest that the neuropathy is primarily demyelinating.

The sensory nerve action potential is a summation of action potentials from individual large-diameter sensory axons. In axonal neuropathies, amplitudes of the compound muscle action potential or sensory nerve action potential are reduced. When there has been a loss of individual sensory axons, amplitudes of the sensory nerve action potential are reduced.

The presence of spontaneous activity on EMG, such as fibrillations or positive sharp waves, suggests that an acute or active process is damaging axons and denervating muscle. The presence of large, polyphasic motor units suggests partial reinnervation of muscle by regenerating axons (i.e., a more chronic process). Recruitment of motor units is also reduced in patients with demyelinating and axonal neuropathies.

Quantitative Sensory Testing

Quantitative sensory testing can assess and quantify vibratory, thermal, or painful sensory function in patients with peripheral neuropathies or other sensory disorders. Although the stimulus is an objective physical event, the response represents a subjective report and requires cooperation from the patient; as a result, this test by itself cannot diagnose sensory neuropathies or sensory loss.

Nerve and Skin Biopsy

Nerve biopsy is occasionally indicated to address specific questions, such as whether vasculitis, tumor, or another infiltrative or metabolic disorder is present. Biopsy of sural nerves is performed just above the ankle. After biopsy, patients lose sensation over the region on the lateral aspect of the foot that is innervated by the sural nerve, and transient painful dysesthesias may develop around the biopsy site. Teased sural nerve fiber analysis can demonstrate segmental demyelination or remyelination, and electron microscopy can demonstrate features of nerve regeneration and identify specific pathologic processes.

Epidermal skin biopsies with quantification of the loss of small epidermal nerve fibers may aid in the diagnosis of sensory neuropathies, particularly in neuropathies that involve a loss of small fibers, such as diabetes mellitus, human immunodeficiency virus (HIV) infection, or chemotherapeutic drugs. Skin biopsies also are increasingly being used to evaluate myelinated sensory nerves.

Laboratory Findings

Evaluation of all patients with suspected neuropathy should include blood glucose and creatinine levels as well as a complete blood count (including red blood cell indices to detect possible macrocytosis). If the history and EMG are consistent with exposure to a toxin or a vitamin-deficiency state, specific testing is indicated. Most patients should also have vitamin B_{12} level measurement (Chapter 167), rapid plasmin reagent test (Chapter 327), and serum immunofixation electrophoresis for possible monoclonal gammopathy (Chapter 193). In unexplained sensory neuropathies, HIV testing should be considered (Chapter 401). In selected patients, electrodiagnostic studies will suggest the need to test for specific antibodies, such as antibodies reacting to ganglioside GM_1 or myelin-associated glycoprotein (MAG). Genetic testing is most cost-effective when selection of candidate genes is based on the patient's nerve conduction studies, inheritance pattern, and clinical findings.

INHERITED NEUROPATHIES

DEFINITION

Inherited neuropathies are frequently called Charcot-Marie-Tooth (CMT) disease based on the names of the three physicians who initially characterized the disorders in the late 19th century. They are also referred to as hereditary motor and sensory neuropathies, hereditary motor neuropathies, or hereditary sensory and autonomic neuropathies, depending on their clinical manifestation. Autosomal dominant forms are subdivided into demyelinating (CMT1) and dominantly inherited axonal (CMT2) forms based on electrophysiologic and neuropathologic criteria. X-linked (CMTX) and autosomal recessive (CMT4) forms are also seen. Each type of CMT disease is subdivided according to the specific genetic cause of the neuropathy. For example, the most common form of CMT1, termed CMT1A, is caused by a duplication of a fragment of chromosome 17 containing the peripheral myelin protein 22-kD (*PMP22*) gene (see later). Currently, mutations in more than 40 genes have been identified as causes of inherited neuropathies (available at *www.uia.ac.be/CMTMutations/*) (Table 428-3).

EPIDEMIOLOGY

The prevalence of CMT is about 1 in 2500 people, without ethnic predisposition. The 17p11.2 duplication causing CMT1A accounts for 60 to 70% of CMT1 patients, CMT1X for approximately 10 to 20% of CMT cases, CMT1B for less than 5% of patients, and CMT2 for about 20% of cases. The prevalence of hereditary neuropathy with liability to pressure palsies is not known, but about 85% of patients with clinical evidence of this syndrome have a chromosome 17p11.2 deletion.

PATHOBIOLOGY

Pathology

Segmental demyelination, remyelination, and axonal loss are characteristic features of the various demyelinating forms of CMT1. In Dejerine-Sottas neuropathy, the demyelination is more severe. In CMT1, onion bulbs of concentric Schwann cell lamellae are usually present on nerve biopsies, with loss of both small- and-large diameter myelinated fibers and sometimes axons. Focal, sausage-like thickenings of the myelin sheath (tomacula) are characteristic of hereditary neuropathy with liability to pressure palsies (HNPP) but may also be found in other forms of CMT1, particularly CMT1B. In CMT1, disability typically correlates better with secondary axonal degeneration than with demyelination itself, thereby demonstrating the importance of Schwann cell–axonal interactions in demyelinating disease (Fig. 428-2).

Genetics

Mutations in *PMP22* and *MPZ* cause CMT1, and mutations in *GJB1* cause CMT1X. All three genes code for myelin proteins. Mutations in the neurofilament light (*NEFL*), gigaxonin (*GAN*), and *dynactin* genes cause CMT2; all three genes have roles in the axonal cytoskeleton and axonal transport. LITAF/SIMPLE, the myotubulin-related proteins 2 and 13, and RAB7 are involved in intracellular trafficking. MFN2 and ganglioside-induced differentiation-associated protein-1 (GDAP1) are nuclearly encoded mitochondrial proteins.

CLINICAL MANIFESTATIONS

Despite phenotypic variability, the typical clinical course of CMT1 and CMT2 patients includes normal development before weakness, and sensory loss appearing gradually within the first two decades of life. Affected children are often slow runners and have difficulty with activities that require balance (e.g., skating, walking across a log). Ankle-foot orthoses are frequently required by the third decade. Fine movements of the hands for activities such

TABLE 428-3 INHERITED NEUROPATHIES

DISORDER	LOCUS/GENE	INHERITANCE	PROTEIN	MUTATION (FREQUENCY)	TESTING METHOD	TYPE OF TESTING
HEREDITARY MOTOR AND SENSORY NEUROPATHIES						
CMT1A	17p11.2/*PMP22*	AD	Peripheral myelin protein 22	Duplication (98%) Sequence alteration (2%)	Pulsed-field gel electrophoresis, FISH, Southern blot Sequencing	Clinical
HNPP	17p11.2/*PMP22*	AD	Peripheral myelin protein 22	Deletion (80%) Sequence alteration (20%)	Pulsed-field gel electrophoresis, FISH, Southern blot Sequencing	Clinical
CMT1B	1q22/*MPZ*	AD	Myelin protein zero	Sequence alteration	Sequencing, mutation scanning, mutation analysis	Clinical
CMT1C	16p13.1-p12.3/*LITAF*	AD	SIMPLE	Sequence alteration		Research
CMT1D	10q21.1-q22.1/*EGR2*	AD	Early growth response protein 2	Sequence alteration	Sequencing, mutation scanning, mutation analysis	Clinical
CMT2A	1p36.2/*MFN2*	AD	Mitofusin 2	Sequence alteration	Direct DNA, linkage analysis	Research
CMT2B	3q21/*RAB7*	AD	Ras-related protein Rab-7	Sequence alteration	Direct DNA, linkage analysis	Research
CMT2C	12q23-24/unknown	AD	Unknown		Direct DNA, linkage analysis	
CMT2D	7p15/*GARS*	AD	Glycyl-tRNA synthetase	Sequence alteration	Direct DNA, linkage analysis	Research
CMT2E	8p21/*NEFL*	AD	Neurofilament triplet L protein	Sequence alteration	Sequencing	Clinical
CMT2F	7q11-21	AD	Heat shock protein 27 (B1)	Sequence alteration	Sequencing	Research
CMT2L	12q24	AD	Heat shock protein 22 (B8)	Sequence alteration	Sequencing	
CMT4A	8q13-q21.1/*GDAP1*	AR	Ganglioside-induced differentiation protein 1	Sequence alteration	Sequencing	Clinical
CMT4B1	11q22/*MTMR2*	AR	Myotubularin-related protein 2	Sequence alteration		Research
CMT4B2	11p15/*CMT4B2*	AR	SET binding factor 2	Sequence alteration		Research
CMT4C	5q32/*KIAA1985*	AR	KIAA1985	Sequence alteration		Research
CMT4D	8q24.3/*NDRG1*	AR	NDRG1 protein	Sequence alteration		Research
CMT4E	10q21.1-q22.1/*EGR2*	AR	Early growth response protein 2	Sequence alteration	Mutation analysis, sequencing	Clinical
CMT4F	19q13.1-q13.2/*PRX*	AR	Periaxin	Sequence alteration	Sequencing	Clinical
CMT4G (HMSN-R)	10q23	AR	Unknown			
CMT4H	12p11.21-q13.11	AR	FRABIN	Sequence alteration	Sequencing	Research
CMT4J	6q21	AR	FIG4	Sequence alteration	Sequencing	Clinical
CMT1X	Xq13.1/*GJB1*	X-linked	Gap junction β1 protein (connexin 32)	Sequence alteration (deletion rare)	Sequencing	Clinical
DI-CMTA	10q24.1-q25.1	AD	Unknown			
DI-CMTB	19p12-p13.2	AD	Dynamin 2	Sequence alteration	Sequencing	Research
DI-CMTC	1p34-p35	AD	Tyrosine tRNA Synthetase	Sequence alteration	Sequencing	Research
Slow-NCV	8p23	AD	ARHGEF10	Sequence alteration	Sequencing	Research
DISTAL HEREDITARY MOTOR NEUROPATHIES						
dHMN I	Unknown	AD	Unknown			Research
dHMN II	12q24.3/unknown	AD	Unknown			Research
dHMN III	1q21-23/unknown	AR	Unknown			Research
dHMN V	7p15/*GARS*	AD	Glycyl-tRNA synthetase	Sequence alteration	Sequencing	Clinical
dHMN VI	Unknown	AR	Unknown			Research
dHMN VII	2q14/unknown	AD	Unknown			Research
dHMN Jerash	9p21.1-p12/unknown	AR	Unknown			Research
ALS4	9q34/unknown	AD	SETX	Sequence alteration		Research
HMN Dynactin	2p13/*DCTN1*	AD	Dynactin	Sequence alteration		Research
HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES						
HSAN I	9q22.1-q22.3/*SPTLC1*	AD	Serine palmitoyltransferase light chain 1	Sequence alteration	Sequencing	Clinical
HSAN II	Unknown	AR	Unknown			Research
HSAN III (Riley-Day syndrome)	9q31/*IKBKAP*	AR	IκB kinase complex-associated protein	Two mutations account for 99% of affected patients of Ashkenazi Jewish descent	Mutation analysis, quantitative PCR	Clinical
HSAN IV	1q21-q22/*NTRK1*	AR	Tyrosine kinase for nerve growth factor	Sequence alteration		Research

CMT = Charcot-Marie-Tooth disease; FISH = fluorescence in situ hybridization; HNPP = hereditary neuropathy with liability to pressure palsies; dHMN = distal hereditary motor neuropathy; HSAN = hereditary sensory and autonomic neuropathy; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism.

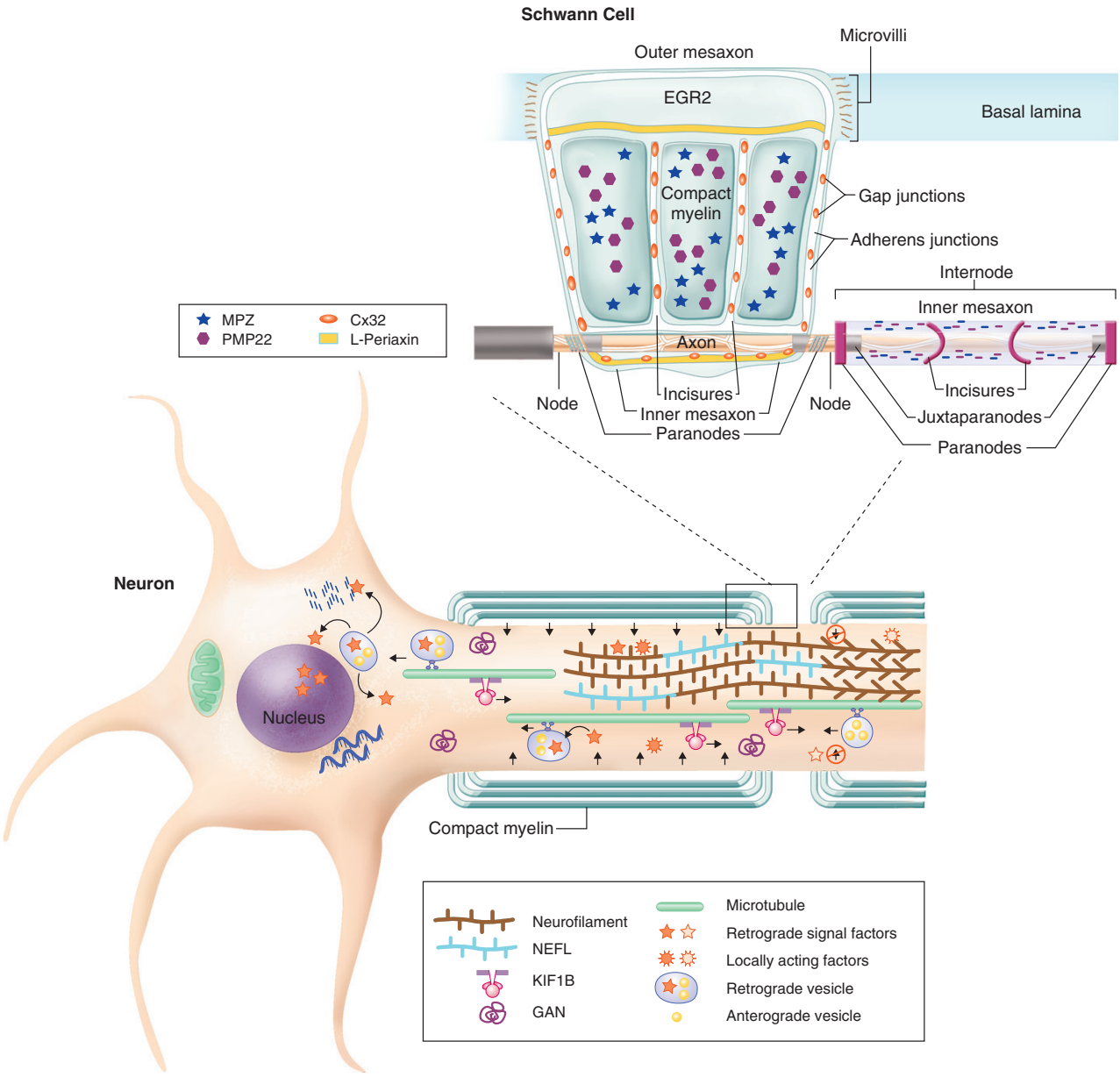


FIGURE 428-2. Schematic view of an axon and its myelinating Schwann cell. Proteins mutated in inherited peripheral neuropathies are shown in color at their cellular location. In the *upper part* of the panel, the myelinating Schwann cell has been unraveled to show the nucleus and regions of both compact myelin and noncompact myelin. Cytoskeletal elements within the axon are also illustrated. (From Shy ME, Garbern JY, Kamholz J. Hereditary motor and sensory neuropathies: a biological perspective. *Lancet Neurol.* 2002;1:110-118.)

as turning a key or using buttons and zippers may be impaired, but the hands are rarely as affected as the feet. Most patients remain ambulatory throughout life and have a normal lifespan.

A minority of CMT patients have a more severe phenotype with delayed motor milestones and onset in infancy, termed *Dejerine-Sottas neuropathy.* Especially severe cases are classified as congenital hypomyelination if myelination appears to be disrupted during embryologic development. Many patients have de novo autosomal dominant disorders, and the term *Dejerine-Sottas neuropathy* is currently used primarily to denote severe early-onset clinical phenotypes regardless of the inheritance pattern. Patients with hereditary motor neuropathies sometimes have mild sensory abnormalities, and patients with hereditary sensory and autonomic neuropathies usually have some weakness. The same mutations in the same gene (*GARS*) cause both CMT2D and hereditary motor neuropathy type V.

DIAGNOSIS

Molecular testing, performed after the family history, neurologic examination, and neurophysiologic testing have suggested the probable candidate genes (GeneClinics—available at *www.geneclinics.org*), is the "gold standard" for the diagnosis of inherited neuropathies. Nerve conduction velocity testing can distinguish between demyelinating and axonal neuropathies. Most CMT1 patients, particularly those with CMT1A, have a uniformly slow nerve conduction velocity of about 20 m/second. Asymmetrical slowing, which is characteristic of hereditary neuropathy with liability to pressure palsies, may be found in patients with missense mutations in *PMP22*, *MPZ*, *EGR2*, and *GJB1*. Although CMT2 is characterized by axonal loss and reduced compound muscle action potential or sensory nerve action potential amplitudes, virtually all forms of CMT1 have axonal loss as well as demyelination.

Differential Diagnosis

Inherited neuropathies must be distinguished from acquired neuropathies (see later). Additionally, genetic disorders of the CNS such as hereditary spastic paraplegia (Chapter 417) or leukodystrophies (Chapter 419) may mimic inherited neuropathies by causing length-dependent weakness, sensory loss, and foot deformities such as pes cavus; these patients will frequently have upper motor neuron signs, such as increased reflexes or Babinski's signs, and do not have neurophysiologic evidence of neuropathy.

TREATMENT

Rx

There is no specific therapy for the inherited neuropathies, but clinical and genetic counseling and symptomatic and rehabilitative treatment are important. A detailed family history and often examination of family members are required for prognosis and genetic counseling.

Ankle-foot orthoses to correct footdrop may return gait and balance to normal for years. Foot surgery is sometimes offered to correct inverted feet, pes cavus, and hammertoes. Surgery may improve walking, alleviate pain over pressure points, and prevent plantar ulcers. However, foot surgery is generally unnecessary and does not improve weakness and sensory loss.

Ascorbic acid, antagonists to progesterone, and subcutaneous injections of neurotrophin 3 have demonstrated improvement in animal models of CMT1A. However, no medication has yet demonstrated efficacy in patients with CMT1A or any other form of CMT.

INFLAMMATORY AND IMMUNOLOGIC NEUROPATHIES

Guillain-Barré Syndrome

DEFINITION

Guillain-Barré syndrome refers to acquired, inflammatory peripheral neuropathies that have (1) an acute onset, (2) elevated cerebrospinal fluid (CSF) protein levels with low CSF cell counts (cytoalbuminologic dissociation), and (3) a monophasic illness with at least partial recovery. Guillain-Barré syndrome is subdivided into acute inflammatory demyelinating polyneuropathy, acute motor and sensory axonal neuropathy, acute motor axonal neuropathy, and Miller-Fisher syndrome (Table 428-4).

EPIDEMIOLOGY

Acute inflammatory demyelinating polyneuropathy accounts for up to 97% of cases of Guillain-Barré syndrome in North America and Europe. It is a sporadic disorder with an incidence of 0.6 to 1.9 cases per 100,000 people in North America and Europe. Men are more likely to be affected than women (1.4:1). In 60% of cases, acute inflammatory demyelinating polyneuropathy is preceded by a respiratory tract infection (e.g., cytomegalovirus [Chapter 384], Epstein-Barr virus [Chapter 385], or gastroenteritis (*Campylobacter jejuni* [Chapter 311]). Acute motor axonal neuropathy and acute motor and sensory axonal neuropathy are rare in North America and Europe but more frequent in China, Japan, Mexico, Korea, and India.

PATHOBIOLOGY

All forms of Guillain-Barré syndrome probably result from postinfectious molecular mimicry in which nerve antigens are attacked by the immune system because they resemble antigens presented by microbes, in particular, *C. jejuni*. For example, the HS/0:19 serotype of *C. jejuni* is common in northern Chinese patients with Guillain-Barré syndrome and has also been isolated from such patients in other countries. Assays with antiganglioside antibodies, bacterial toxins, and lectins have characterized potential immunogenic regions of diarrhea-associated *C. jejuni* strains. However, it is not clear that molecular mimicry is the cause of acute inflammatory demyelinating polyneuropathy, which is the most common form in the United States and Europe.

CLINICAL MANIFESTATIONS

Weakness, which is the most common initial symptom in both acute inflammatory demyelinating polyneuropathy and acute motor and sensory axonal neuropathy, can be mild, such as difficulty walking, or severe, such as total quadriplegia and respiratory failure. Bilateral weakness of facial muscles (facial diplegia) occurs in about 50% of cases. The most common manifestation is leg weakness that subsequently "ascends" into the arms. Although Guillain-Barré syndrome has been described as an "ascending paralysis," proximal weakness is common, and 5% of cases have isolated cranial nerve involvement that subsequently descends into the limbs. Sensory loss occurs in most patients. The autonomic nervous system is involved in about 65% of patients.

Length-dependent weakness without sensory loss develops in patients with acute motor axonal neuropathy, including cranial nerve involvement in about 25%. Miller-Fisher syndrome consists of the triad of ophthalmoplegia, ataxia, and areflexia. Facial weakness, ptosis, and pupillary abnormalities may be present. Nerve conduction velocities in Miller-Fisher syndrome are generally normal, unlike the case with acute inflammatory demyelinating polyneuropathy.

