13 - Neurologic Disorders

Chapter 168. Approach to the Neurologic Patient

Introduction

Patients with neurologic symptoms are approached in a stepwise manner termed the neurologic method, which consists of the following:

• Identifying the anatomic location of the lesion or lesions causing symptoms

• Identifying the pathophysiology involved

• Generating a differential diagnosis

• Selecting specific, appropriate tests

Identifying the anatomy and pathophysiology of the lesion through careful history taking and an accurate neurologic examination markedly narrows the differential diagnosis and thus the number of tests needed. This approach should not be replaced by reflex ordering of CT, MRI, and other laboratory testing; doing so leads to error and unnecessary cost.

To identify the anatomic location, the examiner considers questions such as

• Is the lesion in one or multiple locations?

• Is the lesion confined to the nervous system, or is it part of a systemic disorder?

• What part of the nervous system is affected?

Specific parts of the nervous system to be considered include the cerebral cortex, subcortical white matter, basal ganglia, thalamus, cerebellum, brain stem, spinal cord, brachial or pelvic plexus, peripheral nerves, neuromuscular junction, and muscle.

Once the location of the lesion is identified, categories of pathophysiologic causes are considered; they include

• Vascular

• Infectious

• Neoplastic

• Degenerative

• Traumatic

• Toxic-metabolic

• Immune-mediated

When appropriately applied, the neurologic method provides an orderly approach to even the most complex case, and clinicians are far less likely to be fooled by neurologic mimicry—eg, when symptoms of an acute stroke are actually due to a brain tumor or when rapidly ascending paralysis suggesting Guillain-Barre is actually due to spinal cord compression.

History

The history is the most important part of the neurologic evaluation. Patients should be put at ease and allowed to tell their story in their own words. Usually, a clinician can quickly determine whether a reliable history is forthcoming or whether a family member should be interviewed instead.

Specific questions clarify the quality, intensity, distribution, duration, and frequency of each symptom. What aggravates and attenuates the symptom and whether past treatment was effective should be determined. Specific disabilities should be described quantitatively (eg, walks at most 25 ft before stopping to rest), and their effect on the patient's daily routine noted. Past medical history and a complete review of systems are essential because neurologic complications are common in other disorders, especially alcoholism, diabetes, cancer, vascular disorders, and HIV infection. Family history is important because migraine and many metabolic, muscle, nerve, and neurodegenerative disorders are inherited. Social, occupational, and travel history provides information about unusual infections and exposure to toxins and parasites.

Sometimes neurologic symptoms and signs are functional or hysterical, reflecting a psychiatric disorder. Typically, such symptoms and signs do not conform to the rules of anatomy and physiology, and the patient is often depressed or unusually frightened. However, functional and physical disorders sometimes coexist, and distinguishing them can be challenging.

Neurologic Examination

The neurologic examination begins with careful observation of the patient entering the examination area and continues during history taking. The patient's speed, symmetry, and coordination while moving to the examining table are noted, as are posture and gait. The patient's demeanor, dress, and responses provide information about mood and social adaptation. Abnormalities in language, speech, or praxis; neglect of space; unusual posturing; and other disorders of movement may be apparent before formal testing.

As information is obtained, a skilled examiner may include certain components of the examination and exclude others based on a preliminary hypothesis about the anatomy and pathophysiology of the problem. If the examiner is less skilled, complete neurologic screening is done.

Mental status: (See also Ch. 157.) The patient's attention span is assessed first; an inattentive patient cannot cooperate fully and hinders testing. Any hint of cognitive decline requires examination of mental status (see Sidebar 168-1), which involves testing multiple aspects of cognitive function (eg, orientation to time, place, and person; attention and concentration; memory; verbal and mathematical abilities; judgment; reasoning). Loss of orientation to person (ie, not knowing one's own name) occurs only when obtundation, delirium, or dementia is severe; when it occurs as an isolated symptom, it suggests malingering. Insight into illness and fund of knowledge in relation to educational level are assessed, as are affect and mood (see p. 1538).

The patient is asked to follow a complex command that involves 3 body parts and discriminates between right and left (eg, "Put your right thumb in your left ear, and stick out your tongue"). The patient is asked to name simple objects and body parts and to read, write, and repeat simple phrases; if deficits are noted, other tests of aphasia are needed (see p. 1642). Spatial perception can be assessed by asking the patient to imitate simple and complex finger constructions and to draw a clock, cube, house, or interlocking pentagons; the effort expended is often as informative as the final product. This test may identify impersistence, perseveration, micrographia, and hemispatial neglect. Praxis (cognitive ability to do complex motor movements) can be assessed by asking the patient to use a toothbrush or comb, light a match, or snap the fingers.

Cranial nerves: (See also Ch. 181.) Smell, a function of the 1st (olfactory) cranial nerve, is usually evaluated only after head trauma or when lesions of the anterior fossa (eg, meningioma) are suspected or patients report abnormal smell or taste. The patient is asked to identify odors (eg, soap, coffee, cloves) presented to each nostril. Alcohol, ammonia, and other irritants, which test the nociceptive receptors of the 5th (trigeminal) cranial nerve, are used only when malingering is suspected.

The 2nd (optic), 3rd (oculomotor), 4th (trochlear), and 6th (abducens) cranial nerves involve the visual

system.

For the **2nd cranial nerve**, visual acuity is tested using a Snellen chart for distance vision and a handheld chart for near vision; each eye is assessed individually, with the other eye covered. Color perception is tested using standard pseudoisochromatic Ishihara or Hardy-Rand-Ritter plates that have numbers or figures embedded in a field of specifically colored dots. Visual fields are tested by directed confrontation in all 4 visual quadrants. Direct and consensual pupillary responses are tested (see also p. 1745). Funduscopic examination is also done.

For the **3rd, 4th, and 6th cranial nerves**, eyes are observed for symmetry of movement, globe position, asymmetry or droop of the eyelids (ptosis), and twitches or flutters of globes or lids. Extraocular movements controlled by these nerves are tested by asking the patient to follow a moving target (eg, examiner's finger, penlight) to all 4 quadrants (including across the midline); this test can detect nystagmus and palsies of ocular muscles. Anisocoria or differences in pupillary size should be noted in a dimly lit room. The pupillary light response is tested for symmetry and briskness.