DIAGNOSIS

The diagnosis of acute inflammatory demyelinating polyneuropathy and acute motor and sensory axonal neuropathy is based on the history, physical examination, and CSF evaluation. Deep tendon reflexes are decreased or absent, and the CSF is abnormal with cytoalbuminologic dissociation. The weakness is symmetrical. The presence of CNS abnormalities should cast doubt on the diagnosis. Acute inflammatory demyelinating polyneuropathy is distinguished from acute motor and sensory axonal neuropathy by nerve conduction studies. In both acute inflammatory demyelinating polyneuropathy and acute motor and sensory axonal neuropathy, the CSF should have fewer than five white blood cells (WBCs)/mL. If the CSF cell count is greater than 50 WBCs/mL, another diagnosis, such as HIV infection (Chapter 401) or Lyme disease (Chapter 329), should be considered. Elevated CSF protein may not be apparent in the first 7 to 10 days of the illness; in up to 10% of cases, CSF protein levels remain normal. Approximately 5% of patients with Guillain-Barré syndrome have Miller-Fisher syndrome, and more than 85% of these patients have polyclonal antibodies that react with the ganglioside GQ_{1b}.

Differential Diagnosis

The differential diagnosis varies in different parts of the world. Historically, poliomyelitis (Chapter 423) was the major cause of acute flaccid quadriparesis. In North America, polio has been eradicated, but other viral illnesses may induce polio-like syndromes: ECHO 70 (Chapter 387), coxsackievirus

TABLE 428-4 INFLAMMATORY AND IMMUNE-RELATED NEUROPATHIES

DISORDER	TYPE	CLINICAL TRAITS	PATHOBIOLOGY	TREATMENT*
Guillain-Barré syndrome	AIDP	Acute flaccid weakness, sensory loss	Demyelination, lymphocyte infiltration	Plasma exchange, IVIG
	AMAN/AMSAN	Acute flaccid weakness, no sensory loss in AMAN	Molecular mimicry, association with *Campylobacter jejuni*	? Plasma exchange or IVIG
	Fisher's syndrome	Acute ataxia, ophthalmoparesis and areflexia	Anti-GQ1b antibodies	? Plasma exchange or IVIG
CIDP		Slower onset of weakness, sensory loss	Inflammatory/immune-mediated demyelination	Corticosteroids, plasma exchange, IVIG
Monoclonal gammopathy	IgM	Sensory > motor	Particularly anti-MAG	Immune suppression (Chapter 193)
	IgG	Sensorimotor	Many probably chance associations, osteosclerotic myeloma, solitary plasmacytoma; POEMS may be immune mediated	Treatment of myeloma
Multifocal motor neuropathy		Pure motor	Focal demyelination, antibodies to GM_1 frequent	IVIG

*Typical regimens: IVIG, 0.4 g/kg/day × 5 days for a total of 2 g/kg; may be repeated monthly as needed. Corticosteroids: prednisone, 60 to 80 mg/day for up to 3 months, followed by gradual tapering, depending on the clinical response, with a goal to about 20 mg on an alternate-day regimen.

AIDP = acute idiopathic demyelinating polyneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy; CIDP = chronic inflammatory polyradiculoneuropathy; IgG = immunoglobulin G; IVIG = intravenous immune globulin; MAG = myelin-associated glycoprotein; POEMS = polyneuropathy, organomegaly, M protein, skin changes.

(Chapter 387), West Nile virus (Chapter 390), and rarely, rabies (Chapter 422). Because these diseases are not demyelinating disorders, they can be distinguished from acute inflammatory demyelinating polyneuropathy by their normal nerve conduction velocity. However, the results of electrodiagnostic studies are similar in both acute motor axonal neuropathy and the polio-like syndromes, thus making distinction between acute motor axonal neuropathy and these syndromes difficult.

Tick paralysis (Chapter 390), caused by a toxin within the tick, can mimic Guillain-Barré syndrome, particularly in children. Usually, removal of the tick is associated with improvement within hours, although progression can occur. Progression is particularly likely in Australia, where the toxin differs from that found in North America.

Botulism (Chapters 304 and 430) rapidly produces a flaccid paralysis. Patients have ophthalmoplegia, bulbar weakness, dry mouth, constipation, and orthostatic hypotension, but sensory symptoms do not develop. Other entities that can mimic Guillain-Barré syndrome are acute spinal cord compression (Chapter 407), acute transverse myelitis (Chapter 419), and vascular myelopathies, all of which are characterized by decreased reflexes before the development of upper motor neuron signs such as increased reflexes. Carcinomatous or lymphomatous meningitis can also cause a rapidly developing quadriparesis, but both are associated with elevated CSF WBC counts.

TREATMENT

Rx

Patients with Guillain-Barré syndrome require hospitalization because of the potential for respiratory compromise. Pulmonary function tests should be performed frequently; a vital capacity of less than 1 L or a negative inspiratory force of less than –70 suggests that ventilator support may be needed in an intensive care unit setting. Autonomic instability and difficulty swallowing also need to be monitored.

Therapies directed at modulating the immune system are effective in Guillain-Barré syndrome. Intravenous immunoglobulin (IVIG) therapy, which is the preferred treatment, is typically given as 2 g/kg divided over 2 to 5 days within the first 2 weeks. Although plasma exchange and IVIG are equally effective,[1] at least in the first 2 weeks, IVIG is often preferred for its convenience unless there are contraindications, such as low serum immunoglobulin A (IgA) levels, renal failure, or severe hypertension.

Plasma exchange, usually four exchanges of 1.5 L of plasma spread over a 10-day period, is also effective.[2] Two plasma exchanges may be sufficient in mild cases, and six exchanges are not superior to four in severely affected patients. This therapy should ideally be administered within the first 2 weeks and not later than 4 weeks from clinical onset.

Ten percent of patients with Guillain-Barré syndrome relapse after initially responding to plasma exchange or IVIG; they usually respond to a second cycle of the previously effective treatment. The combined use of plasma exchange followed by IVIG does not improve the prognosis.[3]

Corticosteroids in different forms (intravenous methylprednisolone, oral prednisolone or prednisone, intramuscular adrenocorticotropic hormone) are not of benefit. Intravenous methylprednisolone (500 mg/day for 5 days) in association with IVIG has a slight initial advantage over IVIG alone but no benefit in terms of long-term disability.

PROGNOSIS

Fifty percent of patients progress to their nadir, or maximal disability, within 2 weeks, 75% within 3 weeks, and more than 90% within 4 weeks of the onset of symptoms. With modern supportive care, acute mortality is about 2%. After a brief period of stabilization, slow spontaneous recovery occurs over a period of weeks or months. Most patients either undergo complete recovery or are left with minor sequelae; about 20% have a persistent disability. The long-term prognosis depends at least in part on the extent of axonal loss. Patients with low compound muscle action potential amplitudes in the upper extremities are more likely to have a poor prognosis.

Patients with acute motor axonal neuropathy will recover after approximately 2 months, but the extent of recovery may be less than in Guillain-Barré syndrome. In general, the prognosis for recovering from Miller-Fisher syndrome is excellent.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

DEFINITION

CIDP is a chronic acquired demyelinating sensorimotor neuropathy that may be monophasic, relapsing, or progressive. By definition, CIDP develops over at least a 2-month period as opposed to acute inflammatory demyelinating polyneuropathy, which it otherwise resembles.

EPIDEMIOLOGY

CIDP occurs in all age groups, with a mean age range of 30 to 50 years. Women are slightly more likely to be affected than men. Antecedent events are less common than in Guillain-Barré syndrome; they occur in about 30% of patients and include upper respiratory infections, gastrointestinal infections, vaccinations, surgery, and trauma.

PATHOBIOLOGY

CIDP is considered an autoimmune disorder based on pathologic findings in nerve biopsy samples from patients and on findings in animal models such as experimental allergic neuritis, in which a similar disorder follows immunization with peripheral nervous system myelin components and Freund's adjuvant. Nerve biopsy shows macrophage-mediated segmental demyelination, occasional endoneurial lymphocytic T-cell infiltrates, and endoneurial edema. The major histocompatibility complex class I and II antigens are upregulated, and there are often deposits of immunoglobulins and complement split products on the outer Schwann cell membranes or myelin sheaths. CIDP can be passively transferred to animals by patient sera, but no clear autoantigen has been identified.

CLINICAL MANIFESTATIONS

Weakness and sensory loss begin insidiously and progress over a period of months to years. Weakness is commonly proximal as well as distal. Patients can become bedridden. Loss of proprioception from damage to large-diameter sensory nerves may affect balance and result in an action tremor. Deep tendon reflexes are usually absent or markedly decreased. Facial weakness (15%), ptosis or ophthalmoparesis (5%), and papilledema occur occasionally. Variant forms include pure motor, pure sensory, and multifocal disease.

DIAGNOSIS

Diagnosis is based on clinical symptoms and signs, electrodiagnostic studies, and CSF examination. Nonuniform, asymmetrical slowing on nerve conduction studies is characteristic. One portion of a nerve may have different conduction than another. For example, if damage is primarily in the spinal roots, proximal conduction velocities and F wave latencies may be most affected. Compound muscle action potentials are generally reduced because of the concomitant axonal degeneration that occurs with demyelinating neuropathies. However, temporal dispersion and conduction block may also reduce the amplitude of muscle action potential in any demyelinating neuropathy. Sensory nerve conduction is also slow in CIDP, but because sensory nerve action potentials are often not detectable, sensory conduction velocity may be unmeasurable.

CSF results resemble those of acute inflammatory demyelinating polyneuropathy: WBC counts are usually less than 10 cells/mm^3, and protein levels are higher than 60 mg/dL. CSF cell counts higher than 50/mm^3 suggest another diagnosis, such as HIV infection or hematologic malignancy. CSF protein levels may be normal early in the course of CIDP.

Differential Diagnosis

CIDP is distinguished from acute inflammatory demyelinating polyneuropathy by its time course. A similar manifestation can also occur in diabetes, lymphoma, monoclonal gammopathies (see later), and asymmetrical inherited neuropathies (see earlier).

TREATMENT

Rx

Corticosteroids are effective in more than two thirds of patients with CIDP. A standard approach is to use oral prednisone (1 mg/kg/day) for 6 to 8 weeks, followed by slow tapering over a 3- to 12-month period to a maintenance level of about 0.1 mg/kg/day. A response to prednisone may take months to occur, and occasional patients may worsen before they respond. As a result, plasma exchange[1] or IVIG[4,5] is often used as initial treatment. Because of the side effects of long-term corticosteroids or the lack of response to them, azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab, and interferon-α or -β have been used with variable success in uncontrolled reports.

Neuropathy Associated with Monoclonal Gammopathy

DEFINITION

Monoclonal gammopathy refers to the presence in the β-γ region of serum protein electrophoresis of an abnormal spike (variably called a paraprotein, monoclonal protein, or M protein) consisting of immunoglobulins of the same isotype, all produced by a single clone of abnormally proliferating lymphocyte and plasma cells. In some cases, the M protein is part of a malignant lymphoproliferative disease such as multiple myeloma, solitary plasmacytoma (IgG and IgA), Waldenström's macroglobulinemia (IgM) (Chapter 193), lymphoma (Chapter 191), chronic lymphocytic leukemia (IgM) (Chapter 190), primary amyloidosis (Chapter 194), or cryoglobulinemia (Chapter 193). In most instances, however, monoclonal gammopathy is not initially associated with any of these disorders and is classified as a monoclonal gammopathy of uncertain significance (MGUS), although in patients with MGUS, the gammopathy may evolve into a malignant form (Chapter 193).

EPIDEMIOLOGY

Monoclonal gammopathy occurs in up to 8% of patients with peripheral neuropathy of unknown etiology. However, MGUS is frequent, being found in 1% of the population older than 50 years and in 3% older than 70 years, and most subjects with MGUS do not have neuropathy. In some cases, the co-occurrence of neuropathy and M protein may be a coincidence, but in other cases, the M protein is clearly related to the neuropathy.

The prevalence of neuropathy is higher in patients with IgM versus IgG or IgA M proteins. The prevalence of symptomatic neuropathy associated with IgM monoclonal gammopathy in patients older than 50 years is approximately 20 per 100,000. In half of such patients, the M protein reacts either with the HNK1 carbohydrate moiety of MAG or with other glycoproteins (MPZ, PMP22) and glycolipids (sulfoglucuronyl paragloboside [SGPG] and lactosaminyl paragloboside [SGLPG]). IgM M proteins associated with neuropathy may also bind to other neural antigens.

In patients with IgG monoclonal gammopathy and neuropathy, the relationship is less clear than with IgM. Although about 10% of patients with multiple myeloma have neuropathy, in most cases, the M protein does not react with a neural antigen, and patients do not improve with immunotherapy (see later). Conversely, approximately 50% of patients with the osteosclerotic form of myeloma have neuropathy, often associated with the non-neurologic manifestations of *o*rganomegaly, *e*ndocrine abnormalities, and brown, tannish discoloration of the *s*kin. Collectively, the *M* protein, *p*olyneuropathy, and other features are referred to by the acronym POEMS (Chapter 193). Similarly, about 50% of patients with light-chain amyloidosis have neuropathy.

PATHOBIOLOGY

In patients with IgM M proteins that immunoreact with MAG, nerve biopsies demonstrate segmental demyelination with deposits of M protein and complement. The myelin lamellae are often widened on sural nerve biopsies, but a biopsy is not necessary for diagnosis. High titers (>1:10,000) of anti-MAG IgM antibodies are associated with neuropathy, and intraneural or systemic injection of anti-MAG IgM M proteins causes complement-mediated demyelination of nerves in animals.

CLINICAL MANIFESTATIONS

Most patients with anti-MAG neuropathies are initially seen in their sixth to seventh decade of life with dysesthesias and paresthesias in their legs and unsteadiness while walking because of loss of proprioception. Physical examination shows a length-dependent large fiber sensory neuropathy. Weakness may develop later.

DIAGNOSIS

Nerve conduction velocities are slow (about 25 m/second) with pronounced delays in distal motor latencies, thus prompting the designation *distal acquired demyelinating symmetrical neuropathy* to distinguish the disorder from CIDP.

TREATMENT

Rx

Treatment of neuropathies associated with monoclonal gammopathy is similar to that for CIDP (see earlier). However, patients with anti-MAG-related neuropathies do not respond as well to treatment as do patients with CIDP. Anecdotal data support the benefit of rituximab in some patients.

PROGNOSIS

Progression of the neuropathy of monoclonal gammopathy disables about 25% of patients after 10 years and 50% after 15 years. The course of patients with osteosclerotic myeloma and neuropathy depends on the response to treatment of the myeloma. In patients whose myeloma responds to treatment, more than 50% have improvement in neuropathy. In other patients with sensorimotor neuropathies associated with plasma cell dyscrasias, the course is variable, and the M protein may not be related to their neuropathy.

Multifocal Motor Neuropathy and Lewis-Sumner Syndrome

DEFINITION

Multifocal motor neuropathy is characterized by progressive, distal more than proximal, asymmetrical limb weakness, mostly affecting the upper limbs with minimal or no sensory impairment.

EPIDEMIOLOGY

The prevalence of multifocal motor neuropathy is estimated at 2 per 100,000. Men are more frequently affected than women (2.6:1). Initial symptoms develop in 80% between the ages of 20 and 50 years, with a mean age at onset of 40 years. Lewis-Sumner syndrome occurs less frequently than multifocal motor neuropathy.

PATHOBIOLOGY

Multifocal motor neuropathy is considered an autoimmune neuropathy based on its clinical improvement with immunologically based therapies and because of a frequent association with antiglycolipid antibodies. Patients with MMN often have serum antibodies that react with ganglioside GM_1, and these titers decrease during effective treatment. GM_1 is highly represented in neural membranes at the nodes of Ranvier, compact myelin, and the motor end plate at the neuromuscular junction. A blocking effect on mouse distal motor nerve conduction has been induced in vitro by sera from multifocal motor neuropathy patients with and without high anti-GM_1 antibody titers. These data support the presence of serum factors responsible for conduction block in the sera of patients with multifocal motor neuropathy, although these factors are not invariably related to anti-GM_1 antibodies. The Lewis Sumner syndrome, however, is not associated with anti-ganglioside antibodies.

CLINICAL MANIFESTATIONS

The usual pattern is progressive, distal, asymmetrical arm weakness, often in the distribution of a single nerve. In a minority of patients, weakness may start proximally or in the legs. The disease will frequently affect other nerves, occasionally with a crossed distribution (i.e., one arm and the contralateral leg). Asymmetry and predominance of arm weakness may become less evident as the disease progresses. Localized muscle atrophy may be mild or absent in the early stage of the disease but can become prominent later as a result of axonal degeneration.

Fasciculations, cramps, and myokymia occur in patients with multifocal motor neuropathy and those with amyotrophic lateral sclerosis (Chapter 418), making distinction between the two disorders difficult. Marked asymmetry in the degree of clinical findings and electrophysiologic abnormalities between contiguous nerves is suggestive of multifocal motor neuropathy rather than amyotrophic lateral sclerosis. Cranial nerve involvement or respiratory failure as a result of unilateral or bilateral phrenic nerve palsy rarely occurs in multifocal motor neuropathy. The presence of sensory loss suggests Lewis-Sumner syndrome.

DIAGNOSIS

The diagnosis is established by the presence of multifocal, persistent partial conduction blocks on motor but not sensory nerve conduction studies. Lewis-Sumner syndrome has sensory loss as well as weakness, with conduction block in both sensory and motor nerves.

TREATMENT

Rx

IVIG (2 g/kg) is the initial treatment of multifocal motor neuropathy, and almost 80% of patients respond within a week. However, improvement is typically brief (3 to 6 weeks), so repeated treatments are required indefinitely. Clinical improvement is often accompanied by a reduction or resolution of the

motor conduction block in some nerves, but it does not consistently correlate with a reduction in antiganglioside antibody titers. Patients may eventually become refractory to IVIG, and another agent may be needed, such as rituximab (e.g., 375 mg/m^2 weekly for four weeks) or azathioprine (2 to 3 mg/kg/day). Plasma exchange and corticosteroids are generally ineffective and have been associated with worsening neuropathy in some patients. Lewis-Sumner syndrome is considered a multifocal variant of CIDP and responds to the same treatments as CIDP.

PARANEOPLASTIC NEUROPATHIES

DEFINITION

Paraneoplastic neuropathies (Chapter 187) are a "remote effect of cancer" not caused by metastatic invasion of neural tissue; radiation therapy or chemotherapy; metabolic, vascular, or hormonal disturbances; or opportunistic infections. It is hypothesized that they are the result of host immune responses to a tumor antigen or antigens that are also present in neural tissues.

EPIDEMIOLOGY

Paraneoplastic syndromes occur in less than 1% of patients with cancer; peripheral neuropathy is only one of the paraneoplastic syndromes. Although more than 25% of patients with cancer have evident neuropathy on neurologic examination, the relationship to malignancy is unclear in most. Paraneoplastic neuropathy may develop before, during, or after the tumor is diagnosed. In certain tumors, neuropathies are distinctive and should prompt a thorough investigation for cancer. Small cell carcinoma of the lung (Chapter 197) is by far the most common underlying neoplasm, followed by carcinoma of the stomach, breast, colon, rectum, ovary, and prostate.

PATHOBIOLOGY

Subacute sensory neuropathy, the most characteristic paraneoplastic neuropathy, results from an immune-mediated ganglionitis that destroys sensory neurons in the dorsal root ganglia. Mononuclear inflammatory infiltrates composed of $CD4^+$ and prominent $CD8^+$ T cells, along with plasma cells, are found in the stroma surrounding the dorsal root ganglion neurons. Other findings include atrophy of the dorsal roots; loss of sensory neurons, which appear to be replaced by a proliferation of satellite cells (Nageotte's nodule); axonal degeneration; and secondary degeneration of the dorsal column of the spinal cord. Inflammatory infiltrates can also be found in peripheral nerves or muscle. Sural nerve biopsies typically reveal only loss of myelinated nerve fibers and are not useful for diagnosis.

CLINICAL MANIFESTATIONS

Subacute sensory neuropathy is characterized by subacute, progressive impairment of all sensory modalities and is associated with severe sensory ataxia and areflexia. Subacute sensory neuropathy may precede the diagnosis of tumor by months or even years.

At onset, patients may have shooting pain and burning sensations. Other symptoms include numbness, tingling, and a progressive sensory loss that may be asymmetrical. Symptoms usually progress rapidly to involve all four limbs, the trunk, and face. Findings may then stabilize, although by this time the patient is often totally disabled. Occasional patients have an indolent course.

Neurologic examination reveals loss of deep tendon reflexes and involvement of all modalities of sensation; large fiber modalities such as vibration and joint position sense are most severely affected. The loss of position sense may lead to severe sensory ataxia with pseudoathetoid movements of the hands and an inability to walk despite normal strength. Cranial nerve involvement may cause sensorineural deafness, loss of taste, and facial numbness. The frequent asymmetrical pattern of symptoms sometimes suggests a radiculopathy or plexopathy.

A paraneoplastic encephalomyelitis characterized by patchy, multifocal neuronal loss in regions of the cerebral hemispheres, the limbic system, the cerebellum, the brain stem, the spinal cord, and autonomic ganglia often develops in patients with subacute sensory neuropathy. Autonomic symptoms include impotence, dry mouth, and constipation.

DIAGNOSIS

The diagnosis is based on recognizing the typical neuropathy in the setting of malignancy. The results of routine laboratory studies are generally normal. The diagnosis is supported by finding serum polyclonal IgG anti-Hu antibodies, also called antineuronal antibodies type 1, or by indirect immunofluorescence or immunohistochemistry and confirmed by Western blot analysis.

Subacute painful, asymmetrical neuropathy or neuronopathy in an elderly patient should prompt a search for carcinoma of the lung because small cell lung cancer (Chapter 197) accounts for more than 80% of the associated tumors. Subacute sensory neuropathy has also been reported in patients with adenocarcinoma of the lung, breast, ovary, stomach, colon, rectum, and prostate as well as Hodgkin's and non-Hodgkin's lymphoma. In patients with no evidence of cancer, detection of anti-Hu antibodies should prompt a computed tomography study of the chest with special attention to the mediastinal lymph nodes. The use of whole body positron emission tomography with fluorodeoxyglucose has been advocated for early diagnosis in patients with anti-Hu antibodies or clinical suspicion of subacute sensory neuropathy because it may reveal neoplastic adenopathy months before computed tomography or magnetic resonance imaging can detect them.

TREATMENT Rx

Subacute sensory neuropathy responds poorly to plasma exchange, IVIG, or various immunosuppressant medications, even when such treatment is started early in the course of the disease, possibly before the loss of sensory neurons. Even successful treatment of the tumor rarely induces remission of subacute sensory neuropathy, but the symptoms may stabilize.

Other Neuropathies Possibly Associated with Cancer

SENSORIMOTOR NEUROPATHY

Sensorimotor neuropathy occurs in approximately 25% of patients with all types of tumors. The neuropathy can have an acute or subacute onset, with a progressive or relapsing remitting course. Because no antineuronal antibody has been specifically associated with these neuropathies, their paraneoplastic nature is not established. Severe or relapsing neuropathies often precede the diagnosis of cancer, but the search for malignancy is generally limited to a chest radiograph, stool samples for blood, and routine blood tests. There are no specific treatments of these neuropathies, and their progression does not necessarily correlate with that of the malignancy.

PARANEOPLASTIC VASCULITIS OF NERVES

A nonsystemic vasculitic neuropathy, which may also involve muscle, occurs with various types of tumor, including small cell lung cancer, lymphoma, and carcinoma of the kidney, stomach, and prostate. Neurologic symptoms may develop either before or after the tumor is diagnosed. The neuropathy is subacute and progressive and usually affects older men. Like many paraneoplastic disorders, these neuropathies often do not respond well to treatment, which is similar to that for the vasculitic neuropathies (see later).

VASCULITIC NEUROPATHIES

DEFINITION

Vasculitic neuropathies (Table 428-5) typically present as painful acute or semiacute axonal mononeuritis multiplex. There is acute motor and sensory loss in multiple nerve territories. The number of nerves involved may be extensive enough to make the distinction between a multifocal and diffuse neuropathy difficult. Occasionally, vasculitic neuropathy can present as sensory neuropathy, trigeminal neuropathy, compressive neuropathy, or autonomic neuropathy. Neuropathy can occur in systemic vasculitis associated with other organ systems as well as in nonsystemic vasculitis affecting just nerve and muscle.

EPIDEMIOLOGY

Systemic vasculitic neuropathy is more common than nonsystemic vasculitic neuropathy. Peak ages at onset of both are the fifth to eighth decades, but vasculitis can occur at any age. Neuropathy, particularly mononeuritis multiplex, is common in several forms of systemic vasculitis. Rheumatoid arthritis (Chapter 272) evolves into systemic rheumatoid vasculitis in 5 to 15% of patients, and vasculitic neuropathy will develop in about 50% of these patients. More than 50% of patients with Churg-Strauss syndrome (Chapter 278), 40 to 50% with Wegener's granulomatosis (Chapter 278), 35 to 75% with polyarteritis nodosa (Chapter 278), and most patients with mixed

TABLE 428-5 SYSTEMIC VASCULITIS AND NEUROPATHY

TYPE	SEROLOGY FEATURES	ASSOCIATED FEATURES	USUAL NEUROPATHY TYPE	NEUROPATHY PREVALENCE
Rheumatoid arthritis	RF 80-90%	Arthralgias, arthritis frequent; multiple organs	Mononeuritis multiplex and sensorimotor neuropathy	50% of patients with vasculitis
Churg-Strauss syndrome	c-ANCA < 30% p-ANCA < 50%	Eosinophilia Asthma	Mononeuritis multiplex	20% of patients
Wegener's granulomatosis	c-ANCA 75-90% p-ANCA < 20%	Pulmonary and renal	Mononeuritis multiplex	15% of patients
Polyarteritis nodosa	c- and p-ANCA rare	Multiple organs, 30% hepatitis B	Mononeuritis multiplex	60% of patients
Mixed cryoglobulinemia	No	Hepatitis C, purpura frequent	Mononeuritis multiplex	20-90% of patients
Sjögren's syndrome	α-Ro/SS-A 60%, α-La/SS-B 50%	Dry eyes, dry mouth; women 90%	Sensory	25% of patients
Systemic lupus erythematosus	ANA screen > 90%	Multiorgan	Sensorimotor neuropathy	5-20% of patients

ANA = antinuclear antigen; p- and c-ANCA = perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies; RF = rheumatoid factor; α-Ro/SS-A and α-La/SS-B = antibodies to the Ro/SS-A and La/SS-B antigens.

cryoglobulinemia (Chapter 193) have neuropathy. Patients with Sjögren's syndrome (Chapter 276) are often initially found to have sensory neuropathies. Neuropathies are uncommon in systemic lupus erythematosus.

PATHOBIOLOGY

In patients with mononeuritis multiplex, axonal degeneration develops as a result of nerve ischemia caused by the vasculitic process. Immune-mediated inflammation and necrosis of blood vessel walls occlude the vessel's lumen, thereby resulting in ischemic damage. Small arteries or arterioles (50 to 300 μm) are most commonly affected, particularly those that occur in watershed areas between the distribution of the major nutrient arteries of proximal nerves. True nerve infarcts are rare.

The immune-mediated inflammation is associated with antibody-antigen complexes that are deposited in the wall of the blood vessel. Antibodies also bind directly to endothelial cell antigens. In both circumstances, complement is activated, as evidenced by deposition of membrane attack complex. Chemotactic factors then recruit neutrophils, which release proteolytic enzymes and generate toxic oxygen free radicals.

The sensory neuropathy of Sjögren's syndrome probably results from the infiltration of dorsal root ganglia by cytotoxic T cells. Some patients with systemic vasculitis have symmetrical neuropathies rather than mononeuritis. The pathogenesis of such cases is not defined.

CLINICAL MANIFESTATIONS

Patients typically have a relatively sudden onset of painful, focal or multifocal weakness or sensory loss. These symptoms reflect ischemia anywhere along the length of the nerve or nerves, generally in the lower extremities. Onset usually occurs rapidly (hours to days) as a result of the abrupt, ischemic etiology.

DIAGNOSIS

Nerve biopsy of clinically affected sensory nerves (sural, superficial peroneal, or superficial radial) is often necessary and is justified because therapy may be aggressive and long-term. Superficial peroneal nerve biopsy may be combined with muscle biopsy from the same incision. Pathologic features diagnostic of vasculitis occur in 60% of patients, and less specific features such as multifocal loss of fibers occur in others. Findings diagnostic of vasculitis include destruction of the vessel and inflammation within the vessel wall. Fibrinoid necrosis, vessel wall scarring, recanalization, neovascularization, and hemosiderin are common, but not essential, histopathologic features of vasculitis.

Although nerve biopsy is the gold standard for diagnosis, clinical, serologic, and electrophysiologic findings can suggest the diagnosis. For example, EMG and nerve conduction velocity studies can distinguish between mononeuritis multiplex and symmetrical neuropathy. It is essential to confirm nerve conduction velocity abnormalities in a nerve before biopsy, which is always required before treatment. An acute or subacute onset of asymmetrical weakness or sensory loss in the distribution of individual nerves suggests mononeuritis multiplex, particularly in the setting of a known connective tissue disorder. Systemic symptoms, such as unexplained weight loss and purpura, or constitutional symptoms, such as fever, myalgias, arthralgias, pulmonary disease, abdominal complaints, rashes, or night sweats, suggest systemic vasculitis in a patient with mononeuritis multiplex.

The erythrocyte sedimentation rate is usually elevated in the systemic vasculitides but is normal in nonsystemic cases. Perinuclear and cytoplasmic antineutrophil cytoplasmic antibody (p-ANCA and c-ANCA) suggests Wegener's granulomatosis (Chapter 278) or Churg-Strauss syndrome (Chapter 278). Hepatitis C (Chapter 151) is usually associated with the presence of cryoglobulins. Serum complement levels, extractable nuclear antigen, angiotensin-converting enzyme levels, serum protein electrophoresis, and HIV serology are generally indicated. CSF analysis is not usually helpful in cases of vasculitic neuropathy but may be needed to exclude infectious (e.g., Lyme disease [Chapter 329]) or other inflammatory causes.

Differential Diagnosis

Acute or subacute mononeuritis multiplex may also result from diabetes, sarcoidosis, Lyme disease, and malignant infiltration of nerves. Multifocal motor neuropathy with conduction block and Lewis-Sumner syndrome can resemble vasculitic mononeuritis multiplex. Sensory neuropathies similar to those in Sjögren's syndrome may occur in patients with diabetes, paraneoplastic syndromes associated with anti-Hu antibodies, and pyridoxine deficiency.

TREATMENT Rx

Systemic Vasculitis

Corticosteroid therapy is used for most vasculitic neuropathies (Chapter 278). Oral prednisone (1 mg/kg) is appropriate for relatively mild cases, but intravenous methylprednisolone (1000 mg/day for 3 to 5 days) may be indicated as initial treatment in severe cases. Daily dosing is commonly used for the first 2 months or longer if the disease remains active. Subsequently, the dose is gradually tapered, with a transition to alternate-day dosing and discontinuation depending on the clinical picture and associated systemic features.

Corticosteroid treatment may be adequate for Churg-Strauss syndrome, but additional medication is generally needed in other forms of systemic vasculitic neuropathy. In most cases of Wegener's granulomatosis and microscopic polyangiitis, combined therapy with glucocorticoids and oral cyclophosphamide (2 mg/kg/day) or weekly oral methotrexate (7.5 mg/week) is used. Azathioprine (2 to 3 mg/kg/day) is also used.

Nonsystemic Vasculitis

Because patients with nonsystemic vasculitic neuropathy may recover spontaneously or have a relatively benign course, low-dose or alternate-day oral prednisone (60 to 80 mg/day) is often adequate therapy. Azathioprine or weekly methotrexate can be used as a glucocorticoid-sparing agent. Doses such as 60 mg of prednisone on alternate days, 2 to 3 mg/kg/day of azathioprine, or 7.5 to 15 mg/week of methotrexate, are reasonable starting doses that can ultimately be tapered if the treatments prove effective.

PROGNOSIS

Most systemic and nonsystemic vasculitis responds to treatment, and patients make at least partial recovery with gradual return of function after a static period. The prognosis of patients with nonsystemic vasculitis is better than that of patients with systemic vasculitis, with fewer episodes of nerve damage; the disease may be monophasic or relapsing remitting over a period of years, and most patients recover the ability to walk.

CRITICAL ILLNESS NEUROPATHY

DEFINITION

Critical illness polyneuropathy is an acute or subacute axonal length-dependent neuropathy that occurs in critically ill patients, not as a direct consequence of their underlying illness. The neuropathy is monophasic and recovers, at least in part, if the patient survives the underlying illness.

EPIDEMIOLOGY

The incidence of critical illness polyneuropathy is uncertain because of variable diagnostic criteria. Moreover, it frequently accompanies critical illness myopathy (Chapter 429), which may be indistinguishable from it. Critical illness polyneuropathy frequently occurs in patients with systemic inflammatory response syndrome (Chapters 106 and 108), a generalized inflammatory host response to severe illness; up to 70% of patients with sepsis have a length-dependent axonal neuropathy.

PATHOBIOLOGY

Nerve biopsies have identified perivascular lymphocytic infiltration, macrophages, and cytokines such as interleukin-1β, interferon-γ, and interleukin-12. Ischemia caused by a sepsis-induced abnormal distribution of capillary blood flow, nutritional deprivation, and hypoglycemia has also been implicated in critical illness polyneuropathy.

CLINICAL MANIFESTATIONS

The typical finding is rapid development of profound limb weakness days to weeks after acquiring a severe illness that necessitated intensive care unit admission and ventilator support. Respiratory muscles are often involved, and inability to wean from the ventilator is a common problem. Elicitable deep tendon reflexes distinguish critical illness polyneuropathy from acute inflammatory demyelinating polyneuropathy. Sensory findings are typically absent, but sensory testing is difficult to perform in severely disabled patients.

DIAGNOSIS

Laboratory studies are rarely helpful. CSF protein is normal, unlike the case with acute inflammatory demyelinating polyneuropathy. A lack of cells also excludes infectious or inflammatory disorders. Creatine kinase levels are normal, unlike critical illness myopathy, in which they may be elevated.

Motor conduction velocities are normal with reduced or absent compound muscle action potential amplitudes. Critical illness polyneuropathy is a predominantly motor disorder, so sensory conduction velocities and sensory nerve action potential amplitudes are normal. Abnormal spontaneous activity from axonal damage may occur within 1 to 3 weeks of onset. The presence of neuropathic and myopathic abnormalities suggests that critical illness polyneuropathy and critical illness myopathy coexist.

Differential Diagnosis

Distinguishing between critical illness myopathy and critical illness polyneuropathy can be difficult. Glucocorticoids and neuromuscular blocking agents predispose to critical illness myopathy (Chapter 429), which occurs in up to 5% of critically ill patients and is also manifested as rapidly progressive weakness of the limbs and diaphragm. Muscle biopsy and special electrical techniques are often needed to diagnose critical illness myopathy. If patients with critical illness myopathy survive their critical illness, their long-term prognosis may be better than that of patients with critical illness polyneuropathy.

Acute inflammatory demyelinating polyneuropathy can mimic critical illness polyneuropathy but can be distinguished by slow nerve conduction velocity and abnormal CSF. Acute motor axonal neuropathy or acute motor and sensory axonal neuropathy may be more difficult to distinguish, particularly if sepsis or another underlying disorder induces an abnormal CSF; nevertheless, the presence of antiganglioside antibodies may help distinguish these disorders from critical illness polyneuropathy. Myasthenia gravis (Chapter 430), botulinum toxin (Chapter 304), acetylcholinesterase inhibitor poisoning (Chapter 110), and other toxins can cause a similar clinical picture.

TREATMENT

Rx

The main treatment is directed at the underlying disease or diseases, such as sepsis. Glucocorticoids and neuromuscular blocking agents should be avoided if possible because both have been associated with critical illness myopathy.

PROGNOSIS

In-hospital mortality has been reported to be as high as 84% in patients with critical illness polyneuropathy, compared with 50% in similarly ill patients without it. Although most patients improve if they survive their underlying illness, up to 10% have persistent severe limb weakness and are ventilator dependent. Most patients have at least some evidence of weakness 2 years after discharge.

DIABETIC AND OTHER METABOLIC NEUROPATHIES

DEFINITION

Diabetic peripheral neuropathies can be separated into two large groups: (1) symmetrical, predominantly sensory or autonomic neuropathies (or both), and (2) asymmetrical mononeuropathies or plexopathies.

EPIDEMIOLOGY

Diabetes (Chapter 236) is the most common cause of neuropathy in the Western world. Diabetic neuropathy occurs in 8 to 70% of patients with diabetes, depending on the criteria used to diagnose neuropathy, and patients with retinopathy or overt albuminuria are more than twice as likely to have neuropathy. Distal symmetrical polyneuropathies are the most common diabetic neuropathy, but distal autonomic neuropathy is also common. For example, impotence develops in 20 to 60% of diabetic men, but widespread autonomic dysfunction develops in less than 5% of diabetic patients.

PATHOBIOLOGY

Distal Symmetrical Polyneuropathy and Autonomic Neuropathy

The pathogenesis of distal symmetrical polyneuropathy and autonomic neuropathy involves both microvascular and metabolic abnormalities, with a causal link between increased blood glucose levels and the development and progression of diabetic neuropathy. The mechanisms by which hyperglycemia causes nerve dysfunction may include activation of the polyol pathway, extensive glycation, altered diacylglycerol and protein kinase activity, and oxidative stress. Evidence from animal models suggests a role for neurotrophic factors, in particular, nerve growth factor, which selectively supports small fiber sensory and sympathetic neurons.

Acute Asymmetrical Neuropathies

The focal nature of these diabetic neuropathies is presumed to result from occlusion of endoneurial arterioles with resultant ischemic damage to the nerve. Changes suggestive of vasculitis are observed in epineurial and perineurial blood vessels in about 50% of cases, and perivascular lymphocytic infiltrates are common.

CLINICAL MANIFESTATIONS

Distal Sensory Polyneuropathy and Autonomic Neuropathy

Distal symmetrical polyneuropathy is typically manifested as insidious symmetrical sensory loss of small (pain and temperature) and large (proprioception) fiber modalities. Paresthesias or painful dysesthesias (e.g., burning or tingling feet) are common, although not invariable. An unsteady gait may be the initial finding. Weakness is usually minimal, even in the distal foot muscles. Ankle reflexes are generally absent, although patellar reflexes may be present. Feet and distal calves are often cold and erythematous. Slow distal proximal progression of sensory symptoms and signs is the rule. By the time that symptoms reach the knees, abnormalities often begin in the hands.

When sensory changes reach the level of the knees, symptoms of autonomic neuropathy often begin: gastroparesis, which may alternate with diarrhea, orthostatic hypotension, anhidrosis, cardiac arrhythmias, and impotence. Autonomic abnormalities can be the most disabling component of diabetic neuropathy.

Acute Asymmetrical Neuropathies

Asymmetrical acute neuropathies cause focal or multifocal symptoms, depending on the peripheral nerve or nerves affected. They are usually accompanied by acute pain in the afflicted region. The pain may be deep and aching or throbbing and lancinating. Most cases of acute focal or multifocal

diabetic neuropathy eventually resolve, at least partially. Pain may resolve within a few months, whereas weakness may take a year or more to recover and may persist. Characteristic manifestations include the following:

1. Compressive *mononeuropathies*. Compressive neuropathies, such as carpal tunnel syndrome, occur more frequently in diabetic patients for unclear reasons. It is not known whether the response of carpal tunnel syndrome to treatment is as effective as when these mononeuropathies occur independently of diabetes.
2. Diabetic *lumbosacral radiculoplexus neuropathy*. Patients are frequently elderly with type 2 diabetes (Chapter 237). Asymmetrical pain in the upper part of the thigh is followed by progressive weakness and atrophy of the proximal leg muscles. Progression to the other leg occurs frequently. In about 50% of those affected, autonomic symptoms also develop, including orthostatic, gastrointestinal, and sexual dysfunction. Weakness may progress for up to 6 months. About 50% of patients require a wheelchair for ambulation, and many require opiates for pain. After the nadir, the patient will usually stabilize for several months, followed by progressive improvement. As many as 50% of patients do not regain full ambulation.
3. *Truncal radiculopathy*. An acute, focal onset of pain and sensory loss develop over a region of the trunk. In extreme cases, the abdominal wall muscles may become weak, resembling a hernia. As with diabetic lumbosacral radiculoplexus neuropathy, at least partial improvement will probably occur after a period of months, but the pain is difficult to control.
4. *Cranial neuropathies*: The classic manifestation is an acute oculomotor nerve palsy in which retro-orbital pain is followed by diplopia and ptosis. Pupillary fibers are often spared, distinguishing the disorder from lesions that compress the oculomotor nerve and cause a dilated pupil. Similar findings may occur with the trochlear (fourth nerve) or abducens nerves. Bell's palsy is more frequent and is less likely to involve taste in diabetic patients than in patients without diabetes.

DIAGNOSIS

Distal Sensory Polyneuropathy

The diagnosis of distal symmetrical polyneuropathy is based on identification of a predominantly sensory length-dependent neuropathy in the presence of either type 1 or type 2 diabetes. Neuropathy can develop independently of good control of blood sugar. Clinically similar neuropathies occur in patients with glucose abnormalities that are detectable only by oral glucose tolerance testing. Nerve conduction studies usually show low-amplitude or nondetectable sensory nerve action potential amplitudes; when detectable, sensory conduction may be slightly slow. Compound muscle action potential amplitudes are often reduced. Motor conduction studies are slightly slowed even if there is only minimal motor involvement clinically. Needle EMG in distal muscles typically demonstrates changes characteristic of chronic denervation. Occasional fibrillations and positive sharp waves may also be present.

Acute Asymmetrical Neuropathy

The focal neuropathies tend to occur in older patients with type 2 diabetes. The characteristic syndromes are diagnosed on the basis of their clinical manifestations and association with diabetes. EMG may demonstrate pronounced denervation in affected muscles. Concomitant evidence of distal symmetrical polyneuropathy is often present clinically and by electrophysiologic studies.

TREATMENT Rx

Distal Symmetrical Polyneuropathy

An important treatment goal in distal symmetrical polyneuropathy is prevention of osteomyelitis and the resultant amputation of toes and feet. Because patients often do not sense injuries to their feet, diligence in foot care is important. Specific treatments to reverse or halt progression of the distal symmetrical polyneuropathy in diabetic patients are not yet available. Current therapy is based on control of hyperglycemia, management of symptoms, and foot care. Careful control of blood glucose (Chapter 236) remains the only treatment proven to delay the onset and slow progression of distal symmetrical polyneuropathy. There is, however, no hemoglobin A_{1c} threshold below which patients avoid risk for neuropathy. For the treatment of pain (Chapter 29), combination therapy of gabapentin (usually starting at about 300 mg three times a day but titrating up to as high as 3600 mg per day) with either nortriptyline (three times a day, titrated to as high as 100 mg per day or as tolerated) or sustained-release morphine (15 mg twice daily) in low doses is effective when less aggressive treatments fail. Pregabalin is effective at doses of 300 mg to 600 mg daily. Duloxetine at 60 to 120 mg daily is another option.

Acute Asymmetrical Neuropathy

Although acute asymmetrical neuropathy generally improves spontaneously, improvement may take months and remain incomplete. Intravenous corticosteroids, IVIG, or plasma exchange may improve the speed and extent of recovery, but these treatments are not of established benefit. Pain management is similar to that just described. Because the pain in patients with diabetic lumbosacral radiculoplexus neuropathy and truncal radiculopathy is focal, topical therapy may be effective.

INFECTIOUS NEUROPATHIES

Neuropathies Associated with HIV Infection

The peripheral nervous system may be involved in all phases of HIV infection (Chapter 401). The most common peripheral neuropathy is a distal, painful, sensory axonal polyneuropathy that is very similar to the toxic neuropathy caused by nucleoside reverse transcriptase inhibitors (NRTIs), including zidovudine, zalcitabine, didanosine, stavudine, and lamivudine. When an iatrogenic neuropathy is suspected, discontinuation of NRTIs may improve symptoms. Conversely, a neuropathy caused by HIV is likely to stabilize or improve with antiretroviral treatment.