Sidebar 168-1 Examination of Mental Status

The mental status examination is an assessment of current mental capacity through evaluation of general appearance, behavior, any unusual or bizarre beliefs and perceptions (eg, delusions, hallucinations), mood, and all aspects of cognition (eg, attention, orientation, memory).

Examination of mental status is done in anyone with an altered mental status or evolving impairment of cognition whether acute or chronic. Many screening tools are available; the Mini-Mental State Examination is one of the most commonly used. Baseline results are recorded, and the examination is repeated yearly and whenever a change in mental status is suspected.

Patients should be told that recording of mental status is routine and that they should not be embarrassed by its being done.

The examination is done in a quiet room, and the examiner should make sure that patients can hear the questions clearly. Patients who do not speak English as their primary language should be questioned in the language they speak fluently.

Mental status examination evaluates different areas of cognitive function. The examiner must first establish that the patient is attentive—eg, by asking the patient to immediately repeat 3 words. Testing an inattentive patient further is not useful.

The parameters of cognitive function to be tested include the following:

Orientation	Test the 3 parameters of orientation: • Person (What is your name?) • Time (What is today's date?) • Place (What is the name of this place?)
Short-term memory	Ask the patient to recall 3 objects after a 3-min delay.
Long-term memory	Ask the patient a question about the past, such as "What color suit did you wear at your wedding?" or "What was the make of your first car?"
Math	Use any simple mathematical test. Serial 7s are common: The patient is asked to start with 100 and to subtract 7, then 7 from 93, etc. Alternatively, ask how many nickels are in $1.35.
Word finding	Ask the patient to name as many objects in a single category, such as articles of clothing or animals, as possible in 1 min.

Concentration	Ask the patient to spell a 5-letter word forward and backward. "World" is commonly used.
Naming objects	Present an object, such as a pen, book, or ruler, and ask the patient to name it.
Following commands	Start with a 1-step command, such as "Touch your nose with your right hand." Then test a 3-step command, such as "Take this piece of paper in your right hand. Fold it in half. Put the paper on the floor."
Writing	Ask the patient to write a sentence. The sentence should contain a subject and an object and should make sense. Spelling errors should be ignored.
Spatial orientation	Ask the patient to draw a house or a clock and mark the clock with a specific time. Or ask the patient to draw 2 intersecting pentagons.
Abstract reasoning	Ask the patient to identify a unifying theme between 3 or 4 objects (eg, all are fruit, all are vehicles of transportation, all are musical instruments). Ask the patient to interpret a moderately challenging proverb, such as "People who live in glass houses should not throw stones."
Judgment	Ask the patient about a hypothetical situation requiring good judgment, such as "What would you do if you found a stamped letter on the sidewalk?" Placing it in the mailbox is the correct answer; opening the letter suggests a personality disorder.

For the **5th (trigeminal) nerve**, the 3 sensory divisions (ophthalmic, maxillary, mandibular) are evaluated by using a pinprick to test facial sensation and by brushing a wisp of cotton against the lower or lateral cornea to evaluate the corneal reflex. If facial sensation is lost, the angle of the jaw should be examined; sparing of this area (innervated by spinal root C2) suggests a trigeminal deficit. A weak blink due to facial weakness (eg, 7th cranial nerve paralysis) should be distinguished from depressed or absent corneal sensation, which is common in contact lens wearers. A patient with facial weakness feels the cotton wisp normally on both sides, even though blink is decreased. Trigeminal motor function is tested by palpating the masseter muscles while the patient clenches the teeth and by asking the patient to open the mouth against resistance. If a pterygoid muscle is weak, the jaw deviates to that side when the mouth is opened.

The **7th (facial) cranial nerve** is evaluated by checking for hemifacial weakness. Asymmetry of facial movements is often more obvious during spontaneous conversation, especially when the patient smiles or, if obtunded, grimaces at a noxious stimulus; on the weakened side, the nasolabial fold is depressed and the palpebral fissure is widened. If the patient has only lower facial weakness (ie, furrowing of the forehead and eye closure are preserved), etiology of 7th nerve weakness is central rather than peripheral. Taste in the anterior two thirds of the tongue can be tested with sweet, sour, salty, and bitter solutions applied with a cotton swab first on one side of the tongue, then on the other. Hyperacusis may be detected with a vibrating tuning fork held next to the ear.

Because the **8th (vestibulocochlear, acoustic, auditory) cranial nerve** carries auditory and vestibular input, evaluation involves testing hearing (see p. 431) and balance.

The **9th (glossopharyngeal) and 10th (vagus) cranial nerves** are usually evaluated together. Whether the palate elevates symmetrically is noted. A tongue blade is used to touch one side of the posterior pharynx, then the other, and symmetry of the gag reflex is observed; bilateral absence of the gag reflex is common among healthy people and may not be significant. In an unresponsive, intubated patient, suctioning the endotracheal tube normally triggers coughing. If hoarseness is noted, the vocal cords are inspected. Isolated hoarseness (with normal gag and palatal elevation) should prompt a search for lesions (eg, mediastinal lymphoma, aortic aneurysm) compressing the recurrent laryngeal nerve.

The **11th (spinal accessory) cranial nerve** is evaluated by testing the muscles it supplies. For the sternocleidomastoid, the patient is asked to turn the head against resistance supplied by the examiner's hand while the examiner palpates the active muscle (opposite the turned head). For the upper trapezius, the patient is asked to elevate the shoulders against resistance supplied by the examiner.

The **12th (hypoglossal) cranial nerve** is evaluated by asking the patient to extend the tongue and inspecting it for atrophy, fasciculations, and weakness (deviation is toward the side of a lesion).

Motor system: The limbs and shoulder girdle should be fully exposed, then inspected for atrophy, hypertrophy, asymmetric development, fasciculations, myotonia, tremor, and other involuntary movements, including chorea (brief, jerky movements), athetosis (continuous, writhing movements), and myoclonus (shocklike contractions of a muscle). Passive flexion and extension of the limbs in a relaxed patient provide information about muscle tone. Decreased muscle bulk indicates atrophy, but bilateral atrophy or atrophy in large or concealed muscles, unless advanced, may not be obvious. In the elderly, loss of some muscle mass is common. Hypertrophy occurs when one muscle must work harder to compensate for weakness in another; pseudohypertrophy occurs when muscle tissue is replaced by excessive connective tissue or storage material.

Fasciculations (brief, fine, irregular twitches of the muscle visible under the skin) are relatively common. Although they can occur in normal muscle, particularly in calf muscles of the elderly, fasciculations usually indicate lesions of the lower motor neuron (eg, nerve degeneration or injury and regeneration). Myotonia (slowed relaxation of muscle after a sustained contraction or direct percussion of the muscle) indicates myotonic dystrophy and may be demonstrated by inability to quickly open a clenched hand. Increased resistance followed by relaxation (clasp-knife phenomenon) and spasticity indicates upper motor neuron lesions. Lead-pipe rigidity, often with cogwheeling, suggests a basal ganglia disorder.

Muscle strength: Patients who report weakness may mean fatigue, clumsiness, or true muscle weakness. Thus, the examiner must define the precise character of symptoms, including exact location, time of occurrence, precipitating and ameliorating factors, and associated symptoms and signs (see Weakness on p. 1597). Limbs are inspected for weakness (when extended, a weak limb drifts downward), tremor, and other involuntary movements. The strength of specific muscle groups is tested against resistance, and one side of the body is compared with the other. However, pain may preclude a full effort during strength testing. With hysterical weakness, resistance to movement may be initially normal, followed by a sudden giving way.

Subtle weakness may be indicated by decreased arm swing while walking, pronator drift in an outstretched arm, decreased spontaneous use of a limb, an externally rotated leg, slowing of rapid alternating movements, or impairment of fine dexterity (eg, ability to fasten a button, open a safety pin, or remove a match from its box). Subtle motor weakness can often be detected by Tiller and mini-Tiller testing. With each hand, the patient makes a fist (in the Tiller test) or a fist with the index finger extended (in the mini-Tiller test) and then rotates the 2 around each other. The weaker limb becomes fixed in space while the stronger revolves around it.

Strength should be graded. The following scale, originally developed by The Medical Research Council of the United Kingdom, is now used universally:

0: No visible muscle contraction

1: Visible muscle contraction with no or trace movement

2: Limb movement when gravity is eliminated

3: Movement against gravity but not resistance

4: Movement against resistance supplied by the examiner

5: Full strength

The difficulty with this and similar scales is the large range in strength possible between grades 4 and 5. Distal strength can be semiquantitatively measured with a handgrip ergometer or with an inflated BP cuff squeezed by the patient.

Functional testing often provides a better picture of the relationship between strength and disability. As the patient does various maneuvers, deficiencies are noted and quantified as much as possible (eg, number of squats done or steps climbed). Rising from a squatting position or stepping onto a chair tests proximal leg strength; walking on the heels and on tiptoe tests distal strength. Pushing with the arms to

get out of a chair indicates quadriceps weakness. Swinging the body to move the arms indicates shoulder girdle weakness. Rising from the supine position by turning prone, kneeling, and using the hands to climb up the thighs and slowly push erect (Gowers' sign) suggests pelvic girdle weakness.

Gait, stance, and coordination: Normal gait, stance, and coordination require integrity of the motor, vestibular, and proprioceptive pathways (see also Ch. 183). A lesion in any of the pathways causes characteristic deficits: Cerebellar ataxia requires a wide gait for stability; dropfoot causes a steppage gait (lifting the leg higher than normal to avoid catching the foot on surface irregularities); pelvic muscle weakness causes waddling; and spastic leg causes scissoring and circumduction. Patients with impaired proprioception must constantly observe placement of their feet to avoid tripping or falling. Coordination can be tested with finger-to-nose or knee-to-shin maneuvers, which help detect ataxic movements.

Sensation: The best screening test for sensory loss uses a safety pin to lightly prick the face, torso, and 4 limbs; the patient is asked whether the pinprick feels the same on both sides and whether the sensation is dull or sharp. The pin is discarded after use to avoid potential transmission of bloodborne disorders (eg, HIV infection, hepatitis).

Cortical sensory function is evaluated by asking the patient to identify a familiar object (eg, coin, key) placed in the palm of the hand (stereognosis) and numbers written on the palm (graphesthesia) and to distinguish between 1 and 2 simultaneous, closely placed pinpricks on the fingertips (2-point discrimination).

Temperature sense can be tested with a cold tuning fork that has one prong rubbed warm by the examiner's palm or with test tubes containing warm and cold water.

Joint position sense is tested by moving the terminal phalanges of the patient's fingers, then the toes, up or down a few degrees. If the patient cannot identify these tiny movements with eyes closed, larger up-and-down movements are tried before testing the next most proximal joints (eg, testing the ankles if toe movement is not perceived). Pseudoathetosis refers to involuntary writhing, snakelike movements of a limb that result from severe loss of position sense; motor pathways, including those of the basal ganglia, are preserved. The brain cannot sense where the limb is in space so the limb moves on its own, and the patient must use vision to control the limb's movements. Typically, when the eyes are closed, the patient cannot locate the limb in space. Inability to stand with feet together and eyes closed (Romberg test) indicates impaired position sense in the lower extremities. When cerebellar disease is present, the patient stands with the feet apart but as close together as possible without falling and only then closes the eyes. Rarely, a positive result is due to severe bilateral loss of vestibular function (eg, aminoglycoside toxicity).

To test vibration sense, the examiner places a finger under the patient's distal interphalangeal joint and presses a lightly tapped 128-cycle tuning fork on top of the joint. The patient should note the end of vibration about the same time as the examiner, who feels it through the patient's joint.

A cotton wisp can be used to test light touch.

If sensation is impaired, the anatomic pattern suggests location of the lesion (see Figs. 168-1, 168-2, and 168-3):

- Stocking-glove distribution: Distal peripheral nerves
- Single dermatomal or nerve branch distribution: Isolated nerves (mononeuritis multiplex) or nerve roots (radiculopathy)
- Sensation reduced below a certain dermatomal level: Spinal cord
- Saddle area sensory loss: Cauda equina
- Crossed face-body pattern: Brain stem

• Hemisensory loss: Brain

• Midline hemisensory loss: Thalamus or functional (psychiatric)

Location of the lesion is confirmed by determining whether motor weakness and reflex changes follow a similar pattern. Patchy sensory, motor, and reflex deficits in a limb suggest lesions of the brachial or pelvic plexus.