Inflammatory neuropathies such as chronic or acute inflammatory demyelinating polyneuropathy can also occur in the early stages of HIV infection; the CSF cytoalbumin dissociation usually seen with these conditions may not be evident in these patients because of a mild CSF mononuclear pleocytosis. The response of these neuropathies to plasma exchange or IVIG is generally good. In later stages of HIV infection, cytomegalovirus (Chapter 384) may cause either an acute lumbosacral polyradiculopathy as a result of direct invasion of nerve roots or a mononeuritis multiplex through a vasculitic mechanism.

Neuropathies Associated with Herpes Zoster

Varicella-zoster virus (Chapter 383) usually remains latent in cranial or spinal ganglia after resolution of a systemic infection. Reactivation, which tends to occur in elderly persons and immunocompromised patients, causes a vesicular skin eruption accompanied by pruritus and dysesthesias. Herpes zoster normally undergoes spontaneous resolution but is frequently followed by a severe post-herpetic neuralgia, which is defined as pain persisting for more than 6 weeks after the rash appears. Early treatment with oral acyclovir (800 mg, five times daily for 7 days) may reduce both the duration of the acute phase and the chance of post-herpetic neuralgia developing, which is usually treated with symptomatic drugs for neuropathic pain (Chapter 29).

The use of concomitant corticosteroids in addition to acyclovir appears to reduce acute pain without exacerbating viral spread. However, corticosteroids do not appear to reduce the incidence or severity of post-herpetic neuralgia.

Neuropathy Associated with Lyme Disease

Borrelia burgdorferi causes a disease with three stages (Chapter 329). In the first stage, shortly after and in the same area of a tick bite, a nonpruritic rash (erythema migrans) appears and spontaneously disappears after a few weeks. The second stage is frequently associated with neurologic complications such as lymphocytic meningitis and focal and multifocal peripheral and cranial neuropathies; characteristic manifestations are unilateral or bilateral facial palsy and radiculitis. The third stage is associated with severe neurologic complications, including encephalopathy, encephalomyelitis, and a predominantly sensory axonal polyneuropathy. A lymphocytic pleocytosis in CSF and demonstration of *B. burgdorferi* infection in serum or CSF are the main laboratory findings. Treatment is discussed in Chapter 329.

Neuropathy Associated with Leprosy

Leprosy (Chapter 334) is the most common cause of peripheral neuropathy in developing countries, although it is infrequent in the Western world. Leprosy may be manifested in different forms, depending on the host's immune system. Patients with normal cell-mediated immunity are more likely to have a tuberculoid form characterized by hypopigmented skin

lesions associated with decreased sensation. In patients with abnormal cell-mediated immunity, the more severe lepromatous form with large disfiguring lesions may develop. A mononeuritis multiplex pattern with prominent superficial sensory loss is the most typical clinical manifestation of leprosy.

If treated early, neuropathies in leprosy can improve significantly. World Health Organization recommendations call for combination therapy that includes dapsone (50 to 100 mg/day or 200 to 250 mg/wk), rifampicin (600 mg monthly), and clofazimine (100 mg/day) (Chapter 334).

Neuropathy Associated with Diphtheria

Although vaccination has made diphtheria (Chapter 300) rare in developed countries, it is still an important cause of subacute neuropathy in developing countries. Some strains of *Corynebacterium diphtheriae* produce a potent neurotoxin that causes palatal weakness, accommodation deficits, and extraocular palsies. This acute manifestation is followed by an ascending paralysis secondary to a demyelinating neuropathy that shares many clinical features with acute inflammatory demyelinating polyneuropathy.

The neuropathy caused by the neurotoxin usually resolves with resolution of the infection. The diphtheria organism can be eradicated by therapy with antibiotics such as erythromycin (2 g/day intravenously divided twice daily for adults) or penicillin (procaine penicillin G, 1.2 million U/day intramuscularly divided twice daily for 14 days). However, the neuropathy, as with other manifestations of the disease, generally requires treatment with diphtheria antitoxin, a hyperimmune antiserum produced in horses. Depending on the severity of the disease, antitoxin is administered intramuscularly or intravenously (80,000 to 120,000 units for extensive disease with a duration of 3 or more days) (Chapter 300).

TOXIC AND DEFICIENCY SYNDROMES

In Western countries, toxic neuropathies are frequently the side effects of medications rather than a result of environmental exposure. In most cases, iatrogenic neuropathy is manifested as a length-dependent or "dying-back" axonal neuropathy. Treatment requires a correct diagnosis (Table 428-6) and discontinuation of the drug, but improvement is often slow and may take several months.

Compressive Neuropathies

Peripheral nerves are vulnerable to chronic compression in many sites: median nerve compression at the wrist within the carpal tunnel (*carpal tunnel syndrome*), median nerve compression in the upper part of the forearm, ulnar nerve compression in the hand (*cubital tunnel syndrome*), ulnar nerve compression at the elbow or wrist, tibial nerve compression behind the medial malleolus (*tarsal tunnel syndrome*), and peroneal nerve compression over the lateral fibular head.

CARPAL TUNNEL SYNDROME

Entrapment of the median nerve at the wrist reflects the limited space available for the median nerve because of the surrounding bone, joint, ligaments, tendons, and synovium. Repetitive motion of the fingers is an exacerbating element. Other precipitating factors include trauma, osteoarthritis, synovial cysts, myxedema (Chapter 233), and amyloid deposition (Chapter 194). Mild symptoms typically involve paresthesias of the first three digits, often occur overnight, and are relieved by shaking or elevating the hands. In more severe disease, objective sensory loss in the median nerve distribution, weakness of median-innervated muscles such as the abductor pollicis brevis, and prolongation of nerve conduction across the carpal tunnel (prolonged distal latency) are characteristic. The diagnosis is supported by identification of *Tinel's sign,* in which tapping the carpal tunnel elicits paresthesias in the median nerve distribution, and by paresthesias produced by sustained flexion of the wrist (*Phalen's sign*). Treatment begins with splinting of the wrist in slight dorsiflexion during sleep. Injection of corticosteroids into the carpal tunnel provides temporary benefit. More severe carpal tunnel syndrome is treated surgically by release of the carpal ligament.[10]

TABLE 428-6 TOXIC AND DEFICIENCY NEUROPATHIES

Associated with antineoplastic agents: vincristine, paclitaxel (Taxol), cisplatin, suramin, thalidomide
Associated with antimicrobials: chloroquine, dapsone, isoniazid, metronidazole, nitrofurantoin
Associated with cardiac medications: amiodarone, perhexiline, hydralazine
Associated with other medications: colchicine, tacrolimus, gold salts, phenytoin, disulfiram (Antabuse), pyridoxine (vitamin B_6)
Associated with heavy metals: lead, arsenic, mercury, thallium
Associated with chemical compounds: acrylamide, carbon disulfide, ethylene glycol, hexacarbons, organophosphate esters, Vacor
Deficiency neuropathies: vitamin B_1 deficiency, vitamin B_{12} deficiency, vitamin E deficiency

Bell's Palsy

Unilateral facial paralysis of acute onset frequently occurs on an idiopathic basis (Bell's palsy). The diagnosis is one of exclusion. Facial nerve palsies also occur in the setting of *herpes zoster oticus* (Chapter 383), in which they are typically associated with otalgia and varicelliform lesions affecting the external ear, ear canal, or tympanic membrane. Facial paralysis of a lower motor neuron type can be caused by carcinomatous meningitis (Chapter 195), sarcoidosis (Chapter 95), Lyme disease (Chapter 329), and HIV infection (Chapter 401).

Primary tumors of the facial nerve can occur with apparently rapidly developing facial paralysis. Facial paralysis can also occur in primary *CNS disease* affecting the pontomedullary junction, such as stroke or multiple sclerosis (Chapter 419).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Most cases of facial paralysis are idiopathic. Patients typically notice facial paralysis on inspection in the mirror in the morning. Facial paralysis may be heralded or accompanied by pain behind the ear. The severity of paralysis varies widely.

TREATMENT

Rx

In a randomized trial, 10 days of oral corticosteroids (prednisolone, 25 mg twice daily for 10 days) administered early in the course increased the return of facial function from 63 to 83% at 3 months in patients with idiopathic Bell's palsy;[11] acyclovir added to prednisone is of uncertain benefit.[11] In severe cases, protection of the cornea from drying and injury is essential.

PROGNOSIS

The prognosis is favorable in most cases, but about 10% of patients achieve little recovery. Aberrant regeneration of the facial nerve can cause synkinesias, such as "jaw winking" (when the eye is closed) or tearing accompanying salivation ("syndrome of crocodile tears").

Trigeminal Neuralgia (Tic Douloureux)

Trigeminal neuralgia and other painful cranial neuralgias are discussed in Chapter 405.

Grade A

1. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. *Lancet*. 1997;349:225-230.
2. Hahn AF, Bolton CF, Pillay N, et al. Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy: A double-blind, sham-controlled, cross-over study. *Brain*. 1996;119:1055-1066.
3. Hughes RA, Raphaël JC, Swan AV, et al. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2006;1:CD002063.
4. Mendell JR, Barohn RJ, Freimer ML, et al. Randomized controlled trial of IVIG in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology*. 2001;56:445-449.
5. Hughes R, Bensa S, Willison H, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol*. 2001;50:195-201.
6. Gilron I, Bailey JM, Tu D, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomized controlled crossover trial. *Lancet*. 2009;374:1252-1261.
7. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352:1324-1334.
8. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 2009;3:CD007076.
9. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database Syst Rev*. 2009;4:CD007115.
10. Jarvik JG, Comstock BA, Kliot M, et al. Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial. *Lancet*. 2009;374:1074-1081.
11. Sullivan FM, Swan IR, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med*. 2007;357:1598-1607.

SUGGESTED READINGS

Brannagan TH 3rd. Current treatments of chronic immune-mediated demyelinating polyneuropathies. *Muscle Nerve*. 2009;39:563-578. *Review*.

Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;84:3-14. *Evidence-based review*.

England JD, Gronseth GS, Franklin G, et al. Practice parameter. Evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2009;72:185-192. *Review*.

Kanji JN, Anglin RE, Hunt DL, et al. Does this patient with diabetes have large-fiber peripheral neuropathy? *JAMA*. 2010;303:1526-1532. *Case-based review emphasizing the value of altered vibration and pressure sensation on the physical examination*.

Schenone A, Nobbio L, Monti Bragadin M, et al. Inherited neuropathies. *Curr Treat Options Neurol*. 2011;13:160-179. *Comprehensive review*.

429 MUSCLE DISEASES

PATRICK F. CHINNERY

DEFINITION

Muscle diseases, or myopathies, are disorders of skeletal muscle structure or function. Myopathies can be primary and occur in isolation, or they can be part of multisystem diseases that involve other organs.

EPIDEMIOLOGY

Many muscle diseases (Table 429-1) are genetically determined, with an autosomal dominant, autosomal recessive, X-linked, or maternal (mitochondrial) inheritance pattern. Precipitating environmental factors of muscle disease include recent infections, foreign travel, medications such as statins that may increase the likelihood of muscle pain, and alcohol abuse (Chapter 425). Exercise tends to precipitate symptoms in patients with metabolic disorders, whereas cold and damp conditions and a high-carbohydrate meal can precipitate weakness in muscle channelopathies. The prevalence of muscle disease, which is estimated to be 1 per 1000 people, includes acute or short-lived disorders (e.g., myositis owing to infectious or toxic causes; see later), or chronic inflammatory and genetic disorders that cause substantial morbidity over decades. Muscle disease can cause premature death owing to neuromuscular weakness and secondary chest infections or to involvement of other organs in multisystem diseases. Cardiac involvement, which is particularly common in muscle diseases, can cause life-threatening dysrhythmias or chronic heart failure.

PATHOBIOLOGY

The basic unit of motor function is the motor unit, which is defined as the anterior horn cell body, its axon, the neuromuscular junction, and all the skeletal muscle fibers innervated by the one axon. The number of muscle fibers innervated by each motor nerve varies, from a few (e.g., in muscles controlling very precise movements, such as extra-ocular muscle) to more than 1000 (e.g., large and powerful but less precise muscles, such as the quadriceps).

Skeletal muscle fibers are multinucleate giant cells that are the principal component of skeletal muscle. Muscle also contains fibrous connective tissue, blood vessels, and blood components, all of which can be involved in muscle disease. The muscle fiber itself contains interdigitated myofibrils that are composed of thick (myosin) and thin (actin, troponin, tropomyosin) filaments. The myofibrils are organized into a functional unit called the sarcomere, which is about 2 mm in length and is bound by the Z disc. Subcellular organelles between the myofibrils include mitochondria, which are the principal energy source, the endoplasmic reticulum, transverse tubules that communicate with the extracellular space, and vacuoles that contain glycogen and lipid. The muscle cell nuclei are found in the periphery, just below the plasma membrane, which is the sarcolemma.

Muscle function (Fig. 429-1) is dependent on a chemical energy source—adenosine triphosphate (ATP), which in the first 30 minutes of sustained activity is produced by the breakdown of muscle glycogen (glycolysis) and after 30 minutes by fatty acid β-oxidation and oxidative phosphorylation within the mitochondria. Muscle contraction is initiated by the release of calcium from the endoplasmic reticulum and transverse tubules into the sarcoplasm. The calcium binds to troponin, which interacts with tropomyosin and results in actin-myosin binding. The conformational change that results from actin-myosin binding moves the thick filaments relative to the thin filaments, and the Z discs are pulled closer together, thereby leading to muscle contraction in an ATP-dependent process.

The structural integrity of the muscle fiber is maintained by a network of interlinking protein fibers within the muscle, including the cytoskeletal scaffolding protein, titin. These fibers are connected to the sarcomere, to the sarcolemma, and then to the extracellular matrix and connective tissue. Dystrophin anchors the sarcomere to the sarcolemma through its interaction with several glycoproteins called sarcoglycans (α, β, γ, δ), dystroglycans (α, β), and syntrophins (α, β1, β2), which form the dystrophin-sarcoglycan complex that links to the extracellular basal lamina. The basal lamina contains several important proteins that, when abnormal, cause clinical disease, including collagen types I or VI, fibronectin, and laminin, which includes merosin and related proteins.

TABLE 429-1 CLASSIFICATION OF MYOPATHIES

HEREDITARY
Muscular dystrophies
Congenital myopathies
Myotonias and channelopathies
Metabolic myopathies
Mitochondrial myopathies
ACQUIRED
Inflammatory myopathies
Endocrine myopathies
Myopathies associated with systemic illness
Drug-induced/toxic myopathies

CLINICAL MANIFESTATIONS

Muscle diseases are often present with nonspecific symptoms, including fatigue, muscle pain, and generalized weakness. As a consequence, muscle disease is often overlooked in patients with multisystem diseases, or its symptoms are masked by other neurologic or systemic features.

History

Weakness is usually symmetrical. In the legs, proximal weakness causes difficulties in getting out of low chairs or a bathtub or in climbing stairs. Distal weakness can lead to the "flapping feet" characteristic of a bilateral foot drop or to frequent tripping over small objects, such as uneven paving stones or the curb of the sidewalk. In the arms, proximal weakness leads to difficulties with self-care, including washing, brushing the hair, or feeding. Distal hand weakness leads to problems opening jars or bottles, typing at a computer keyboard, or writing. Weakness of the bulbar muscles can lead to swallowing and speech difficulties, neck weakness can lead to a dropped head, and respiratory muscle weakness can lead to symptoms suggestive of nocturnal hypoventilation or respiratory failure.

Fatigue and exercise intolerance can be the presenting features of primary muscle diseases, but they also are common in many systemic and psychiatric disorders. In the absence of objective clinical signs, these symptoms are unlikely to be caused by muscle pathology.

Muscle pain can be difficult to distinguish from joint pain (Chapter 264) or fibromyalgia (Chapter 282). Diffuse, generalized, and persistent muscle pain is rarely due to muscle disease, and sometimes patients describe muscle stiffness as pain. Proximal muscle pain at rest may suggest an underlying inflammatory myopathy, whereas pain precipitated by exercise may suggest a metabolic myopathy. Pain beginning within the first 30 minutes of exercise suggests a disorder of carbohydrate metabolism; symptoms typically are short lived, and further exercise leads to their resolution (the warm-up phenomenon). Muscle pain developing later during exercise suggests a disorder of fatty acid β-oxidation.

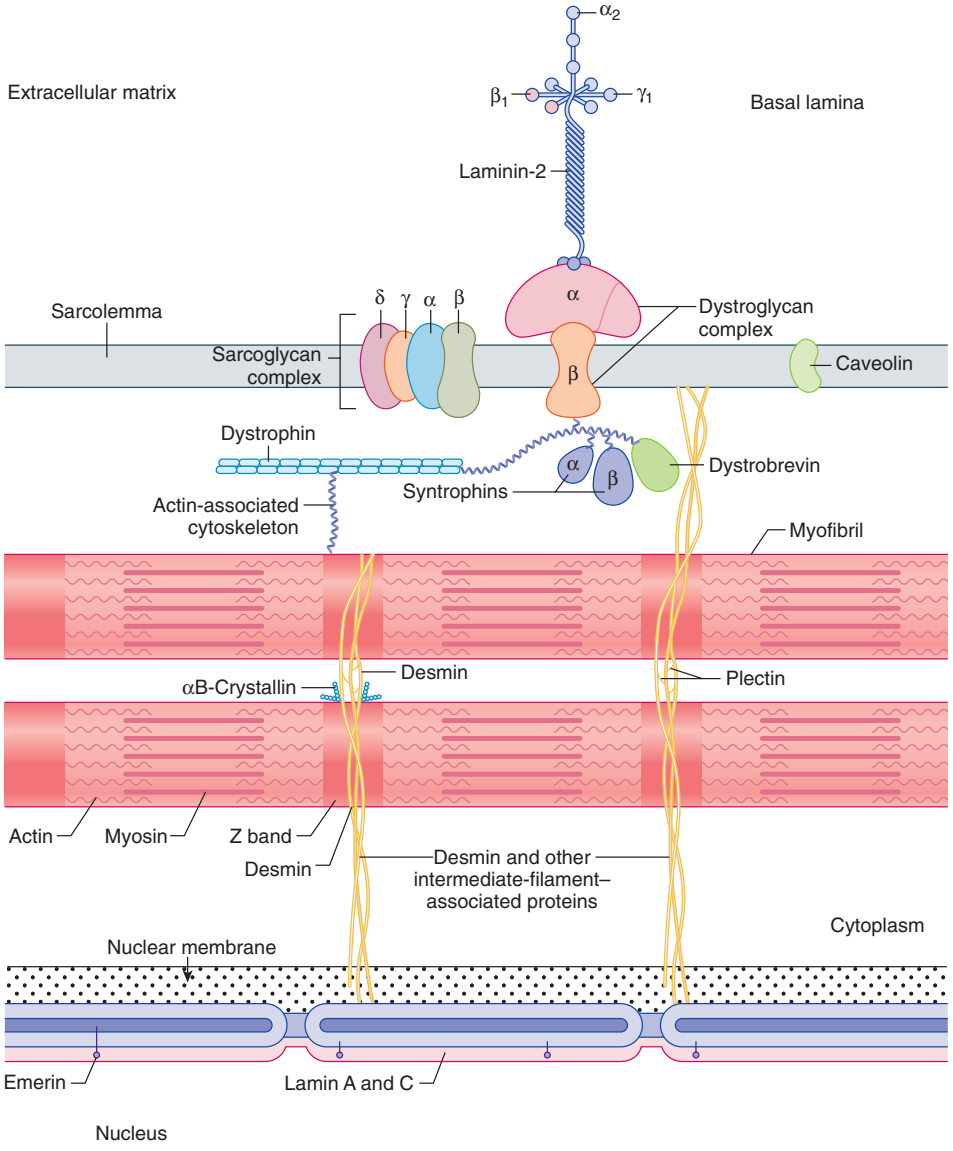


FIGURE 429-1. Muscle structure.

Muscle pain should be distinguished from muscle cramps, which typically affect specific muscles, persist for seconds or minutes, and rarely indicate muscle disease. However, persistent muscle contraction results in contractures, which are particularly seen in the myophosphorylase deficiency of McArdle's disease.

Muscle stiffness, which can be totally subjective and not associated with abnormal muscle fiber contraction, can occur in inflammatory, metabolic, and ion-channel muscle diseases and in nonmuscle diseases such as multiple sclerosis, polymyalgia rheumatica, and connective tissue diseases. Conversely, stiffness associated with weakness or an inability to move the affected muscle suggests myotonia. Myotonia can be painful (paramyotonia), painless, or associated with perceived stiffness if caused by a muscle channelopathy; it can affect limb, facial, or bulbar muscles and lead to persistent limb muscle contraction, eyelid closure, or dysphagia. Patients who describe their hands as "locking" but do not have objective myotonia rarely have a physical explanation for the symptom. Severe acute muscle damage, termed *rhabdomyolysis* (Chapter 115), results in myoglobinuria that presents as dark brown or red urine.

The family history should include questions about muscle diseases as well as systemic illnesses such as heart failure or diabetes that can be the clue to an underlying multisystem mitochondrial disorder.

Physical Examination

A full physical examination is critical to assess for systemic diseases with muscular involvement. The skin also should be evaluated for any signs of systemic disease, including the characteristic heliotrope rash of dermatomyositis (Chapter 277).

The neurologic and motor examinations should help distinguish muscle disease from nerve diseases (Table 429-2). Patients may have facial muscle wasting and weakness, ptosis, or dysmorphic features that lead to an instant diagnosis, such as the characteristic appearance of patients with myotonic dystrophy (Fig. 429-2). Proximal muscle weakness may be evident if patients push themselves up on their thighs or waddle into the consultation room.

Patients should be asked to rise from a low crouched posture and walk on their toes to assess calf muscle weakness or their heels to assess ankle dorsiflexion weakness. The posture should be examined, and the spine should be inspected for evidence of scoliosis. The spine and joints should be moved passively to determine whether there are any contractures, which are usually asymptomatic.

All muscle groups should be inspected for evidence of muscle wasting, hypertrophy, and fasciculation, which is the spontaneous firing of muscle fibers innervated by a single motor unit. Palpation of the large muscles occasionally reveals an unusual texture. The examiner should test for myotonia with both percussion (inability to relax the muscle belly after percussion with a reflex hammer) and grip (inability to relax the fingers from a firm grip).

Muscle strength should be assessed at the bedside (Table 429-3) while distinguishing proximal (limb-girdle), distal (in the legs and arms), axial, neck, orofacial, extraocular, and bulbar muscle weakness. Weakness is usually but not always symmetrical in muscle disease, and specific patterns of weakness can be highly specific for a particular diagnosis.

TABLE 429-2 CLINICAL FINDINGS DIFFERENTIATING MUSCLE FROM NERVE DISEASE

FINDING	MYOPATHY	ANTERIOR HORN CELL DISEASE	PERIPHERAL NEUROPATHY	NEUROMUSCULAR JUNCTION DISEASE
Distribution	Usually proximal, symmetrical	Distal, asymmetrical, and bulbar	Distal, symmetrical	Extraocular, bulbar, proximal limb
Atrophy	Slight early, marked late	Marked early	Moderate	Absent
Fasciculations	Absent	Frequent	Sometimes present	Absent
Reflexes	Lost late	Variable, can be hyperreflexic	Lost early	Normal
Pain	Diffuse in myositis	Absent	Variable, distal when present	Absent
Cramps	Rare	Frequent	Occasional	Absent
Sensory loss	Absent	Absent	Usually present	Absent
Serum creatine kinase	Usually elevated	Occasionally slightly elevated	Normal	Normal

Adapted from Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine,* 23rd ed. Philadelphia: Elsevier; 2008.

TABLE 429-3 UNITED KINGDOM MEDICAL RESEARCH COUNCIL SCALE

5—Normal power
4—Active movement against gravity and resistance (often subdivided into 4–, 4, and 4+)
3—Active movement against gravity but not against resistance
2—Active movement only possible when gravity has been eliminated
1—Observable muscle contraction, but not capable of initiating movement
0—No contraction

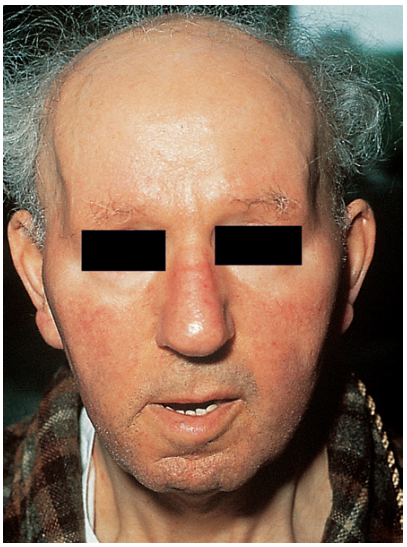


FIGURE 429-2. Myotonic dystrophy in a 50-year-old man. His appearance is typical, with facial weakness, atrophy of the temporal muscles and sternomastoids, and frontal baldness, which gives a monklike appearance. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine,* 3rd ed. London: Mosby; 2003.)

TABLE 429-4 GUIDING PRINCIPLES FOR ASSESSING MUSCLE DISEASES

1. **History**
   - Age of onset (most inherited and acquired disorders have a characteristic age of onset)
   - Rate of progression (acute suggests an acquired, often inflammatory cause)
   - Fluctuating weakness (may indicate a neuromuscular junction disorder, metabolic muscle disease, or a channelopathy)
   - Relationship to exercise (may indicate a metabolic myopathy)
   - Muscle pain (may indicate inflammatory or metabolic muscle disease)
   - Relevant multisystem involvement (may indicate a mitochondrial disorder or myotonic dystrophy)
   - Family history (may indicate a genetically determined muscular dystrophy or myopathy)
2. **Pattern of weakness**
   - Limb-girdle weakness is relatively nonspecific.
   - Inherited disorders often have specific patterns of muscle involvement and are usually symmetrical.
   - Fluctuating weakness may indicate a neuromuscular junction disorder, metabolic muscle disease, or a channelopathy.
3. **Testing**
   - The serum creatine kinase may be normal.
   - Electromyography is often normal in metabolic muscle disease.
   - All patients should have an electrocardiogram and echocardiogram to look for cardiomyopathy and/or a conduction defect.
   - Muscle magnetic resonance imaging is increasingly being used to guide the muscle biopsy or reveal diagnostic patterns of muscle involvement.
   - Some inherited muscle diseases can be diagnosed clinically and confirmed by genetic testing without requiring other investigations (e.g., myotonic dystrophy; Duchenne's, facioscapulohumeral, and Becker's muscular dystrophies)
   - Muscle biopsy will reveal the cause in most cases—it identifies specific inflammatory myopathies and muscular dystrophies and often provides diagnostic clues for other muscle and neurogenetic disorders.

DIAGNOSIS

A systematic approach can help guide the diagnosis of muscle diseases (Table 429-4).

Serum Enzymes

The muscle (MM) isoform of creatine kinase (CK) is frequently elevated in patients with muscle disease, although the CK is often normal in metabolic myopathies and in chronic, slowly progressive myopathies. A mild to moderate increase in CK is also seen in patients with acute and subacute neurogenic weakness, including amyotrophic lateral sclerosis (Chapter 418). The degree of CK elevation can be a strong clue for a specific muscle disease in an appropriate clinical context; for example, calf muscle weakness and a very high CK (>1000 I/U) is suggestive of dysferlinopathy, and a CK of more than 20,000 I/U indicates rhabdomyolysis (Chapter 115). Alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase levels, which are increased in liver disease (Chapter 148), also can be elevated in muscle disease, but the CK level usually exceeds the upper limit of normal by about ten-fold in muscle disease before these other enzymes can be detected in the plasma.

Neurophysiologic Tests

Nerve conduction studies (see Table 403-5 in Chapter 403), which identify focal or general disturbances of the conduction velocity or amplitude of the nerve impulse, are normal in myopathies. Electromyograms (EMGs) (see Table 403-6 in Chapter 403), together with nerve conduction studies, can distinguish neuropathies and disturbances of the neuromuscular junction from myopathies based on such features as prolonged insertional activity, myotonic discharges, rapid recruitment, and myopathic potentials, which are short amplitude, short duration, and polyphasic. Contractures are electrically silent on EMGs, but muscle cramps are associated with persistent bursts of motor unit activity. EMG changes can be highly focal, particularly in inflammatory myopathies, so the EMG can be normal in patients with muscle disease. Metabolic myopathies also are often associated with a normal EMG.

Imaging

Muscle computed tomography (CT) and magnetic resonance imaging (MRI) can show specific patterns of atrophy and the replacement of muscle

with fat in some inherited myopathies. The MRI can also be used to guide the EMG or muscle biopsy if the pathology is patchy or focal, as in inflammatory myopathy. In specific circumstances, functional MRI is used to investigate suspected metabolic muscle disease, especially mitochondrial disorders.

Muscle Biopsy

Muscle biopsy remains a key investigation for patients with suspected muscle disease, although it has been replaced by molecular genetic analysis in patients with typical Duchenne's or Becker's muscular dystrophy. The biopsy can be the final step in discerning whether limb weakness is neurogenic or myopathic. In addition to the overall appearance, the size distribution of muscle fibers, the degree and distribution of atrophic fibers, the presence of necrosis or inflammatory infiltrates, muscle fiber regeneration, and the replacement of muscle with fat and fibrous connective tissue provide important diagnostic clues.

Molecular Genetic Tests

The widespread availability of molecular genetic testing has had a dramatic impact on the investigation of suspected muscle disease. Disorders that can now be diagnosed with a blood test include Becker's muscular dystrophy and several of the channelopathies. However, given the large number of possible genes, a systematic approach to the investigation of suspected muscle disorders is recommended. Furthermore, molecular diagnosis is currently not possible in some patients, and many of the tests are available only in research laboratories or expensive commercial laboratories.

Other Investigations

Routine hematologic and biochemical tests of liver and kidney function (complete blood count, sedimentation rate, and levels of alanine and aminotransferases, creatine kinase, and creatinine) can assess possible systemic involvement. The erythrocyte sedimentation rate and C-reactive protein level are elevated in inflammatory muscle diseases, and antibody studies (antinuclear antibodies, extractable nuclear antigens, rheumatoid factor, and antineutrophil cytoplasmic antibodies) are useful in patients with suspected autoimmune disorders.

In patients with dermatomyositis (Chapter 277), the evaluation should include an appropriate evaluation for a possible underlying paraneoplastic myopathy (Chapter 187). For patients with suspected metabolic muscle disease, useful screening tests include a fasting blood lactate level in patients with suspected mitochondrial myopathy and a blood acylcarnitine analysis in those with suspected fatty acid β-oxidation disorders.

SPECIFIC MUSCLE DISEASES

Inherited Muscle Diseases

Inherited muscle diseases fall into four main categories: muscular dystrophies (Table 429-5), hereditary myopathies, muscle ion-channel disorders (channelopathies; Table 429-6), and metabolic myopathies (Table 429-7). Some diseases overlap these categories, such as myotonic dystrophy, which includes a characteristic muscular dystrophy, myotonic discharges indicating an ion-channel disorder on EMG, and secondary mitochondrial abnormalities in skeletal muscle suggestive of a metabolic component. Some specific gene defects cause specific phenotypes, now instantly recognizable at the bedside, but other phenotypes are caused by a range of different diseases. A confident clinical diagnosis remains challenging, even in expert hands, so a systematic approach is key to the investigation of these disorders.

Muscular Dystrophies

The term *muscular dystrophy* refers to a pathologic description of muscle fiber degeneration and abnormal muscle regeneration (dystrophy), usually associated with an increase in fat and fibrous connective tissue. From a clinical perspective, muscular dystrophies are a group of genetically determined clinical syndromes with a particular pattern of muscle involvement owing to known or presumed genetic defects. Although the molecular basis of common muscular dystrophies has been defined, new genes are still being identified.

BECKER AND DUCHENNE MUSCULAR DYSTROPHY

Becker and Duchenne muscular dystrophies are both due to mutations in the *DYSTROPHIN* gene, which is located on the X chromosome and determines the amount and structure of the dystrophin protein. Female carriers can develop milder adult-onset disease but can be very difficult to diagnose, especially if there is no family history.

TABLE 429-5 MUSCULAR DYSTROPHIES

X-LINKED
Duchenne's/Becker's (dystrophin)
Emery-Dreifuss (emerin)
LIMB-GIRDLE
Thirteen different autosomal dominant (3) and recessive (10) conditions
CONGENITAL
Autosomal Recesssive with CNS Involvement
Fukuyama's, Walker-Warburg, muscle-eye-brain
Autosomal Recesssive without CNS Involvement
Merosin-deficient, merosin-positive, integrin-deficient, rigid spine syndrome
DISTAL
Autosomal Dominant
Late adult onset
Autosomal Recessive
Early adult onset 1A (Nonaka)
Autosomal Dominant
Early adult onset
OTHER
Autosomal dominant facioscapulohumeral
Autosomal dominant oculopharyngeal
Autosomal dominant myotonic dystrophy
Autosomal dominant myofibrillar myopathy
Autosomal dominant Bethlem myopathy

CNS = central nervous system.

TABLE 429-6 CHANNELOPATHIES AND RELATED DISORDERS

DISORDER	PATTERN OF CLINICAL FEATURES
Thomsen's disease	Myotonia
Becker's disease*	Myotonia and weakness
Paramyotonia congenita	Paramyotonia
Hyperkalemic periodic paralysis	Periodic paralysis with myotonia and paramyotonia
Hypokalemic periodic paralysis	Periodic paralysis
Myotonia fluctuans	Myotonia
Myotonia permanens	Myotonia
Acetazolamide-responsive myotonia	Myotonia
Hypokalemic periodic paralysis	Periodic paralysis
Schwartz-Jampel syndrome (chondrodystrophic myotonia)	Myotonia, dysmorphic
Rippling muscle disease	Muscle mounding/stiffness
Andersen-Tawil syndrome	Periodic paralysis, cardiac arrhythmia, skeletal abnormalities
Brody's disease*	Delayed relaxation, no EMG myotonia
Malignant hyperthermia	Anesthetic-induced delayed relaxation

*Becker's disease, Schwartz-Jampel syndrome, and Brody's disease are autosomal recessive diseases; all other listed diseases have autosomal dominant inheritance.

Duchenne's Muscular Dystrophy

Duchenne's muscular dystrophy affects about 1 in 3500 males. About one third of cases arise from a de novo mutation without a family history. Most patients have a frame-shift mutation in the *DYSTROPHIN* gene with a complete loss of the dystrophin protein. The absence of dystrophin disrupts the mechanical link between the sarcomere and the sarcolemma, probably with a calcium leak that leads to muscle cell necrosis.

TABLE 429-7 METABOLIC AND MITOCHONDRIAL MYOPATHIES

GLYCOGEN METABOLISM DEFICIENCIES
Type II: α-1,4-Glucosidase (acid maltase)
Type III: Debranching
Type IV: Branching
Type V: Phosphorylase (McArdle's disease)*
Type VII: Phosphofructokinase (Tarui's disease)*
Type VIII: Phosphorylase B kinase*
Type IX: Phosphoglycerate kinase*
Type X: Phosphoglycerate mutase*
Type XI: Lactate dehydrogenase*
LIPID METABOLISM DEFICIENCIES
Carnitine palmitoyltransferase*
Primary systemic/muscle carnitine deficiency
Secondary carnitine deficiency
β-Oxidation defects
Medications (valproic acid)
PURINE METABOLISM DEFICIENCIES
Myoadenylate deaminase deficiency*
MITOCHONDRIAL MYOPATHIES
Alpers-Huttenlocher syndrome
Chronic progressive external ophthalmoplegia
Kearns-Sayre syndrome
Pearson's syndrome
Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS)
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
Myoclonic epilepsy with ragged-red fibers (MERRF)
Leber's hereditary optic neuropathy
Leigh's syndrome
Infantile myopathy and lactic acidosis

*Deficiency can produce exercise intolerance and myoglobinuria.

CLINICAL MANIFESTATIONS

Duchenne's muscular dystrophy typically presents in young boys between 3 and 5 years of age with delayed motor milestones and proximal muscle weakness. The disorder is relentlessly progressive and causes a cardiomyopathy (Chapter 60) that can result in heart failure and fatal arrhythmias. Mild cognitive impairment is also a feature. By 10 to 12 years of age, most affected individuals are usually confined to a wheelchair. By age 20 years, most patients develop joint contractures and a kyphoscoliosis that lead to respiratory muscle weakness and eventual respiratory failure.

DIAGNOSIS

Affected individuals have a high CK level that is 20- to 100-fold the upper limit of normal from birth. EMG and muscle biopsy are abnormal, with characteristic dystrophic features and reduced size and amount of the protein on immunoblotting studies. However, these investigations are rarely needed to make the diagnosis because the *DYSTROPHIN* gene rearrangement can be detected in blood.

TREATMENT

Rx

Management is largely supportive, including physical therapy to prevent contractures, management of the cardiomyopathy using β-blockers and angiotensin-converting enzyme inhibitors (Chapter 59), and noninvasive ventilation in later stages. Prednisolone (0.75 mg/kg/day) prolongs the period of ambulation and other functions in Duchenne's muscular dystrophy.■ Creatine (30 mg/kg/day and sometimes higher doses) increases muscle strength and lean body mass.■ Albuterol is of uncertain benefit, and calcium-channel blockers are not beneficial.

PROGNOSIS

Without ventilating support, patients usually die in their late teens to early 20s. With such support, patients often live well into the third or fourth decades before succumbing to pneumonia, cardiac failure, or gastrointestinal complications.

Becker's Muscular Dystrophy

Becker's muscular dystrophy is a milder form of Duchenne's muscular dystrophy due to a non-frame-shift mutation in the *DYSTROPHIN* gene. It has a similar spectrum of findings but a much wider variation in course of progression.

CLINICAL MANIFESTATIONS

Becker's muscular dystrophy typically presents in boys older than 5 years, teenagers, or even adults with proximal weakness and prominent calf hypertrophy. The clinical course is progressive, and cardiac features are frequent.

DIAGNOSIS

The CK is elevated, although not to the same degree as seen in Duchenne's muscular dystrophy. In about two thirds of patients, a mutation in *DYSTROPHIN* can be detected in blood. The muscle biopsy findings resemble Duchenne's muscular dystrophy but are less dramatic. On immunocytochemistry or on immunoblotting of muscle sections, the amount of the dystrophin protein is decreased.

Female carriers of a *DYSTROPHIN* gene mutation can develop mild symptoms with proximal muscle weakness and an elevated CK in adult life. Diagnosis can be difficult in the absence of a family history, and protein abnormalities are often subtle in the muscle biopsy.

TREATMENT AND PROGNOSIS

Rx

Management is largely supportive. Corticosteroids are rarely used. Careful cardiac monitoring is essential. Heart transplantation (Chapter 82) has been performed in patients with severe restrictive cardiomyopathy (Chapter 60).

Many patients have a normal lifespan, although some develop respiratory failure in middle age and have a shortened lifespan owing to respiratory complications. Heart failure and arrhythmias occur late in the course of disease.

EMERY-DREIFUSS MUSCULAR DYSTROPHY

Emery-Dreifuss muscular dystrophy is due to mutations in the X-chromosomal gene encoding the nuclear membrane protein emerin.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Emery-Dreifuss muscular dystrophy is characterized by progressive joint contractures, scapula-peroneal distribution weakness, and cardiomyopathy with a progressive cardiac conduction disorder.

The CK is often elevated but can be normal. The ECG shows conduction delay. The muscle biopsy shows dystrophic changes, and the protein emerin is deficient on muscle cell nuclear membranes.

TREATMENT AND PROGNOSIS

Rx

Management is supportive, with physical therapy to reduce contractures and cardiac pacing to prevent sudden death due to the conduction defect. Patients usually live many decades with appropriate supportive care.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Facioscapulohumeral muscular dystrophy, which is an autosomal dominant disorder with variable penetrance, affects about 1 person in 20,000 of the population. It is associated with a deletion of chromosome 4q35 in about 95% of patients, although the responsible gene has yet to be identified.

CLINICAL MANIFESTATIONS

The disease has a highly variable penetrance, ranging from severe proximal facial weakness in early childhood to mild, almost asymptomatic distal weakness presenting in late adult life. Some gene carriers never present clinically. The entire range of phenotypes can be seen in the same family. The muscle weakness affects the face, where it causes difficulty with whistling or smiling, and includes periscapular involvement that leads to scapular winging and to weakness of the shoulder girdle, biceps, and triceps. Distal weakness causes a foot drop, and proximal leg weakness is a late feature. Unlike other muscular dystrophies, muscle involvement is often asymmetrical.

DIAGNOSIS

The CK is usually elevated but can be normal. EMG shows myopathic features. Muscle biopsy shows dystrophic changes occasionally with an inflammatory infiltrate.

TREATMENT AND PROGNOSIS

Rx

Clinical management is supportive, and corticosteroids are of no benefit. Cardiac features are not prominent, and respiratory muscle weakness is a late feature. The prognosis is highly variable, depending on the severity and related age of onset. Many patients have a normal lifespan.

LIMB-GIRDLE MUSCULAR DYSTROPHIES

Limb-girdle dystrophies are a diverse group of genetically determined myopathies caused by defects or deficiencies of muscle proteins, often proteins associated with the muscle cell membrane and particularly the dystrophin-sarcoglycan complex. Although it is possible to identify some specific causes at the bedside, muscle biopsy, immunolabeling studies, and genetic studies are often required to make a precise diagnosis. Each form is rare, and management is largely supportive. The prognosis is usually years to decades after diagnosis.

CONGENITAL MUSCULAR DYSTROPHIES

Congenital muscular dystrophies are a group of rare autosomal recessive muscle diseases that present in childhood with hypotonia (floppy infant) and muscle weakness. The main differential diagnosis is spinal muscular atrophy (Chapter 418), although congenital myasthenia gravis (Chapter 430) also should be considered. Affected infants often have joint contractures, which can be severe at birth. Some congenital myopathies have a pure muscle phenotype, with limited disability and survival well into adult life. Others with central nervous system involvement may be fatal in childhood.

Myotonic Dystrophies

Myotonic muscular dystrophies are the most common inherited muscle diseases. The two main genetic causes, DM1 and DM2, are inherited in an autosomal dominant manner. Both forms cause multisystem disease and can be difficult to distinguish from each other. DM1 is due to an abnormal expansion of CTG nucleotide repeats in a protein kinase gene on chromosome 19. DM2 is due to an abnormal tetranucleotide repeat on chromosome 3.

CLINICAL MANIFESTATIONS

Classic myotonic dystrophy can be diagnosed visually owing to characteristic myopathic facies (see Fig. 429-2), frontal balding in males, nasal speech, and high-steppage gait due to the distal myopathy. Additional features include ptosis, proximal weakness of the neck flexor muscles, especially the sternomastoid, and proximal muscle weakness in later stages. Patients show percussion, grip, and eyelid myotonia (inability to open forcibly closed eyelids). Systemic features include premature posterior subcapsular lens cataracts, testicular atrophy, intellectual impairment, impotence, and hypersomnolence mediated by both central and neuromuscular mechanisms. Diabetes mellitus may develop later in the disease, and dysphagia and constipation are common. Progressive cardiac conduction defects lead to sudden death. Women who transmit DM1 have a high risk of having a child with a severe congenital form.

DIAGNOSIS

The CK may be normal or mildly elevated. EMG reveals myopathic features and myotonic discharges. A muscle biopsy, which is rarely required, will reveal myopathic features. Molecular genetic analysis of the DM1 and DM2 loci usually confirms the diagnosis.

TREATMENT

Rx

All patients should have regular electrocardiogram, echocardiogram, respiratory function, and blood glucose level monitoring and undergo sleep studies to detect nocturnal hypoventilation. Management is largely supportive. Physical therapy can help prevent contractures. Cardiac pacing is frequently required. Hypersomnolence can be treated with overnight positive-pressure ventilation and modafinil (200 to 400 mg daily in the morning) for the central component. Diabetes (Chapter 236) and cataracts (Chapter 431) are managed in the standard manner.