Reflexes: Deep tendon (muscle stretch) reflex testing evaluates afferent nerves, synaptic connections within the spinal cord, motor nerves, and descending motor pathways. Lower motor neuron lesions (eg, affecting the anterior horn cell, spinal root, or peripheral nerve) depress reflexes; upper motor neuron lesions (ie, non-basal ganglia disorders anywhere above the anterior horn cell) increase reflexes (see p. 1791).

Reflexes tested include the biceps (innervated by C5 and C6), radial brachialis (by

[**Fig. 168-1.** Sensory dermatomes.]

[**Fig. 168-2.** Cutaneous nerve distribution: upper limb.]

C6), triceps (by C7), quadriceps knee jerk (by L4), and ankle jerk (by S1). Any asymmetric increase or depression is noted. Jendrassik's maneuver can be used to augment hypoactive reflexes: The patient locks the hands together and pulls vigorously apart as a tendon in the lower extremity is tapped. Alternatively, the patient can push the knees together against each other, while the upper limb tendon is tested.

[**Fig. 168-3.** Cutaneous nerve distribution: lower limb.]

Lightly stroking the 4 quadrants of the abdomen should elicit a superficial abdominal reflex. Depression of this reflex may be due to a central lesion, obesity, or lax skeletal muscles (eg, after pregnancy); its absence may indicate spinal cord injury.

Pathologic reflexes (eg, Babinski's, Chaddock's, Oppenheim, snout, root, grasp) are reversions to primitive responses and indicate loss of cortical inhibition.

Babinski's, Chaddock's, and Oppenheim reflexes all evaluate the plantar response. The normal reflex response is flexion of the great toe. An abnormal response is slower and consists of extension of the great toe with fanning of the other toes and often knee and hip flexion. This reaction is of spinal reflex origin and indicates spinal disinhibition due to an upper motor neuron lesion. For Babinski's reflex, the lateral sole of the foot is firmly stroked from the heel to the ball of the foot with a tongue blade or end of a reflex hammer. The stimulus must be noxious but not injurious; stroking should not veer too medially, or it may inadvertently induce a primitive grasp reflex. In sensitive patients, the reflex response may be masked by quick voluntary withdrawal of the foot, which is not a problem in Chaddock's or Oppenheim reflex testing. For Chaddock's reflex, the lateral foot, from lateral malleolus to small toe, is stroked with a blunt instrument. For the Oppenheim reflex, the anterior tibia, from just below the patella to the foot, is firmly stroked with a knuckle.

The **snout reflex** is present if tapping a tongue blade across the lips causes pursing of the lips.

The **rooting reflex** is present if stroking the lateral upper lip causes movement of the mouth toward the stimulus.

The **grasp reflex** is present if gently stroking the palm of the patient's hand causes the fingers to flex and grasp the examiner's finger.

The **palmomental reflex** is present if stroking the palm of the hand causes contraction of the ipsilateral mentalis muscle of the lower lip.

Hoffmann's sign is present if flicking the nail on the 3rd or 4th finger elicits involuntary flexion of the distal phalanx of the thumb and index finger.

For the **glabellar sign**, the forehead is tapped to induce blinking; normally, each of the first 5 taps induces a single blink, then the reflex fatigues. Blinking persists in patients with diffuse cerebral dysfunction.

Testing for **clonus** (rhythmic, rapid alternation of muscle contraction and relaxation caused by sudden, passive tendon stretching) is done by rapid dorsiflexion of the foot at the ankle. Sustained clonus indicates an upper motor neuron disorder.

Sphincteric reflexes may be tested during the rectal examination. To test sphincteric tone (S2 to S4 nerve root levels), the examiner inserts a gloved finger into the rectum and asks the patient to squeeze it. Alternatively, the perianal region is touched lightly with a cotton wisp; the normal response is contraction of the external anal sphincter (anal wink reflex). Rectal tone typically becomes lax in patients with acute spinal cord injury or cauda equine syndrome.

For the **bulbospongiosus reflex**, which tests S2 to S4 levels, the dorsum of the penis is tapped; normal response is contraction of the bulbospongiosus muscle.

For the **cremasteric reflex**, which tests the L2 level, the medial thigh 7.6 cm (3 in) below the inguinal crease is stroked upward; normal response is elevation of the ipsilateral testis.

Autonomic nervous system: (See also p. 1615.) Assessment involves checking for postural hypotension, heart rate changes in response to the Valsalva maneuver, decreased or absent sweating, and evidence of Horner's syndrome (unilateral ptosis, pupillary constriction, facial anhidrosis). Disturbances of bowel, bladder, sexual, and hypothalamic function should be noted.

Cerebrovascular examination: In a patient presenting with acute stroke, radial pulse and BP in the 2 arms are compared to check for painless aortic dissection, which can occlude a carotid artery and cause stroke. The skin, sclerae, fundi, oral mucosae, and nail beds are inspected for hemorrhages and evidence of cholesterol or septic emboli; auscultation over the heart can detect new or evolving murmurs and arrhythmias. Bruits over the cranium may indicate an arteriovenous malformation or fistula or, occasionally, redirected blood flow across the circle of Willis after carotid occlusion. Auscultation over the carotid arteries can detect bruits near the bifurcation; vigorous palpation should be avoided. By running the bell of the stethoscope down the neck toward the heart, the examiner may identify a change in character that can distinguish a bruit from a systolic heart murmur. Decreased vigor of the carotid upstroke suggests a stenotic lesion.

Peripheral pulses are palpated to check for peripheral vascular disease. The temporal arteries are palpated; enlargement or tenderness may suggest temporal arteritis.

Neurologic Diagnostic Procedures

Diagnostic procedures should not be used for preliminary screening, except perhaps in emergencies when a complete neurologic evaluation is impossible. Evidence uncovered during the history and physical examination should guide testing.

Lumbar puncture (spinal tap): Lumbar puncture is used to evaluate intracranial pressure and CSF composition (see Table 168-1), to therapeutically reduce intracranial pressure (eg, pseudotumor), and to administer intrathecal drugs or a radiopaque agent for myelography.

Relative contraindications include

• Infection at the puncture site

- Bleeding diathesis

- Increased intracranial pressure due to an intracranial mass lesion, obstructed CSF outflow (eg, due to aqueductal stenosis or Chiari I malformation), or spinal cord CSF blockage (eg, due to tumor cord compression)

If papilledema or focal neurologic deficits are present, CT or MRI should be done before lumbar puncture to rule out presence of a mass that could precipitate transtentorial or cerebellar herniation.

[**Table 168-1.** Cerebrospinal Fluid Abnormalities in Various Disorders]

For the procedure, the patient is typically in the left lateral decubitus position. A cooperative patient is asked to hug the knees and curl up as tightly as possible. Assistants may have to hold patients who cannot maintain this position, or the spine may be flexed better by having patients, particularly obese patients, sit on the side of the bed and lean over a bedside tray table. An area 20 cm in diameter is washed with iodine, then wiped with alcohol to remove the iodine and prevent its introduction into the subarachnoid space. A lumbar puncture needle with stylet is inserted into the L4- to-L5 interspace (the L4 spinous process is typically on a line between the posterior-superior iliac crests); the needle is aimed rostrally toward the patient's umbilicus and always kept parallel to the floor. Entrance into the subarachnoid space is usually accompanied by a discernible pop; the stylet is withdrawn to allow CSF to flow out. Opening pressure is measured with a manometer; 4 tubes are each filled with about 2 to 10 mL of CSF for testing. The puncture site is then covered with a sterile adhesive strip. A post-lumbar puncture headache (see p. 1724) occurs in about 10% of patients.

Normal CSF is clear and colorless; ≥ 300 cells/µL produces cloudiness or turbidity. Bloody fluid may indicate a traumatic puncture (pushing the needle in too far, into the venous plexus along the anterior spinal canal) or subarachnoid hemorrhage. A traumatic puncture is distinguished by gradual clearing of the CSF between the 1st and 4th tubes (confirmed by decreasing RBC count), absence of xanthochromia (yellowish CSF due to lysed RBCs) in a centrifuged sample, and fresh, uncrenated RBCs. With intrinsic subarachnoid hemorrhage, the CSF remains uniformly bloody throughout collection; xanthochromia is often present if several hours have passed after ictus; and RBCs are usually older and crenated. Faintly yellow fluid may also be due to senile chromogens, severe jaundice, or increased protein (> 100 mg/dL).

Cell count and differential and glucose and protein levels aid in the diagnosis of many neurologic disorders (see Table 168-1). If infection is suspected, the centrifuged CSF sediment is stained for bacteria (Gram stain), for TB (acid-fast stain or immunofluorescence), and for *Cryptococcus* sp (India ink). Larger amounts of fluid (10 mL) improve the chances of detecting the pathogen, particularly acidfast bacilli and certain fungi, in stains and cultures. In early meningococcal meningitis or severe leukopenia, CSF protein may be too low for bacterial adherence to the glass slide during Gram staining, producing a false-negative result. Mixing a drop of aseptic serum with CSF sediment prevents this problem. When hemorrhagic meningoencephalitis is suspected, a wet mount is used to search for amebas. Latex particle agglutination and coagglutination tests may allow rapid bacterial identification, especially when stains and cultures are negative (eg, in partially treated meningitis). CSF should be cultured aerobically and anaerobically and for acid-fast bacilli and fungi. Except for enteroviruses, viruses are seldom isolated from the CSF. Viral antibody panels are available. Venereal Disease Research Laboratories (VDRL) testing and cryptococcal antigen testing are often routinely done. PCR tests for herpes simplex virus and other CNS pathogens are increasingly available.

Normally, CSF: blood glucose ratio is about 0.6, and except in severe hypoglycemia, CSF glucose is typically > 50 mg/dL (> 2.78 mmol/L). Increased CSF protein (> 50 mg/dL) is a sensitive but nonspecific index of disease; protein increases to > 500 mg/dL in purulent meningitis, advanced TB meningitis, complete block by spinal cord tumor, or a bloody puncture. Special examinations for globulin (normally < 15%), oligoclonal banding, and myelin basic protein aid in diagnosis of a demyelinating disorder.

CT: CT provides rapid, noninvasive imaging of the brain and skull. CT is superior to MRI in visualizing fine bone detail in (but not the contents of) the posterior fossa, base of the skull, and spinal canal. A radiopaque contrast agent helps detect brain tumors and abscesses. Noncontrast CT is used to rapidly detect acute hemorrhage and various gross structural changes without concern about contrast allergy or

renal failure. With an intrathecal agent, CT can outline abnormalities encroaching on the brain stem, spinal cord, or spinal nerve roots (eg, meningeal carcinoma, herniated disk) and may detect a syrinx in the spinal cord. CT angiography using a contrast agent can show the cerebral blood vessels, obviating the need for MRI or angiography.

Adverse effects of contrast agents (see p. 3403) include allergic reactions and contrast nephropathy.

MRI: MRI provides better resolution of neural structures than CT. This difference is most significant clinically for visualizing cranial nerves, brain stem lesions, abnormalities of the posterior fossa, and the spinal cord; CT images of these regions are often marred by bony streak artifacts. Also, MRI is better for detecting demyelinating plaques, early infarction, subclinical brain edema, cerebral contusions, incipient transtentorial herniation, abnormalities of the craniocervical junction, and syringomyelia. MRI is especially valuable for identifying spinal abnormalities (eg, tumor, abscess) compressing the spinal cord and requiring emergency intervention.

MRI is contraindicated in patients who have had a pacemaker or cardiac or carotid stents for < 6 wk or who have ferromagnetic aneurysm clips or other metallic objects that may overheat or be displaced within the body by the intense magnetic field.

Visualization of inflammatory, demyelinated, and neoplastic lesions may require enhancement with IV paramagnetic contrast agents (eg, gadolinium). Although gadolinium is thought to be much safer than contrast agents used with CT, nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy) has been reported in patients with impaired renal function and acidosis.