Other Inherited Myopathies

CONGENITAL MYOPATHIES

Congenital myopathies are a group of rare inherited muscle diseases that are generally less severe than congenital muscular dystrophies, both clinically and histopathologically. They often have characteristic morphologic features on the muscle biopsy, present at birth with hypotonia and motor delay, and are slowly progressive. Respiratory muscle weakness is common, and patients can present with ventilator failure at birth or insidiously in adult life.

Central core myopathy, which is a rare autosomal dominant congenital myopathy due to mutations in the ryanodine receptor gene, is associated with malignant hyperthermia (Chapters 427, 440, and 442). *Nemaline myopathies* are a group of diseases with characteristic "nemaline rods" apparent in the muscle biopsy. Different genetic forms have been defined, including mutations in the *NEBULIN, TITIN,* and *α-TROPOMYOSIN* genes. *Myotubular myopathy*, which is an X-linked myopathy defined by the presence of central nuclei within muscle fibers, is due to mutations in the *MYOTUBULARIN* gene. Patients typically have ptosis and ophthalmoplegia.

Myofibrillar myopathies are inherited muscle diseases characterized by the presence of desmin fibrils in the muscle biopsy. Other features in the muscle biopsy include the presence of vacuoles with blue rims and the presence of eosinophilic inclusions. Autosomal dominant or sporadic mutations in *ZASP*, a Z-line association protein, *DESMIN, MYOTILIN,* and *AB-CRYSTALLIN* have been identified. The phenotypes overlap, and patients typically present with very slowly progressive distal muscle weakness that cause a foot drop, pes cavus, and proximal weakness. Cardiomyopathy is common in desmin myopathy.

Other distal myopathies include *Welander's myopathy*, an autosomal disorder that presents with finger extensor weakness and appears to be largely restricted to families of Scandinavian origin. *Tibial muscular dystrophy*, which is an autosomal dominant disorder due to mutations in *TITIN,* presents with bilateral foot drop due to tibialis anterior weakness. *Nonaka myopathy*, which is an autosomal recessive disorder due to mutations in *GNE,* affects the post-translational glycosylation of muscle proteins.

Oculopharyngeal muscular dystrophy is an autosomal dominant inherited disorder due to a triplet repeat expansion of the *PABP2* gene. The disorder typically presents in late life (>50 years of age) with dysphagia and marked ptosis without ophthalmoplegia. Mild distal and proximal weakness occurs later in the disease course. Surgical correction of the ptosis often yields excellent results, but the dysphagia can be difficult to manage. Patients often have a normal lifespan.

Ion-Channel Myopathies

Ion-channel myopathies (see Table 429-6) are genetically determined muscle ion-channel disorders, with specific molecular causes but substantial clinical overlap.

CHLORIDE CHANNELOPATHIES

Autosomal dominant (Thomson's) and autosomal recessive (Becker's) myotonia congenita, which are due to a mutation in the muscle chloride-channel gene *CLC1,* present with painless myotonia, muscle hypertrophy, grip and percussion myotonia, and myotonic discharges on EMG. Patients usually complain that their symptoms get worse in cold and damp conditions and improve with exercise (the warm-up phenomenon). There are usually no cardiac complications. The myotonia responds to mexiletine (150 to 200 mg three times a day).■ Patients usually have a normal lifespan.

SODIUM CHANNELOPATHIES

Mutations in the voltage-gated sodium-channel gene *SCN4A* cause a range of autosomal dominant phenotypes, including hyperkalemic periodic paralysis, paramyotonia congenital (Eulenburg's disease), and potassium-aggravated myotonia. Periodic paralysis is typically precipitated by sustained exercise, which leads to weakness during the rest period, or by a high carbohydrate meal. The attacks can persist for hours, during which patients can be quadriplegic with no tendon reflexes but normal sensation, normal eye movements, and normal respiration. The serum potassium level may be high during attacks. The physical examination is usually normal between attacks, although later in the disease course, some patients develop fixed proximal weakness associated with tubular aggregates on muscle biopsy. Patients with paramyotonia congenita have myotonia that paradoxically improves with exercise, is often painful, and affects the eyelids. For both phenotypes, avoidance of high carbohydrate loads and treatment with dichlorphenamide■ (50

TABLE 429-8 SECONDARY CAUSES OF PERIODIC PARALYSIS

HYPOKALEMIC
Thyrotoxic
Primary hyperaldosteronism (Conn's syndrome)
Renal tubular acidosis (e.g., Fanconi's syndrome)
Juxtaglomerular apparatus hyperplasia (Bartter's syndrome)
Gastrointestinal potassium wastage
Villous adenoma
Laxative abuse
Pancreatic non–insulin-secreting tumors with diarrhea
Nontropical sprue
Barium intoxication
Potassium-depleting diuretics
Amphotericin B
Licorice
Corticosteroids
Toluene toxicity
p-Aminosalicylic acid
Carbenoxolone
HYPERKALEMIC
Addison's disease
Hypoaldosteronism
Excessive potassium supplementation
Potassium-sparing diuretics
Chronic renal failure

From Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine,* 23rd ed. Philadelphia: Elsevier; 2008.

to 100 mg twice daily) or acetazolamide (125 to 250 mg three times daily) are effective.

CALCIUM CHANNELOPATHIES

Mutations in the muscle sodium-channel gene *CNA4A* cause hypokalemic periodic paralysis, which is an autosomal dominant disorder that resembles hyperkalemic periodic paralysis, except that the episodes of weakness can persist for up to 24 hours. Avoidance of high carbohydrate loads and treatment with dichlorphenamide■ (50 to 100 mg twice daily) or acetazolamide (125 to 250 mg three times daily) are effective.

OTHER FORMS OF PERIODIC PARALYSIS AND MUSCLE STIFFNESS

Periodic paralysis can occur secondary to a wide range of metabolic and electrolyte disorders (Table 429-8).

Mutations in *KCNJ2* cause *Andersen-Tawil syndrome,* an autosomal dominant periodic paralysis associated with mild distinctive facial features, including hypertelorism and low-set ears, and a propensity to ventricular dysrhythmias. *Brody's disease,* which is an autosomal recessive disorder due to mutations in the SR calcium ATPase gene, is characterized by exercise-induced muscle stiffness that is electrically silent on EMG. *Rippling muscle disease,* which is due to mutations in the *CAVEOLIN3* gene, is characterized by rippling muscles triggered by exercise or percussion.

Neuromyotonia (Isaacs' syndrome) is an autoimmune disorder associated with voltage-gated potassium-channel antibodies and is part of a spectrum of disorders including limbic encephalitis.

Metabolic Myopathies

Metabolic myopathies are caused by enzyme defects that affect the three principal stages of muscle metabolism: (1) carbohydrate disorders due to a defect of glucose-glycogen metabolism; (2) disorders of fatty acid oxidation; and (3) disorders of mitochondrial oxidative phosphorylation. Symptoms can be mild and develop in adult life but can sometimes cause rhabdomyolysis (see Table 429-7).

DISORDERS OF CARBOHYDRATE METABOLISM

Glucose and glycogen are the primary energy source for immediate muscle contraction, so defects of this metabolic pathway cause muscle pain, cramps, contracture, and weakness within the first 30 minutes of exercise, thereby leading to exercise intolerance and muscle deconditioning. Severe episodes are associated with CK levels higher than 1000 I/U, rhabdomyolysis, and myoglobinuria. Most diseases are autosomal recessive, although phosphoglycerate kinase deficiency is X-linked. The most common is McArdle's disease, and the others are extremely rare.

Mcardle's Disease

McArdle's disease (type IV glycogenosis, myophosphorylase), which typically presents with muscle pain or cramps after short bursts of exercise, leads to contractures and exercise intolerance. Some patients present with recurrent rhabdomyolysis. Persistent exercise beyond about 30 minutes leads to the "second wind" phenomenon, when symptoms subside as fatty acids become the primary source of muscle energy. Clinical examination and the CK can be normal between the attacks, although some patients develop fixed proximal muscle weakness with myopathic features on EMG. Histochemical and enzyme analysis of skeletal muscle confirms the diagnosis. Common founder mutations (e.g., R49X) are often found in blood DNA samples. Graded exercise and 75 g of oral sucrose■ before exercise may improve symptoms.

Pompe's Disease

Pompe's disease (type II glycogenosis, α-1,4-glucosidase, or acid-maltase deficiency; Chapter 215) can present in childhood with proximal weakness, hypotonia, and a fatal cardiomyopathy, or in adult life with progressive ventilatory failure. The EMG can reveal myotonic discharges. Abnormal glycogen storage is seen in the muscle biopsy. Enzyme replacement therapy has been shown to be effective in children with the severe form.■ The disorder can be diagnosed by measuring the enzyme activity in leukocytes.

DISORDERS OF FATTY ACID METABOLISM

Fatty acids are the principal source of muscle energy during sustained exercise, especially when the muscle glycogen reserves become exhausted after about 30 minutes of exercise. Fatty acid metabolism involves the transport of fatty acids from the serum into the muscle cell and into mitochondria, where key components of the β-oxidation pathway reside. Both carnitine and carnitine palmitoyltransferase are required to complete this process.

Clinically, disorders of fatty acid metabolism can present with a proximal myopathy, exercise intolerance, muscle pain, and rhabdomyolysis. Cardiomyopathy is an important component of some fatty acid oxidation disorders, and multiorgan metabolic crises, such as hypoketotic hypoglycemia, can occur along with neurologic complications, including a peripheral neuropathy.

Carnitine palmitoyltransferase I deficiency presents in childhood with an encephalopathy and liver failure associated with hypoglycemia and a high blood ammonia during metabolic crises. Despite the similar name, *carnitine palmitoyltransferase II deficiency* presents with muscle pain, exercise intolerance, and myoglobinuria, typically after a long period of fasting or sustained exercise. All standard clinical investigations, including the CK, EMG, and muscle biopsy, can be normal. The measurement of fasting acylcarnitines by tandem mass spectrometry on a dried blood spot is the key to making the diagnosis, and molecular genetic blood tests can detect common mutations in the *CPTII* gene.

Carnitine deficiency can be primary or secondary. Primary carnitine deficiency causes myopathy, cardiomyopathy, and encephalopathy in association with hypoketotic hypoglycemia, although pure muscle presentations have been described. Blood carnitine levels below the laboratory reference range reveal the diagnosis, although prominent fat deposition in muscle is another clue.

Many metabolic myopathies cause a secondary carnitine deficiency, including β-oxidation disorders, disorders of mitochondrial oxidative phosphorylation, and other systemic diseases. The accumulation of lipid within the muscle fibers leads to a lipid storage myopathy. Low carnitine levels can be detected in blood.

TREATMENT Rx

Both primary and secondary carnitine deficiencies respond well to oral carnitine replacement (200 to 400 mg/kg/day in divided doses). Modifying the diet to increase the intake of carbohydrates relative to fat can improve symptoms in carnitine palmitoyltransferase deficiency. Some patients have a multiple acyl-coenzyme A dehydrogenase deficiency (also called trifunctional enzyme deficiency, or glutaric aciduria type II), which responds well to riboflavin (100 mg daily).

DISORDERS OF MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION

Disorders of mitochondrial oxidative phosphorylation (see Table 429-7) are among the most common causes of inherited metabolic disease. They can

present with isolated muscle disease, but often they are multisystemic with cardiac involvement, diabetes mellitus, and both central and peripheral neurological features.

Mitochondria are present in every nucleated cell and are the major source of ATP, which is generated by oxidative phosphorylation, which in turn involves five respiratory chain complexes situated on the inner mitochondrial membrane. Mitochondrial dysfunction results in an energy deficit and, if severe, ultimately leads to organ failure. The genetic basis of mitochondrial disorders is complex because mitochondrial proteins have two genetic origins: mitochondrial DNA (mtDNA), which is maternally inherited, and nuclear DNA. Autosomal dominant, recessive, and X-linked nuclear genetic mitochondrial disorders have been described. Mitochondrial DNA disorders affect the structure or amount of the respiratory chain proteins. Both deletions of mtDNA and point mutations of mtDNA are important causes of disease. Nuclear genetic disorders can affect the proteins, the assembly of the respiratory chain, or the maintenance of mtDNA.

CLINICAL MANIFESTATIONS

Mitochondrial diseases should be considered in all patients with a complex, multisystemic myopathy, especially patients with neuromuscular, ocular, and endocrine involvement. The myopathy is often only a minor feature. Although the list of mitochondrial disorders is extensive, they can be divided into defined clinical syndromes, or ill-defined multisystem disorders.

Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes is usually due to a specific point mutation of mtDNA (m.3243A>G). Patients can have myopathy, cardiomyopathy, encephalopathy, complicated migraine, seizures, encephalopathy, and attacks superficially resembling stroke. Some patients have one or only a few of these features, some have a more limited phenotype with only diabetes and deafness, and some have an isolated cardiomyopathy.

Myoclonic epilepsy with ragged-red fibers presents with a proximal myopathy associated with slowly progressive degenerative ataxia, epilepsy, myoclonus, and peripheral neuropathy; it is usually caused by a point mutation of mtDNA (m.8344A>G).

Leber hereditary optic neuropathy predominantly affects young adult males who have a history of subacute bilateral visual failure affecting both eyes within 2 to 3 months; more than 95% of cases have mtDNA point mutations in m.3460G>A, m.11778G>A, or m.14484T>C.

Chronic progressive external ophthalmoplegia with ptosis and the gradual limitation of eye movements is seen in up to 20% of mitochondrial disorders. About 95% of patients have sporadic mtDNA point mutations or deletions, but the disease can also be inherited as either an autosomal dominant or recessive trait. This disease can occur in isolation, with a proximal myopathy, or with ataxia, diabetes, deafness, and cardiac conduction block (Kearns-Sayre syndrome).

Mitochondrial disorders in children are invariably severe and result in premature death as a result of subacute necrotizing encephalomyopathy (*Leigh's syndrome*), hepatorenal failure (*mtDNA depletion syndromes*), cardiomyopathy, and severe lactic acidosis. Children with *Pearson's syndrome*, caused by the accumulation of mtDNA deletions, typically present with pancytopenia, sideroblastic anemia, and exocrine pancreatic failure. *Primary coenzyme Q10 (ubiquinone) deficiency* is a rare recessive disorder that can present with myoglobinuria and myopathy in childhood, or with ataxia and seizures in adult life.

DIAGNOSIS, TREATMENT, AND PROGNOSIS Rx

The investigation of suspected mitochondrial disorders involves a systematic screen for multisystem complications, especially diabetes and cardiomyopathy; muscle biopsy to look for histochemical cytochrome *c* oxidase deficiency or biochemical evidence of respiratory chain dysfunction; and molecular genetic tests. Some primary mtDNA defects are not detectable in blood, so skeletal muscle is often required for the genetic tests. For example, the diagnosis of ubiquinone deficiency can be made by measuring coenzyme Q10 in muscle.

Vitamins and cofactors, including thiamine, riboflavin, and ubiquinone (coenzyme Q10), have shown varying degrees of benefit in individual cases. Management is largely supportive, with surveillance and treatment of complications. Prognosis varies depending on the phenotype, ranging from the relatively normal life expectancy with chronic external ophthalmoplegia to a relatively rapid demise with Leigh's syndrome.

TABLE 429-9 TOXIC MYOPATHIES

INFLAMMATORY
Cimetidine
D-Penicillamine
Procainamide
L-Tryptophan
L-Dopa
NONINFLAMMATORY NECROTIZING OR VACUOLAR
Cholesterol-lowering agents
Chloroquine
Colchicine
Emetine
ε-Aminocaproic acid
Labetalol
Cyclosporine and tacrolimus
Isoretinoic acid (vitamin A analogue)
Vincristine
Alcohol
RHABDOMYOLYSIS AND MYOGLOBINURIA
Cholesterol-lowering drugs
Alcohol
Heroin
Amphetamine
Toluene
Cocaine
ε-Aminocaproic acid
Pentazocine
Phencyclidine
MALIGNANT HYPERTHERMIA
Halothane
Ethylene
Diethyl ether
Methoxyflurane
Ethyl chloride
Trichloroethylene
Gallamine
Succinylcholine
MITOCHONDRIAL
Zidovudine
MYOTONIA
2,4-D-Chlorophenoxyacetic acid
Anthracene-9-carboxycyclic acid
Cholesterol-lowering drugs
Chloroquine
Cyclosporine
MYOSIN LOSS
Nondepolarizing neuromuscular blocking agents
Intravenous glucocorticoids

From Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine,* 23rd ed. Philadelphia: Elsevier; 2008.

OTHER METABOLIC AND TOXIC MYOPATHIES

Myopathy can complicate many metabolic disorders, including hypothyroidism (Chapter 233), Addison's disease (Chapter 234), Conn's syndrome, hyperparathyroidism (Chapter 253), vitamin D deficiency (Chapter 252), and liver and renal failure (Chapters 132 and 157). The myopathy is often subtle, the CK level and EMG are often normal, and the muscle biopsy may be nonspecifically abnormal.

Many drugs cause myopathies (Table 429-9) with proximal muscle weakness, muscle pain, and exercise intolerance. The CK and EMG can be normal, and muscle biopsy findings may be nonspecific. Often the diagnosis is reached only after removal of the toxic agent leads to a resolution of symptoms. Statins can cause muscle pain and, rarely, myoglobinuria.

INFLAMMATORY MUSCLE DISEASES

Inflammatory myopathies are a heterogeneous group of acquired muscle diseases (Table 429-10). Most patients present with muscle weakness, with or without pain, and exercise intolerance. Most patients have an elevated CK, abnormal EMG, abnormal muscle MRI, and an inflammatory infiltrate on muscle biopsy. However, the inflammatory process can be patchy and missed

TABLE 429-10 IDIOPATHIC INFLAMMATORY MYOPATHIES: CLINICAL AND LABORATORY FEATURES

	SEX	TYPICAL AGE AT ONSET	RASH	PATTERN OF WEAKNESS	CK LEVEL	MUSCLE BIOPSY	RESPONSE TO IMMUNOSUPPRESSIVE THERAPY	COMMON ASSOCIATED CONDITIONS
Dermatomyositis	F > M	Childhood and adult	Yes	Proximal > distal	Increased (up to 50× normal)	Perimysial and perivascular inflammation; $CD4^+$ T cells, B cells; MAC, Ig, C deposition on vessels	Yes	Myocarditis, interstitial lung disease, vasculitis, other connective tissue diseases, malignancy
Polymyositis	F > M	Adult	No	Proximal > distal	Increased (up to 50× normal)	Endomysial inflammation; $CD8^+$ T cells, macros	Yes	Myocarditis, interstitial lung disease, other connective tissue diseases; ? malignancy
Inclusion body myositis	M > F	Elderly (>50 yr)	No	Proximal = distal; predilection for finger/wrist flexors, knee extensors	Increased (<10× normal)	Endomysial inflammation; $CD8^+$ T cells, macros; rimmed vacuoles; amyloid deposits; EM: 15- to 18-nm tubulofilaments	No	Neuropathy

C = complement; CK = creatine kinase; F = female; Ig = immunoglobulin; M = male; MAC = membrane attack complex; macros = macrophages.
From Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine,* 23rd ed. Philadelphia: Elsevier; 2008.

TABLE 429-11 CLASSIFICATION OF INFLAMMATORY MYOPATHIES

IDIOPATHIC

Polymyositis
Dermatomyositis
Inclusion body myositis
Overlap syndromes with other connective tissue disease (scleroderma, systemic lupus erythematosus, mixed connective tissue disease, Sjögren's syndrome, rheumatoid arthritis, polyarteritis nodosa)
Sarcoidosis and other granulomatous myositis
Behçet's syndrome
Inflammatory myopathies and eosinophilia
  Eosinophilic polymyositis
  Diffuse fasciitis with eosinophilia
Focal myositis
Myositis ossificans

INFECTIOUS

Bacterial: *Staphylococcus aureus*, streptococci, *Escherichia coli, Yersinia* sp., *Legionella* sp., gas gangrene (*Clostridium welchii*), leprous myositis, Lyme disease (*Borrelia burgdorferi*)
Viral: acute myositis after influenza or other viral infections (adenovirus, coxsackievirus, echovirus, parainfluenza virus, Epstein-Barr virus, arbovirus, cytomegalovirus), retrovirus-related myopathies (HIV, HTLV-1), hepatitis B and C
Parasitic: trichinosis (*Trichinella spiralis*), toxoplasmosis (*Toxoplasma gondii*), cysticercosis, sarcosporidiosis, trypanosomiasis (*Taenia solium*)
Fungal: *Candida, Cryptococcus,* sporotrichosis, actinomycosis, histoplasmosis

HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotropic virus 1.
From Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine,* 23rd ed. Philadelphia: Elsevier; 2008.

on the EMG and the muscle biopsy. Similarly, a short period of corticosteroid treatment can mask the findings.

Inclusion body myositis is the most common inflammatory myopathy presenting in men older than 50 years. It typically begins insidiously with proximal weakness and then evolves to affect the quadriceps, the long finger flexors in the arms, and the tibialis anterior, where it results in a foot drop. The signs are often asymmetrical. Bulbar and respiratory muscle weakness occur later in the disease course, which is usually refractory to immunomodulatory therapy. No treatment has been proved to influence the disease's slow progression, with significant disability resulting within 5 years.

Polymyositis, Dermatomyositis, and Other Inflammatory Myopathies

Polymyositis and dermatomyositis are covered in Chapter 277. Systemic lupus erythematosus (Chapter 274), mixed connective tissue disease (Chapter 278), Sjögren's syndrome (Chapter 276), and rheumatoid arthritis (Chapter 272) can cause an inflammatory myopathy, as can sarcoidosis (Chapter 95). Systemic viral illnesses frequently cause muscle pain and an elevated CK, which are rarely a major clinical concern. Other microorganisms also cause myositis (Table 429-11), which rarely dominates the clinical picture.

Grade A

1. Manzur AY, Kuntzer T, Pike M, et al. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2008;1:CD003725.
2. Kley RA, Vorgerd M, Tarnopolsky MA, et al. Creatine for treating muscle disorders. *Cochrane Database Syst Rev*. 2007;1:CD004760.
3. Logigian EL, Martens WB, Moxley RT 4th, et al. Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. *Neurology*. 2010;74:1441-1448.
4. Sansone V, Meola G, Links TP, et al. Treatment for periodic paralysis. *Cochrane Database Syst Rev*. 2008;1:CD005045.
5. Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *N Engl J Med*. 2003;349:2503-2509.
6. van der Ploeg AT, Clemens PR, Corzo D, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N Engl J Med*. 2010;362:1396-1406.

SUGGESTED READINGS

Dalakas MC. Inflammatory muscle diseases: a critical review on pathogenesis and therapies. *Curr Opin Pharmacol*. 2010;10:346-352. *Review emphasizing dermatomyositis, polymyositis, necrotizing myositis, and inclusion body myositis.*
Rider LG, Miller FW. Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. *JAMA*. 2011;305:183-190. *Case-based review.*
Rocha CT, Hoffman EP. Limb-girdle and congenital muscular dystrophies: current diagnostics, management, and emerging technologies. *Curr Neurol Neurosci Rep*. 2010;10:267-276. *Review including the potential usefulness of DNA sequencing technologies and potential new therapies.*
Selcen D. Myofibrillar myopathies. *Neuromuscul Disord*. 2011;21:161-171. *Review.*
Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. *J Neurol Neurosurg Psychiatry*. 2010;81:358-367. *Review.*

430

DISORDERS OF NEUROMUSCULAR TRANSMISSION

ANGELA VINCENT AND AMELIA EVOLI

DEFINITION

Neuromuscular transmission depends on the release of acetylcholine from synaptic vesicles that are stored in the terminal boutons of the motor nerve axon (Fig. 430-1). Invasion of the motor nerve terminal by the action potential opens voltage-gated calcium channels, resulting in the Ca^{2+}-dependent

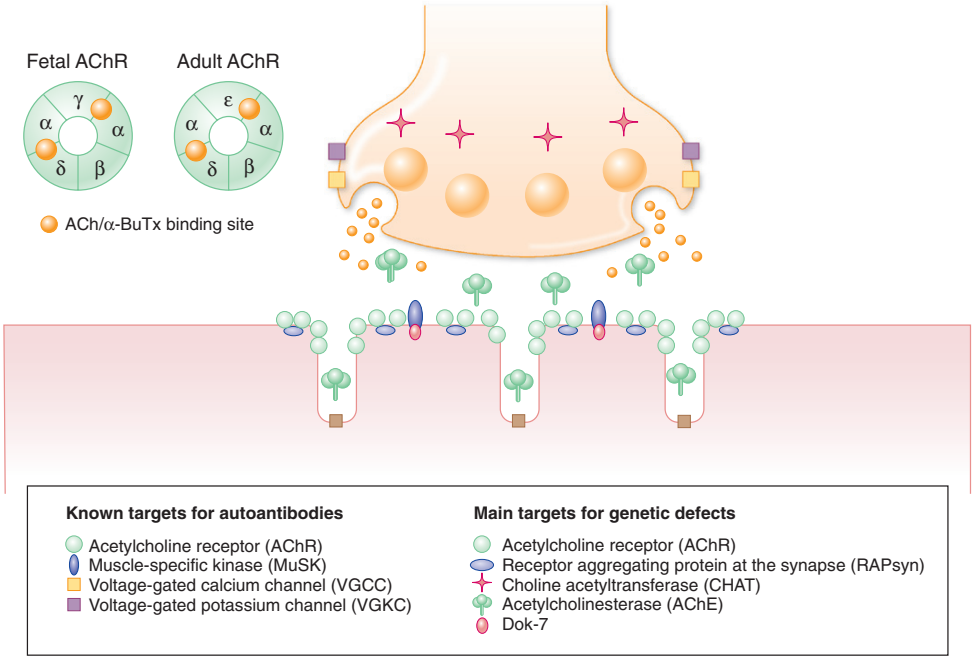


FIGURE 430-1. **Diagrammatic representation of the neuromuscular junction, indicating the ion channels, receptors, enzymes, and associated proteins that are the most frequent targets for autoimmune diseases *(left)* or mutations in genetic diseases *(right)*.** The acetylcholine receptor exists in fetal and adult isoforms as illustrated at *top left*. The replacement of the fetal form by the adult form takes place toward the end of gestation in humans. Voltage-gated sodium channels are located at the bottom of the postsynaptic folds.

release of the vesicular contents into the synaptic space. Acetylcholine binds to the acetylcholine-gated ion channels (acetylcholine receptors [AChRs]) on the postsynaptic membrane, thereby leading to the opening of these channels and a local depolarization, the end plate potential. If the end plate potential exceeds the critical firing threshold, voltage-gated sodium channels (sited at the bottom of the postsynaptic folds) open to generate the muscle action potential that propagates along the muscle fiber and activates muscle contraction. The action of acetylcholine is terminated by its dissociation from the AChRs, which close spontaneously after 1 to 4 milliseconds; hydrolysis of acetylcholine by acetylcholinesterase; and acetylcholine diffusion from the synaptic cleft. Meanwhile, in the motor nerve terminal, the voltage-gated calcium channels close spontaneously, and the resting membrane potential is restored through the transient opening of voltage-gated potassium channels.

The extent to which the amplitude of the end plate potential exceeds the threshold for activation of the voltage-gated sodium channels is called the safety factor. In healthy individuals, the amplitude decreases during repeated activity but does not fall below this threshold; thus, neuromuscular transmission is not compromised. However, if there is a an abnormally low end plate potential amplitude, failure of neuromuscular transmission may occur. Causes include defects in the release of acetylcholine, the postsynaptic response to acetylcholine, or the number or sensitivity of the voltage-gated sodium channels. Morphologic changes to the presynaptic or postsynaptic components or to the basal lamina between them may also influence the efficacy of transmission. Although myasthenia gravis and some neurotoxic envenomations (Chapter 113) are the most common disorders of neuromuscular transmission, a number of conditions have been implicated (Table 430-1).

AUTOIMMUNE DISEASES

Myasthenia Gravis

EPIDEMIOLOGY

Myasthenia is the most common disorder of neuromuscular transmission, with a prevalence of about 15 per 100,000 in Western countries. All races can be affected. It can occur at any age from about year 1 onward, with a small peak in the third decade. It also increasingly is being recognized at later ages, with an annual incidence rising above 5 per 100,000 in individuals older than 70 years, in whom it is important to differentiate from other causes of limb or bulbar muscle weakness.

Myasthenia gravis itself is heterogeneous and can be divided into different subtypes; the relative frequency of these different forms is not known, but relatively mild childhood forms are frequent in some Asian countries. Neonatal myasthenia gravis, due to the placental transfer of maternal antibodies to the AChR or to the muscle-specific kinase, affects up to one in eight babies born to mothers with myasthenia gravis. Autoimmune myasthenia gravis must be distinguished from congenital myasthenic syndromes, which are caused by gene mutations.

PATHOBIOLOGY

Pathophysiology

Myasthenia gravis is the result of a defect in neuromuscular transmission. The postsynaptic response to acetylcholine, the end plate potential, is reduced so that the threshold for activation of the muscle action potential is not reached. At a severely affected end plate, this deficiency can occur at the initiation of contraction, but it is most common during repetitive activity when the end plate potential naturally declines. This phenomenon, occurring across many end plates within a muscle, is responsible for the decrement in the amplitude of the compound muscle action potential on repetitive nerve stimulation, a finding that is diagnostic of a disorder of neuromuscular transmission.

In myasthenia gravis, the reduced end plate potentials result from loss of functional AChRs on the postsynaptic membrane and also from morphologic damage to the membrane. This damage leads to loss of AChR-containing membrane and to simplification of the postsynaptic folds, which contain the voltage-gated sodium channels. The result is a raised threshold for generation of the action potential, thereby further compromising neuromuscular transmission. In most patients, these changes are caused by antibodies against the AChRs. The pathophysiology in patients without such antibodies, including patients with muscle-specific kinase antibodies, is not well studied.

Like most synapses, the neuromuscular junction is highly regulated. If the nerve is cut, leading to loss of neuromuscular transmission, the muscle responds by upregulating the expression of AChR that revert to a fetal phenotype (see Fig. 430-1). Alternatively, if the activity of the postsynaptic muscle decreases, the motor nerve attempts to compensate. Consequently, in myasthenia gravis, there is some increase in the release of acetylcholine from the motor nerve and an increase in the synthesis of AChRs in the muscle fiber.

Pathogenesis

Myasthenia gravis is an antibody-mediated autoimmune disease that is associated with other autoimmune diseases, most often thyroid disease, and, in younger patients, with an increased incidence of the human leukocyte antigen (HLA)-B8 and -DR3 haplotype that also is associated with several other autoimmune diseases. Anti-AChR antibodies act by three main mechanisms (Fig. 430-2). First, a few antibodies directly inhibit the binding of

TABLE 430-1 DISORDERS OF NEUROMUSCULAR TRANSMISSION

DISEASE	TARGET	PATHOBIOLOGY
AUTOIMMUNE		
Myasthenia gravis	AChRs	Antibodies to AChR in 85% reduce AChR numbers and EPP amplitude Antibodies to MuSK in 5-10%—mechanism not clear
Transient neonatal myasthenia	AChRs, MuSK	Maternal antibodies cause transient disease in neonate; not seen commonly if mother receiving treatment
Arthrogryposis	Fetal AChR	Maternal antibodies that inhibit fetal AChR function paralyze baby in utero, leading to joint contractures; very rare cause of arthrogryposis
Lambert-Eaton myasthenic syndrome	VGCCs	Antibodies to VGCC in 90% reduce VGCC numbers and ACh release and EPP amplitude
Acquired neuromyotonia	VGKCs	Antibodies to VGKCs in 40% lead to increased and spontaneous ACh release
GENETIC		
Acetylcholine receptor deficiency	AChR	Recessive mutations in AChR-subunit genes cause reduced AChR expression
Acetylcholine receptor deficiency		Recessive mutations in *RAPSYN* cause reduced anchoring of AChR on the postsynaptic membrane, or in *DOK-7* causing a synaptopathy
AChR kinetic abnormalities	AChR	Dominant or recessive mutations in AChR-subunit genes cause kinetic defects—"slow" and "fast" channel syndromes
Choline acetyltransferase deficiency	Choline acetyltransferase	Recessive mutations in the gene for choline acetyltransferase (*CHAT*) cause reduced ACh release
Acetylcholine esterase deficiency	AChE	Recessive mutations in the collagen tail (*COLQ*) that anchors AChE at the neuromuscular junction cause absence of AChE
Arthrogryposis, multiple pterygium, Escobar's syndrome	Can occur with rapsyn, δ- or γ-subunit AChR mutations	Fetal akinesia
NEUROTOXIC		
Botulism	Presynaptic ACh release	Botulinum toxin gains entry into the presynaptic motor nerve and cleaves proteins involved in ACh release mechanism
Envenomation following bites from snakes, spiders, scorpions, etc.	Varied sites of action	Neurotoxins specific for VGCCs, VGKCs, AChE, AChRs, voltage-gated sodium channels, and other targets are frequent in many animal venoms and generally inhibit function
Drugs and insecticides	Varied sites of action	Muscle relaxants and other drugs Many antibiotics and quinine-related drugs can alter neuromuscular transmission at high dose Organophosphates block AChE and have complicated acute and chronic actions

AChE = acetylcholinesterase; AChR = acetylcholine receptor; EPP = end plate potential; MuSK = muscle-specific kinase; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel.

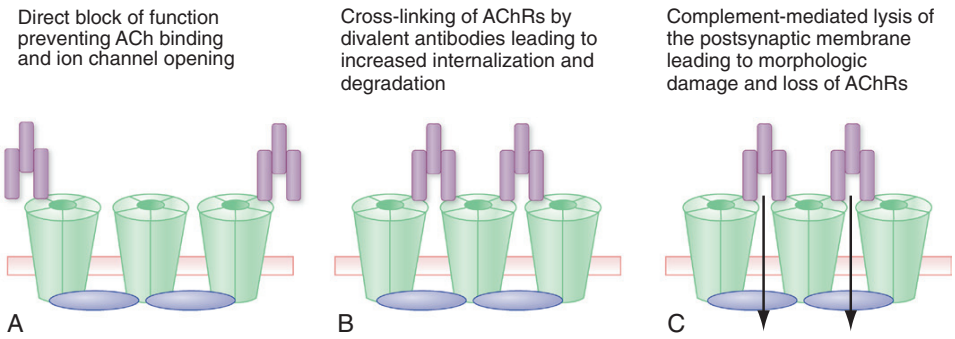


FIGURE 430-2. Mechanisms of loss of the acetylcholine receptor (AChR) at the neuromuscular junction. Antibodies can act (**A**) by directly blocking ACh binding or ion channel function; (**B**) by cross-linking the AChRs in the membrane, thereby leading to increased internalization and degradation; or (**C**) by complement-dependent lysis of the AChR-containing postsynaptic membrane. In myasthenia gravis, complement-dependent lysis is likely to be the most important mechanism overall. Interestingly, there is no evidence of complement-dependent mechanisms in either the Lambert-Eaton myasthenic syndrome or acquired neuromyotonia, in which cross-linking of the respective ion channels with increased internalization seems to be the main mechanism.

acetylcholine to the AChR and cause a pharmacologic-like blockade of function. Second, because of their divalence, antibodies can bind simultaneously to two adjacent AChRs, through the α-subunits that are present in duplicate in each receptor, to form AChR-antibody complexes that are internalized and degraded by the muscle fiber, thereby leading to loss of AChRs. Third, most of the antibodies are immunoglobulin G1 (IgG1) subclass, a subclass that binds and activates complement. As a result, the membrane attack complex is activated, leading to destruction of the postsynaptic membrane and probably causing the morphologic damage that is frequently seen. All these effects are strictly limited to the neuromuscular junction; the remainder of the muscle fiber is essentially normal.

The AChR antibodies are IgG, have high affinity, and are highly specific for the native human AChR. Although the antibodies are the effector mechanism for the loss of AChRs, their characteristics indicate that specific antibody production requires helper T cells that can recognize AChR epitopes. The thymus gland, which is often abnormal in myasthenia, is at least one site where the immune response occurs. In early-onset myasthenia gravis, the thymus is often "hyperplastic," with numerous T- and B-cell lymphocytic infiltrates in the medulla. These infiltrates are very similar to the germinal centers found in lymph nodes, and some contain B cells that express surface immunoglobulin specific for AChRs. Plasma cells are also present and synthesize AChR antibodies. In the thymic medulla, muscle-like "myoid" cells have AChRs on their surface in both normal and myasthenic individuals; these cells probably provide the antigenic stimulus responsible for the germinal center formation and AChR antibody production in myasthenia gravis.

In late-onset myasthenia gravis, the thymus is mostly normal for age. In patients without AChR antibodies, the thymus gland is more likely to appear normal for age, particularly in patients with muscle-specific kinase antibodies. However, in patients without either AChR or muscle-specific kinase antibodies, a typical thymic hyperplasia is often present.

Thymoma

Thymoma occurs in about 10% of myasthenic patients, reaching a peak in middle age. Thymomas are epithelial cell tumors and correspond mainly to the World Health Organization types B1 and B2. The epithelial cells attract large numbers of T lymphocytes, which may be sensitized to the AChR in the tumor and then exported to the periphery. Rarely, myasthenia gravis arises after removal of a thymoma.

CLINICAL MANIFESTATIONS

Myasthenia gravis presents clinically with painless muscle weakness that increases with muscle use and improves after rest. In many patients, the weakness starts in the eye muscles, where it results in double vision and ptosis (drooping eyelids). In others, it may first affect bulbar muscles or limb muscles (Fig. 430-3). Virtually any skeletal muscle may be involved as the illness progresses. Typically, the weakness varies in distribution and severity from day to day or from week to week, and it is often worse in the evening. It may first appear following an infection. Established weakness can increase with anxiety, with infection, or with the menstrual period and tends to improve with rest.

Ptosis, which is often asymmetrical, and diplopia initially can be transient and first noticed while driving, for example. Severity can range from mild unilateral ptosis or minimal diplopia to profound bilateral ptosis, which obscures vision, combined with almost complete ophthalmoplegia. Bulbar symptoms include weakness of facial muscles with difficulties in closing eyes and a "snarling" smile, difficulty in chewing, nasal or slurred speech that can noticeably deteriorate as speech continues, impaired swallowing sometimes associated with nasal regurgitation of fluids, reduced tongue movements, and head droop related to neck weakness.

Limb muscle involvement is common, and proximal muscles are usually more involved than distal. Proximal weakness of the legs can lead to collapse when walking and can be misinterpreted as a functional (psychogenic) disorder. Weakness of elbow extension and of finger abduction may be prominent. By contrast, ankle dorsiflexion is rarely affected except in severe disease.

Respiratory muscle involvement is less common but can be life threatening, especially if associated with dysphagia. Selective involvement of the diaphragm can cause severe breathlessness in the supine posture. Wasting is uncommon but can affect the facial muscles and tongue, for example, in long-standing disease. Tendon reflexes are typically brisk. Bladder disturbances are rare, and sensory symptoms do not occur.

Subtypes of Myasthenia Gravis

Several subgroups can be distinguished on the basis of clinical and pathologic criteria and can help to inform treatment.

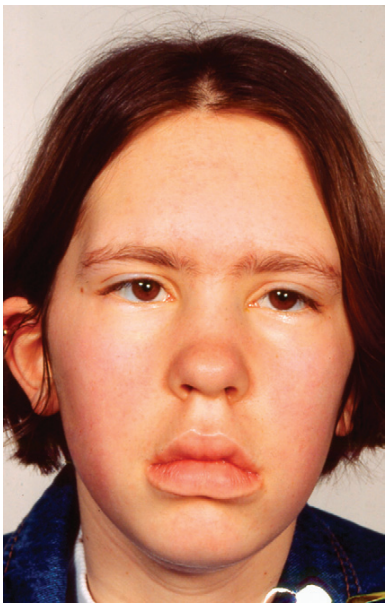


FIGURE 430-3. Marked ocular and facial muscle weakness in a young female with myasthenia gravis.

Ocular Myasthenia Gravis

Ocular myasthenia gravis is confined to extraocular muscles; if it remains localized for at least 2 years, subsequent generalized weakness is unlikely. AChR antibody levels are generally low and are undetectable in about 50% of patients. This subgroup rarely is associated with a thymoma. The neuromuscular junction of ocular muscles shows structural and physiologic differences from typical limb muscles. Ocular weakness is often the presenting symptom not only in myasthenia gravis but also in neurotoxin poisoning, for example, botulism (Chapter 304). Thus, physiologic factors or accessibility of the neuromuscular junctions of ocular muscles to circulating factors may make them particularly vulnerable to antibodies in myasthenia gravis.

Generalized Myasthenia Gravis with Acetylcholine Receptor Antibodies

Among patients with generalized disease and AChR antibodies, there are three clinical subgroups. Early-onset myasthenia gravis is more frequent in females and associates strongly with HLA-A1, -B8, and -DR3. The thymus is generally hyperplastic. AChR antibody titers are usually high and decline to varying degrees after successful treatments, including thymectomy.

Late-onset myasthenia gravis is becoming increasingly common with the aging of the population and, when associated with bulbar weakness, may be mistaken for amyotrophic lateral sclerosis (Chapter 418) or brain stem cerebrovascular disease. Among older patients, males are more frequently affected, and the thymus is usually normal for age.

Thymoma-associated myasthenia gravis is an important distinction because thymectomy or other specific tumor therapy is required. Most patients with thymomas and myasthenia gravis present between the ages of 30 and 60 years.

Generalized Myasthenia Gravis with Muscle-Specific Kinase Antibodies

About 15% of myasthenic patients with generalized symptoms do not have detectable AChR antibodies. A variable proportion of these patients have antibodies to another neuromuscular junction protein, the muscle-specific kinase. Muscle-specific kinase antibodies are mainly IgG4 and are absent or very infrequent in patients with AChR antibody–positive myasthenia gravis, patients with persistent ocular myasthenia gravis, and patients with thymoma. Muscle-specific kinase antibodies are found more often in younger females, including children, with marked ocular, bulbar, neck, or respiratory muscle weakness but are seen less frequently in older patients. It is not yet clear how these antibodies cause the neuromuscular junction defect.

Generalized Myasthenia Gravis with Neither Acetylcholine Receptor nor Muscle-Specific Kinase Antibodies

Some patients with generalized myasthenia gravis have neither AChR nor muscle-specific kinase antibodies. These patients can develop severe disease but usually respond well to treatment and may have low-affinity antibodies to AChR.

DIAGNOSIS

Diagnosis is based on the clinical features, serologic testing for specific antibodies, clinical electrophysiology, and, if doubt still remains or specialized facilities are not available, the clinical response to anticholinesterase medication (Table 430-2). Mediastinal imaging is needed to exclude a thymoma in patients with AChR antibodies.

AChR antibodies are present in about 85% of patients with generalized symptoms but in only 50% of patients with purely ocular involvement. In the absence of AChR antibodies, especially in subjects with generalized symptoms, testing for muscle-specific kinase antibodies is recommended. Both AChR and muscle-specific kinase antibodies are very specific, and their detection in symptomatic patients confirms the diagnosis.

The electrophysiologic abnormality is an abnormally large decrement (>10%) in the amplitude of the compound muscle action potential on low-rate (3-Hz) stimulation with increased jitter or blocking on single-fiber electromyogram (EMG). In patients with muscle-specific kinase antibodies, EMG abnormalities may be detectable only in facial muscles. These EMG changes are not specific for myasthenia gravis but can occur in any disorder that interferes with neuromuscular transmission.