There are several MRI techniques (see p. 3406); choice of technique depends on the specific tissue, location, and suspected disorder. Diffusion-weighted imaging (DWI) allows rapid, early detection of ischemic stroke. Perfusion-weighted imaging (PWI) can detect areas of hypoperfusion in early ischemic stroke but cannot yet reliably distinguish areas with benign oligemia from those with injurious hypoperfusion that results in infarction. Diffusion tensor imaging (DTI) is an extension of DWI that can show white matter tracts in 3 dimensions (tractography) and can be used to monitor the integrity of CNS tracts affected by aging and disease. Functional MRI (fMRI) detects brain regions activated (shown by increased flow of oxygenated blood) by a specific cognitive or motor task, but its clinical use is still being defined.

Magnetic resonance angiography (MRA) uses MRI with or without a contrast agent to show cerebral vessels and major arteries and their branches in the head and neck. Although MRA has not replaced cerebral angiography, it is used when cerebral angiography cannot be done (eg, because the patient refuses or has increased risk). As a check for stroke, MRA tends to exaggerate severity of arterial narrowing and thus does not usually miss occlusive disease of large arteries.

Magnetic resonance venography (MRV) uses MRI to show the major veins and dural sinuses of the cranium. MRV obviates the need for cerebral angiography in diagnosing cerebral venous thrombosis and is useful for monitoring thrombus resolution and guiding the duration of anticoagulation. Magnetic resonance spectroscopy can measure metabolites in the brain regionally to distinguish tumors from abscess or stroke.

Echoencephalography: Ultrasonography can be used at the bedside (usually in the neonatal ICU) to detect hemorrhage and hydrocephalus in children < 2 yr. CT has replaced echoencephalography in older children and adults.

Cerebral catheter angiography: X-rays taken after a radiopaque agent is injected via an intraarterial catheter show individual cerebral arteries and venous structures of the brain. With digital data processing (digital subtraction angiography), small amounts of agent can produce high-resolution images. Cerebral angiography supplements CT and MRI in delineating the site and vascularity of intracranial lesions; it has been the gold standard for diagnosing stenotic or occluded arteries, congenitally absent vessels, aneurysms, and arteriovenous malformations. Vessels, as small as 0.1 mm, can be visualized. However, its use has decreased dramatically with the advent of MRA and CT angiography. It is still routinely used

when cerebral vasculitis is suspected and when angiographic interventions (eg, angioplasty, stent placement, intra-arterial thrombolysis, aneurysm obliteration) may be necessary.

Duplex Doppler ultrasonography: This noninvasive procedure can assess dissection, stenosis, occlusion, and ulceration of the carotid bifurcation. It is safe and rapid, but it does not provide the detail of angiography. It is preferable to periorbital Doppler ultrasonography and oculoplethysmography for evaluating patients with carotid artery transient ischemic attacks and is useful for following an abnormality over time. Transcranial Doppler ultrasonography helps evaluate residual blood flow after brain death, vasospasm of the middle cerebral artery after subarachnoid hemorrhage, and vertebrobasilar stroke.

Myelography: X-rays are taken after a radiopaque agent is injected into the subarachnoid space via lumbar puncture. MRI has replaced myelography for evaluation of intraspinal abnormalities, but CT myelography is still done when MRI is unavailable. Contraindications are the same as those for lumbar puncture. Myelography may exacerbate the effects of spinal cord compression, especially if too much fluid is removed too rapidly.

EEG: Electrodes are distributed over the brain to detect electrical changes associated with seizure disorders, sleep disorders, and metabolic or structural encephalopathies. Twenty electrodes are distributed symmetrically over the scalp. The normal awake EEG shows 8- to 12-Hz, 50-μV sinusoidal alpha waves that wax and wane over the occipital and parietal lobes and > 12-Hz, 10- to 20-μV beta waves frontally, interspersed with 4- to 7-Hz theta waves. The EEG is examined for asymmetries between the 2 hemispheres (suggesting a structural disorder), for excessive slowing (appearance of 1- to 4-Hz, 50- to 350-μV delta waves, as occurs in depressed consciousness, encephalopathy, and dementia), and for abnormal wave patterns.

Abnormal wave patterns may be nonspecific (eg, epileptiform sharp waves) or diagnostic (eg, 3-Hz spike and wave discharges for absence seizures, 1-Hz periodic sharp waves for Creutzfeldt-Jakob disease). The EEG is particularly useful for appraising episodic altered consciousness of uncertain etiology. If a seizure disorder is suspected and the routine EEG is normal, maneuvers that electrically activate the cortex (eg, hyperventilation, photic stimulation, sleep, sleep deprivation) can sometimes elicit evidence of a seizure disorder. Nasopharyngeal leads can sometimes detect a temporal lobe seizure focus when the EEG is otherwise uninformative. Continuous ambulatory monitoring of the EEG (with or without video monitoring) over 24 h can often determine whether fleeting memory lapses, subjective auras, or unusual episodic motor behavior is due to seizure activity.

Measurement of evoked responses (potentials): Visual, auditory, or tactile stimuli are used to activate corresponding areas of the cerebral cortex, resulting in focal cortical electrical activity. Ordinarily, these small potentials are lost in EEG background noise, but computer processing cancels out the noise to reveal a waveform. Latency, duration, and amplitude of the evoked responses indicate whether the tested sensory pathway is intact.

Evoked responses are particularly useful for detecting clinically inapparent deficits in a demyelinating disorder, appraising sensory systems in infants, substantiating deficits suspected to be histrionic, and following the subclinical course of disease. For example, visual evoked responses may detect unsuspected optic nerve damage by multiple sclerosis. When integrity of the brain stem is in question, brain stem auditory evoked responses is an objective test. Somatosensory evoked responses may pinpoint the physiologic disturbance when a structural disorder (eg, metastatic carcinoma that invades the plexus and spinal cord) affects multiple levels of the neuraxis.

Electromyography and nerve conduction velocity studies: When determining whether weakness is due to a nerve, muscle, or neuromuscular junction disorder is clinically difficult, these studies can identify the affected nerves and muscles.

In electromyography, a needle is inserted in a muscle, and electrical activity is recorded while the muscle is contracting and resting. Normally, resting muscle is electrically silent; with minimal contraction, action potentials of single motor units appear. As contraction increases, the number of potentials increases, forming an interference pattern. Denervated muscle fibers are recognized by increased activity with needle insertion and abnormal spontaneous activity (fibrillations and fasciculations); fewer motor units are

recruited during contraction, producing a reduced interference pattern. Surviving axons branch to innervate adjacent muscle fibers, enlarging the motor unit and producing giant action potentials. In muscle disorders, individual fibers are affected without regard to their motor units; thus, amplitude of their potentials is diminished, but the interference pattern remains full.

In nerve conduction velocity studies, a peripheral nerve is stimulated with electrical shocks at several points along its course to a muscle, and the time to initiation of contraction is recorded. The time an impulse takes to traverse a measured length of nerve determines conduction velocity. The time required to traverse the segment nearest the muscle is called distal latency. Similar measurements can be made for sensory nerves. When weakness is due to a muscle disorder, nerve conduction is normal. In neuropathy, conduction is often slowed, and the response pattern may show a dispersion of potentials due to unequal involvement of myelinated and unmyelinated axons. A nerve can be repeatedly stimulated to evaluate the neuromuscular junction for fatigability; eg, a progressive decremental response occurs in myasthenia gravis.

Weakness

Weakness is one of the most common reasons patients present to primary care clinicians. Weakness is loss of muscle strength, although many patients also use the term when they feel generally fatigued or have functional limitations (eg, due to pain or limited joint motion) even though muscle strength is normal.

Weakness may affect a few or many muscles and develop suddenly or gradually. Other symptoms may be present depending on the cause. Weakness of specific muscle groups can cause disorders of eye movement, dysarthria, dysphagia, or respiratory weakness.

Pathophysiology

Voluntary movement is initiated in the cerebral motor cortex, at the posterior aspect of the frontal lobe. The neurons involved (upper motor or corticospinal tract neurons) synapse with neurons in the spinal cord (lower motor neurons). Lower motor neurons transmit impulses to the neuromuscular junction to initiate muscle contraction. Common mechanisms of weakness thus include dysfunction of

- Upper motor neurons (corticospinal and corticobulbar tract lesions)
- Lower motor neurons (eg, due to peripheral polyneuropathies or anterior horn cell lesions)
- Neuromuscular junction
- Muscle (eg, due to myopathies)

The location of certain lesions correlates with physical findings:

- Upper motor neuron dysfunction (except in the uncommon case when all other nearby motor pathways are affected) disinhibits lower motor neurons, resulting in increased muscle tone (spasticity) and increased muscle stretch reflexes (hyperreflexia). An extensor plantar (Babinski's) reflex is specific for upper motor neuron (corticospinal tract) dysfunction.
- Lower motor neuron dysfunction disrupts reflex arcs, causing hyporeflexia and decreased muscle tone (flaccidity), and may cause fasciculations; with time, muscles atrophy.
- Peripheral polyneuropathies tend to be most noticeable in the longest nerves (ie, weakness is more prominent in the distal limb than the proximal and in legs more than arms) and produce signs of lower motor neuron dysfunction (eg, decreased reflexes and muscle tone).
- The most common disorder of the neuromuscular junction—myasthenia gravis—typically causes fluctuating weakness that worsens with activity and lessens with rest.
- Diffuse muscle dysfunction (eg, in myopathies) tends to be most noticeable in the largest muscle groups

(proximal muscles).

Etiology

The many causes of muscle weakness are categorized by location of the lesion (see Table 168-2). Usually, lesions in a given location manifest similar clinical findings. However, some disorders have characteristics of lesions in more than one location. For example, patients with amyotrophic lateral sclerosis (ALS) may have findings of both upper and lower motor neuron dysfunction. Disorders of the spinal cord may affect tracts from upper motor neurons, lower motor neurons (anterior horn cells), or both.

Common causes of **focal weakness** include

- Stroke (the most common cause of unilateral weakness)
- Neuropathies, including those that are caused by trauma or entrapment (eg, carpal tunnel syndrome) and that are immunemediated (eg, Bell's palsy)
- Spinal root entrapment (eg, herniated intervertebral disk)
- Spinal cord compression (eg, cervical spondylosis, epidural cancer metastasis, trauma)
- Multiple sclerosis

The most common causes of **generalized weakness** are

- Generalized muscle wasting due to prolonged immobilization in an ICU (ICU myopathy)
- Critical illness polyneuropathy (ICU neuropathy)
- Common myopathies (eg, alcoholic myopathy, hypokalemia, corticosteroid myopathy)
- Use of paralytic drugs in a critical care patient

Fatigue: Many patients report weakness when their problem is fatigue. Fatigue can prevent maximal effort and muscle performance during strength testing. Common causes of fatigue include acute severe illness of almost any cause, cancers, chronic infections (eg, HIV, hepatitis, endocarditis, mononucleosis), endocrine disorders, renal failure, hepatic failure, heart failure, and anemia. Patients with fibromyalgia, depression, or chronic fatigue syndrome may report weakness or fatigue but have no defined objective abnormalities.

Evaluation

Evaluation should try to distinguish true muscular weakness from fatigue, then check for findings that help establish the mechanism and, when possible, the cause.

History: History of present illness should begin with open-ended questions, asking patients to describe in detail what they are experiencing as weakness. Then, specific questions can be asked, particularly about the ability to do specific tasks, including brushing teeth or hair, speaking, swallowing, rising from a chair, climbing stairs, and walking. Clinicians should also ask about the onset (sudden or gradual) and progression (eg, constant,

[**Table 168-2.** Some Causes of Muscle Weakness]

worsening, intermittent) of symptoms. Close questioning is needed to differentiate sudden onset from sudden recognition; patients may suddenly recognize symptoms only after slowly progressive weakness crosses a threshold that prevents them from doing some normally routine task (eg, walking, tying shoes). Important associated symptoms include sensory changes, double vision, memory loss, difficulty using

language, seizures, and headaches. Factors that worsen weakness, such as heat (suggesting multiple sclerosis) or repetitive use of a muscle (suggesting myasthenia gravis), are noted.