Intravenous administration of edrophonium (Tensilon), a short-acting cholinesterase inhibitor, transiently improves myasthenic weakness but requires an appropriate medical setting, including resuscitative facilities and

TABLE 430-2 DIAGNOSTIC EVALUATION (EXCLUDES NEUROMYOTONIA)

	AChR MG	MuSK MG	SERONEG MG	NEONATAL MG	LEMS	CMS	BoTx	MM
Onset birth, recovery of muscle strength within 2 mo	–	–	–	+	–	AChR γ-subunit mutations, variable severity	–	–
Onset birth plus arthrogryposis	–	–	–	+	–	Rapsyn or AChR δ-subunit mutations	–	–
Onset at <1 yr and persistent	–	–	–	–	–	Any CMS Dok-7, rapsyn deficiency, and SCS may present later	+	+/–
Infantile apneas	–	–	–	+/–	–	Fast channel syndrome, rapsyn, or ChAT mutation		
AChR Ab positive	+	–	–	+/–	–	–	–	–
MuSK Ab positive	–	+	–	+/–	–	–	–	–
VGCC Ab positive	–	–	–	–	+	–	–	–
EMG decrement >10%	+/–	+/–	+/–	+/–	+/–	+/–	+/–	–
EMG jitter increased	+	+ Especially face muscles	+	+	+	+	+	+/–
Post-tetanic potentiation	–	–	–	–	+	–	+	–
AChE inhibitor response	+	Often weak	+	+	Often weak	Except *SCS*, *COLQ*, or *DOK7* mutations	+/–	–
Thymoma	+/–	–	–	–	–	–	–	–

AChE = acetylcholinesterase; AChR = acetylcholine receptor; BoTx = botulism; ChAT = choline acetyltransferase; CMS = congenital myasthenic syndromes; Dok-7 = downstream of kinase 7; LEMS = Lambert-Eaton myasthenic syndrome; MG = myasthenia gravis; MM = mitochondrial myopathy; MuSK = muscle-specific kinase; SCS = slow channel syndrome; seroneg = seronegative for AChR and MuSK antibodies.

the availability of atropine, because of the risk for adverse events and severe cholinergic reactions, including syncope. A test dose of 2 mg is given intravenously, followed 30 seconds later by 6 to 8 mg if no adverse event has occurred. The equivalent doses in children are a 20 μg/kg test dose followed by 60 to 80 μg/kg. Some patients improve sufficiently with the test dose that it is not necessary to give the full dose. An alternative pharmacologic test in adults is a single dose of subcutaneous or intramuscular neostigmine (1 to 2.5 mg) or of oral pyridostigmine (60 mg).

Differential Diagnosis

Congenital AChR deficiency syndromes (see later) should be considered in patients who have clinical and EMG evidence of myasthenia but are seronegative for AChR and muscle-specific kinase antibodies. Lambert-Eaton myasthenic syndrome almost always begins with difficulty in walking; ocular symptoms are rare, and specific laboratory tests are available (see later). The ocular muscle involvement that characterizes Miller-Fisher syndrome is more rapid in onset than is usual in myasthenia gravis and is associated with GQ1b antibodies. Mitochondrial myopathy may show signs that are similar to those of myasthenia gravis (e.g., asymmetrical ptosis and limitation of eye movements), and there may be increased jitter on single-fiber EMG, but this condition and oculopharyngeal dystrophy can be distinguished from myasthenia gravis by the nonfluctuating weakness and by muscle biopsy. In neurasthenia and chronic fatigue syndrome (Chapter 282), the laboratory tests for myasthenia gravis are negative.

TREATMENT Rx

Most patients with AChR antibodies respond to oral pyridostigmine, 30 to 60 mg four or five times daily; in patients with mild disease, this dose may adequately control symptoms. Doses in excess of 90 mg are likely to cause gastrointestinal side effects, abdominal cramps and diarrhea, which can be controlled with oral propantheline bromide, 15 mg, or loperamide, 2 mg. Patients with muscle-specific kinase antibodies generally show an unsatisfactory response to pyridostigmine. In some of these patients, pyridostigmine, even at a low doses, can increase weakness and cause nicotinic side effects (muscle cramps and diffuse fasciculations).

Neonatal Myasthenia Gravis

Pyridostigmine, 3 to 5 mg, can be given every 4 hours to about an hour before a feeding. Close monitoring and respiratory support in a special unit may be required.

Ocular Myasthenia

Diplopia can sometimes be helped by the use of prisms. Ocular symptoms that respond incompletely to pyridostigmine are often improved or completely corrected by low-dose prednisone therapy (e.g., 5 mg every other day) increasing by 5 mg at weekly intervals either until symptoms are completely controlled or until a ceiling dose (e.g., 1 mg/kg) is reached. When remission is established, the dose can be slowly reduced (e.g., by 5 mg at 2-weekly intervals) until symptoms recur and then adjusted upward to define the effective minimal dose. Full withdrawal of prednisone is usually followed by a symptomatic relapse. Most centers do not recommend thymectomy for nonthymomatous ocular myasthenia gravis. In patients who fail to respond adequately to prednisone or who are intolerant of the medication, the addition of azathioprine (2 to 2.5 mg/kg body weight) or ocular muscle surgery is an option. However, the diagnosis should be reviewed in patients who show no improvement with high-dose prednisone treatment.

Thymoma

Thymoma usually represents an absolute indication for surgery, but removal of the tumor typically does not result in improvement in muscle weakness. If the tumor is found to be locally invasive, postoperative radiotherapy is indicated. If tumor spread is more extensive, chemotherapy is performed, mainly with cisplatin-containing regimens.

Generalized Nonthymomatous Myasthenia Gravis

When generalized symptoms are inadequately controlled by pyridostigmine, thymectomy is often recommended empirically even for patients without a thymoma, especially patients younger than 45 years. Despite the absence of trials and no clear consensus from observational data, thymectomy in early-onset patients with anti-AChR antibodies appears to be associated with an increased rate of remission. By comparison, thymectomy does not appear to influence the course of the disease in patients who have anti-MuSK antibodies and in whom the thymus is generally devoid of hyperplastic changes. Most patients respond to alternate-day prednisone, started at a low dose (e.g., 10 mg every other day) and increasing by 5 to 10 mg per dose to 1.0 to 1.5 mg/kg. Because starting prednisone can temporarily exacerbate the disease, patients are usually best managed in the hospital, especially if they have bulbar or respiratory muscle involvement. When remission is established, the dose can be reduced by 5 to 10 mg every 2 weeks (or more slowly) until symptoms recur, when it can then be adjusted upward, aiming to define the effective minimal dose. Prophylactic treatment for steroid-induced bone disease should be considered in all patients (Chapter 251).

For chronic treatment, immunosuppressive medication is required in patients who do not respond satisfactorily to prednisone or need high maintenance doses. Because these agents have a long latency of effect, they are generally combined with prednisone (see earlier) during the early phases of treatment and then used as monotherapy if steroids can be withdrawn or are contraindicated. Azathioprine (2.5 mg/kg/day) is the preferred treatment;

compared with prednisone alone, combination treatment is better tolerated and associated with fewer relapses. Cyclosporine (3 to 5 mg/kg daily) is effective as monotherapy or combined with steroids and is frequently used as the second-choice immunosuppressant. Although the efficacy of mycophenolate mofetil in association with prednisone is questioned, this agent at the standard dose of 2000 mg/day is used in patients who are unresponsive to or intolerant of azathioprine. Tacrolimus is also used when the other agents fail or cannot be tolerated. Methotrexate (5 to 15 mg weekly) is an option for those intolerant of azathioprine, but long-term randomized studies are not yet available. When remission has been achieved, doses can be reduced slowly and cautiously; full withdrawal is likely to be followed by relapse.

Immunoglobulin infusion and plasmapheresis are equally efficacious for providing short-term improvement, typically persisting 4 to 6 weeks, and can be used to prepare patients for thymectomy, to cover the initiation of prednisone therapy, or to control an exacerbation of myasthenic weakness. An immunoglobulin infusion of 1 g/kg given on day 1 only is as effective as 1 g/kg given on day 1 and again on day 2. Because of the short-lived benefits of these therapies, they must be accompanied by additional immunosuppressive therapy, as noted previously.

Inhibition of the production of acetylcholinesterase using a short antisense oligonucleotide was both effective and safe in a phase Ib study on patients with anti-AChR positive MG. Rituximab, a monoclonal anti-CD20 antibody that markedly reduces circulating B cells, has been used successfully in patients with refractory disease.

PROGNOSIS

The increasing use of immunologic therapies, coupled with advances in critical care, has improved the prognosis in nonthymomatous myasthenia gravis. Many patients can expect substantial improvement or remission with a normal life expectancy. The prognosis is less good, however, in those with invasive thymoma.

Lambert-Eaton Myasthenic Syndrome

DEFINITION AND EPIDEMIOLOGY

The Lambert-Eaton myasthenic syndrome, which is a rare disorder that can occur in paraneoplastic (Chapter 187) and nonparaneoplastic forms, affects all races. The incidence of the paraneoplastic form is much higher, but its shorter survival results in a similar prevalence of the two types. The paraneoplastic form affects about 2% of patients with small cell lung cancer (Chapter 197) and can also occur with lymphoma (Chapter 191). The nonparaneoplastic form associates with HLA-A1, -B8, and -DR3, as in myasthenia gravis.

PATHOBIOLOGY

Lambert-Eaton myasthenic syndrome is an antibody-mediated presynaptic disorder characterized by a reduced number of acetylcholine quanta (vesicles) released by each nerve impulse. End plate potentials recorded from intercostal muscle biopsies are consequently much reduced in amplitude. During repetitive high-frequency nerve stimulation, the end plate potential amplitude increases, probably because build-up of calcium in the motor nerve terminal leads to increased release of acetylcholine. Freeze-fracture electron microscopic studies of motor nerve terminals show that the "active zone" particles, which represent voltage-gated calcium channels, are reduced in number and disorganized. IgG binds to the presynaptic nerve terminal at the sites of acetylcholine release. The antibodies in Lambert-Eaton myasthenic syndrome appear to act principally by cross-linking the voltage-gated calcium channels on the surface of the presynaptic motor nerve membrane, thereby leading to their clustering and internalization. The antibodies also interfere with transmitter release from postganglionic parasympathetic and sympathetic neurons in injected mice, providing an explanation for the autonomic dysfunction observed in many patients.

CLINICAL MANIFESTATIONS

Almost all patients present with difficulty in walking, which exhibits a rolling characteristic. Weakness in ocular, bulbar, and respiratory muscles is less common than in myasthenia gravis. Weakness predominantly affects proximal muscles, which may show augmentation of strength during the first few seconds of a maximal contraction. Reflexes are absent or depressed but can increase after 10 seconds of maximal contraction of the muscle (post-tetanic potentiation). Autonomic symptoms such as dry mouth, constipation, and erectile dysfunction are present in most patients. Cerebellar ataxia occasionally may be present. Patients with nonparaneoplastic Lambert-Eaton myasthenic syndrome may have other autoimmune diseases, notably vitiligo.

DIAGNOSIS

Diagnosis is based on the clinical features, on a positive serum voltage-gated calcium-channel antibody test, and on the characteristic EMG findings (see Table 430-2). Antibodies specific for the α1A (P/Q) subtype of voltage-gated calcium channels are found in 90% of patients, both with and without small cell lung cancer. Patients may not respond convincingly to intravenous edrophonium. On EMG, the amplitude of the resting compound muscle action potential is reduced, but it increases by more than 100% after 10 seconds of voluntary contraction of the muscle or during high-frequency (40-Hz) nerve stimulation. Chest imaging is required in those at risk for tumor.

Differential Diagnosis

Botulinum poisoning (Chapter 304) causes blockade of presynaptic transmitter release at the neuromuscular junction as well as EMG changes similar to those in the Lambert-Eaton myasthenic syndrome. Botulism is detected by finding the toxin in serum or the *Clostridium botulinum* bacteria in the wound or feces. Myopathies (Chapters 277 and 429) can mimic Lambert-Eaton myasthenic syndrome clinically, but autonomic changes do not occur, EMG findings are different, and muscle biopsy is abnormal.

TREATMENT

Rx

Plasma exchange leads to clinical improvement within a few days in acutely ill patients, and most patients respond to immunosuppressive drugs or intravenous immunoglobulin therapy. Intravenous immunoglobulin therapy (1 g/kg for 2 days) improves strength, with an associated decline in specific antibody. Specific tumor treatments (resection, local radiotherapy, chemotherapy) often lead to improvement of the neurologic disorder. Most patients respond to 3,4-diaminopyridine (10 to 20 mg four times daily). This drug is available in Europe and many other countries; it has yet been approved by the U.S. Food and Drug Administration but can be obtained through some referral centers. Long-term immunosuppressive treatment with prednisone, azathioprine, or cyclosporine may be required in those with severe weakness, using doses similar to those described previously for myasthenia gravis.

PROGNOSIS

Prognosis mainly depends on the association with malignancy. Patients with paraneoplastic Lambert-Eaton myasthenic syndrome tend to have a progressive disease and a less satisfactory response to treatment. The nonparaneoplastic disease responds generally well to therapy as described previously.

ACQUIRED NEUROMYOTONIA

DEFINITION AND EPIDEMIOLOGY

Neuromyotonia, or Isaacs' syndrome, is a rare disorder primarily characterized by myokymia (spontaneous undulating muscle contractions) that can be intermittent or continuous and may be present during sleep or general anesthesia. It results from the hyperexcitability of motor nerves. A milder variant, the cramp-fasciculation syndrome, is more common.

PATHOBIOLOGY

Neuromyotonia may be associated with other autoimmune diseases or other autoantibodies, and cerebrospinal fluid analysis may show oligoclonal bands. In about 15% of patients, it is paraneoplastic, usually associated with thymoma and occasionally with lung cancer. Occasionally, neuromyotonia appears to be triggered by infection or allergic reactions, and it may improve spontaneously within weeks to months in these cases.

CLINICAL MANIFESTATIONS

The clinical presentation is heterogeneous with a combination of muscle stiffness, cramps, myokymia (visible undulation of the muscle), pseudomyotonia (e.g., failure to relax after fist clenching), and weakness. Increased sweating is common. Myokymia persists during sleep. Cramp-fasciculation syndrome shares some features with neuromyotonia. Some patients have sensory symptoms, including paresthesias, dysesthesia, and numbness, and a few have autonomic such as constipation or cardiac irregularities and central nervous system features of an encephalopathy, including insomnia, hallucinations, delusions, and mood change (Morvan's syndrome).

DIAGNOSIS

EMG shows spontaneous motor unit discharges that occur as distinctive doublet, triplet, or multiplet bursts with high intraburst frequency (40 to 300 per second), longer continuous bursts, and postactivation contraction. The abnormal muscle activity may be generated at different sites throughout the length of the nerve, but in most cases it is principally distal. Antibodies to voltage-gated potassium channels are found in 40% of patients. The differential diagnosis includes neuromyotonia caused by acquired and inherited neuropathies and by voltage-gated potassium-channel gene mutations (Kv1.1) that can associate with neuromyotonia and episodic ataxia.

TREATMENT AND PROGNOSIS Rx

Neuromyotonia can be improved by anticonvulsant drugs, such as carbamazepine (up to 800 to 1000 mg daily), phenytoin (up to 300 mg daily), or lamotrigine (up to 100 mg daily), that downregulate sodium channel function, thereby reducing the hyperexcitability of nerves. Plasma exchange and intravenous immunoglobulins, using the same regimen as for myasthenia gravis, may be followed by short-term improvement. Immunosuppressive medications, again using the same drugs as for myasthenia gravis, are effective in some patients. Neuromyotonia is often a monophasic disease that can be successfully managed with symptomatic and immunodulating treatment. Because it is commonly associated with myasthenia gravis, the administration of pyridostigmine can increase symptoms of motor nerve hyperexcitability. Prognosis is less favorable in cases with central nervous system involvement.

GENETIC MYASTHENIC SYNDROMES

Congenital myasthenic syndromes (see Table 430-1) are inherited disorders that result from mutations in genes encoding key proteins at the neuromuscular junction. In the United Kingdom, their prevalence is at least 6 per 1 million population.

PATHOBIOLOGY

The genetic mutations can be presynaptic, synaptic, or postsynaptic and can involve many of the genes specific for neuromuscular junction proteins. The most common is the AChR ε-subunit gene, in which the single nucleotide missense substitutions or frameshift mutations usually result in complete loss of function of the AChR ε-subunit. Because this subunit replaces the AChR γ-subunit around the time of birth, the babies are normal in development but show weakness during late pregnancy and in the neonatal period. Survival probably depends on the continued expression of the γ-subunit. AChR deficiency can also result from defects in the gene for rapsyn, a cytoplasmic protein required for the clustering of the AChRs at the neuromuscular junction. Single nucleotide changes in genes for any of the AChR subunits can affect acetylcholine-induced receptor channel openings, leading to kinetic defects. In the fast channel syndrome (recessive), the result is reduced function of AChR, whereas in the slow channel syndrome (dominant), the channel opens for prolonged periods, thereby resulting in subsynaptic accumulation of ions and degenerative changes.

Mutations in the *COLQ* gene, which gives rise to the collagen tail that anchors acetylcholinesterase in the synaptic cleft, are less common. The resulting continuous exposure of the postsynaptic membrane to acetylcholine leads to degenerative changes and progressive muscle weakness. Mutations in choline acetyltransferase, the enzyme responsible for the synthesis of acetylcholine, do not always lead to dysfunction at rest; during repetitive activity, however, the amount of acetylcholine in each packet decreases, with consequent failure of neuromuscular transmission. Mutations in *DOK7* cause a "synaptopathy" with small, simplified neuromuscular junctions. Dok-7 binds muscle-specific kinase, and the mutations are thought to impair the signaling that maintains the synaptic structure. Other gene mutations are rarely identified.

CLINICAL MANIFESTATIONS

Clinical manifestations may vary from death in utero in severe cases to mild symptoms that present in adulthood. Although most cases present in infancy with ptosis, hypotonia, and difficulties with feeding and breathing, the slightly different patterns of muscle weakness provide clues that point to which gene is involved. Arthrogryposis multiplex congenita, indicative of fetal akinesia, often associates with rapsyn mutations. Life-threatening episodic apneas can occur with mutations in choline acetyltransferase or rapsyn or in fast-channel syndromes. Severe ophthalmoplegia occurs in endplate acetylcholinesterase deficiency, AChR deficiency due to AChR subunit mutations, and fast channel syndromes, but is rarely seen in the other genetic syndromes. Motor symptoms with *DOK7* mutations usually appear at about 2 years of age after the child first learns to walk and are characterized by a limb-girdle proximal pattern of muscle weakness.

DIAGNOSIS

The EMG findings in the AChR deficiencies and fast channel syndromes are similar to those in typical myasthenia gravis. In the slow channel syndrome and acetylcholinesterase deficiency syndrome, there may be a double response to a single nerve stimulus (see Table 430-2). Most patients show a response to cholinesterase inhibitors (edrophonium or neostigmine), with the exception of the slow channel syndrome, acetylcholinesterase deficiency, and Dok-7 congenital myasthenic syndromes. DNA screening is essential. Genetic analysis can confirm the diagnosis and help in treatment, prognosis, and counseling, although the faulty gene has not been identified in many families.

The principal differential diagnoses are spinal muscular atrophy, infant botulism, hereditary neuropathies, and congenital myopathies or muscular dystrophies. Onset in early childhood, adolescence, or adulthood, as can occasionally occur, may mean that the genetic nature of the disorder is not recognized or initially leads to the incorrect diagnosis of seronegative myasthenia gravis.

TREATMENT AND PROGNOSIS Rx

Many of the congenital myasthenic syndromes respond to acetylcholinesterase inhibitors, as used for myasthenia gravis, and to 3,4-diaminopyridine (1 mg/kg/day in four divided doses). For the slow channel syndrome, some patients have responded to fluoxetine (60 to 100 mg/day in adults), but the use of fluoxetine in children or adolescents requires psychiatric supervision. For syndromes in which the neuromuscular junction is destabilized or there are degenerative changes, such as for Dok-7 or end plate acetylcholinesterase deficiency, treatment with ephedrine (75 to 100 mg/day in adults, 3 mg/kg/day in children) or salbutamol (0.5 to 2 mg, three times a day when ephedrine is not available) can be remarkably effective. The beneficial effects of this treatment are not seen immediately but build up over a period of 6 months or more.

Although these congenital disorders can be fatal during infancy, usually because of apneic episodes during infections, most tend to be nonprogressive and stable or even may improve during adolescence or adult life. The exceptions are the slow channel syndrome and acetylcholinesterase deficiency, which, owing to the excess AChR activations that they cause, can be associated with progressive degenerative changes at the neuromuscular junction, although this risk is largely mitigated with treatment.

Grade A

1. Schneider-Gold C, Gajdos P, Toyka KV, et al. Corticosteroids for myasthenia gravis. *Cochrane Database Syst Rev.* 2005;2:CD002828.
2. Palace J, Newsom-Davis J, Lecky B, et al. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. *Neurology.* 1998;50:1778-1783.
3. Hart IK, Sathasivam S, Sharshar T. Immunosuppressive agents for myasthenia gravis. *Cochrane Database Syst Rev.* 2007;4:CD005224.
4. Sanders DB, McDermott M, Thornton C, et al, for the Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. *Neurology.* 2008;71:394-399.
5. Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. *Neurology.* 2007;68:837-841.
6. Gajdos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. *Ann Neurol.* 1997;41:789-796.
7. Gajdos P, Tranchant C, Clair B, et al. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. *Arch Neurol.* 2005;62:1689-1693.
8. Bain PG, Motomura M, Newsom-Davis J, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. *Neurology.* 1996;47:678-683.
9. Oh SJ, Claussen GG, Hatanaka Y, et al. 3,4-Diaminopyridine is more effective than placebo in a randomized, double-blind, cross-over drug study in LEMS. *Muscle Nerve.* 2009;40:795-800.

SUGGESTED READINGS

Argov Z. Current approach to seronegative myasthenia. *J Neurol.* 2011;258:14-18. *Seronegative patients may have low-affinity antibodies or late onset of congenital myasthenia.*

Mao ZF, Mo XA, Qin C, et al. Course of prognosis of myasthenia gravis: a systematic review. *Eur J Neurol.* 2010;17:913-921. *Review.*

Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol.* 2010;17:893-902. *Consensus guidelines.*