Review of systems should seek symptoms suggesting possible causes, including rash (dermatomyositis, Lyme disease, syphilis); fevers (chronic infection); muscle pain (myositis); neck pain (cervical myelopathy); vomiting or diarrhea (botulism); shortness of breath (heart failure, a pulmonary disorder, anemia); anorexia and weight loss (cancer, other chronic illness); change in color of urine (porphyria, liver or kidney disorder); heat or cold intolerance (thyroid dysfunction); and depressed mood, poor concentration, anxiety, and loss of interest in usual activities (mood disorder).

Past medical history should identify known disorders that can cause weakness or fatigue, including thyroid, liver, kidney, or adrenal disorders; cancer or risk factors for cancer (paraneoplastic syndromes —eg, Eaton-Lambert syndrome) such as heavy smoking; osteoarthritis (cervical myelopathy); and infections. Clinicians should assess risk factors for possible causes, including those for infection (eg, unprotected sexual intercourse, blood transfusions, exposure to TB) and stroke (eg, hypertension, atrial fibrillation, atherosclerosis). Complete drug history should be reviewed.

Family history should include known hereditary disorders (eg, hereditary muscle disorders, channelopathies, metabolic myopathies, hereditary neuropathies) and presence of similar symptoms in family members (suggesting a possible unrecognized hereditary disorder). Hereditary motor neuropathies often go unrecognized in families because of variable, incomplete phenotypic expression. Hammer toes, high arches in the feet, and poor performance in sports may indicate an undiagnosed hereditary motor neuropathy.

Social history should note use of alcohol (suggesting alcoholic myopathy), illicit drug use (suggesting increased risk of HIV/AIDS, bacterial infections, TB, or stroke due to cocaine use), occupational or other exposure to toxins (eg, organophosphate insecticides, heavy metals, industrial solvents), recent travel (suggesting Lyme disease, tick paralysis, diphtheria, or a parasitic infection), and social stressors (suggesting depression).

Physical examination: A complete neurologic and muscle examination is done to identify localizing or diagnostic findings. Key findings usually involve

• Cranial nerves

• Motor function

• Reflexes

Cranial nerve examination includes inspection of the face for gross asymmetry and ptosis; mild facial asymmetry can be normal. Extraocular movements and facial muscles, including masseters (for strength), are tested. Palatal weakness is suggested by a nasal voice quality; testing the gag reflex and looking at the palate directly are less helpful. Tongue weakness is suggested by inability to clearly articulate certain consonants (eg, saying "ta-ta-ta") and slurring of speech (lingual dysarthria). Mild asymmetry during tongue protrusion may be normal. Sternocleidomastoid and trapezius strength is tested by having the patient rotate the head and shrug the shoulders against resistance. The patient is asked to blink repeatedly to see whether blinking fatigues.

Motor examination includes inspection, assessment of tone, and strength testing. The body is inspected for kyphoscoliosis (sometimes suggesting chronic weakness of paraspinal muscles) and for surgical and traumatic scars. Dystonic posturing (eg, torticollis) may interfere with movement, mimicking weakness. Muscles are inspected for fasciculations and atrophy; both may begin focally or asymmetrically in ALS. Fasciculations may be most visible in the tongue in patients with advanced ALS. Diffuse atrophy may be most evident in the hands, face, and shoulder girdle.

Muscle tone is assessed using passive motion. Tapping a muscle (eg, hypothenar) may induce fasciculations in neuropathies or a myotonic contraction in myotonic dystrophy.

Strength testing should include muscles that are proximal, distal, extensor, and flexor. Some tests of large, proximal muscles include standing from a sitting position; squatting and rising; and flexing, extending, and turning the head against resistance. Motor strength is often rated on a 0 to 5 scale (see p. 1590).

Although these numbers seem objective, rating strength between 3 and 5 (the typical levels during early weakness, when diagnosis usually occurs) is rather subjective; if symptoms are unilateral, comparison with the unaffected side improves discrimination. Describing specifically what the patient can or cannot do is often more useful than simply assigning a number for level of weakness, particularly for assessing changes in weakness over time. A cognitive deficit may cause motor impersistence (inability to focus attention on completing a motor task), motor perseveration, apraxia, or incomplete effort. Malingering and other functional weakness is often characterized by give-way weakness, in which normal strength of effort suddenly gives way.

Coordination testing includes finger-to-nose and heel-to-shin maneuvers and toe-heel tandem gait to check for cerebellar dysfunction, which can accompany cerebellar stroke, vermian atrophy (eg, due to alcohol abuse), some hereditary spinocerebellar ataxias, multiple sclerosis, and the Miller Fisher variant of Guillain-Barre syndrome.

Gait is observed for ignition failure (temporary freezing in place when starting to walk, followed by festination, as occurs in Parkinson's disease) and apraxia, as when feet stick to the floor (normal-pressure hydrocephalus, other frontal lobe disorders); festination (Parkinson's disease); limb asymmetry, as when patients drag a leg, have reduced arm swing, or both (hemispheric stroke); ataxia (midline cerebellar disease); and instability during turns (parkinsonism). Walking on the toes and heels is tested; distal muscle weakness makes these maneuvers difficult. Walking on the heels is particularly difficult when corticospinal tract lesions are the cause of weakness. Spastic gait is notable for scissoring (legs flexed slightly at the hips and knees, giving the appearance of crouching, with the knees and thighs hitting or crossing in a scissors-like movement) and walking on the toes. A steppage gait may occur with perineal palsy (drop foot).

Sensation is tested; sensory deficits can help localize some lesions causing weakness (eg, sensory level localizes the lesion to a spinal cord segment) or suggest certain specific causes of weakness (eg, distal sensory loss helps confirm clinical suspicion of Guillain-Barre syndrome).

A bandlike tingling and pressure is a spinal cord sign that occurs with both intrinsic and extrinsic lesions.

Reflexes are tested. If deep tendon reflexes appear absent, they may be elicited by augmentation with Jendrassik's maneuver (eg, trying to pull the hands apart while they are clasped together). Hyporeflexia may be normal, particularly with aging, but findings should be symmetric and augmentation should elicit reflexes that are otherwise absent. The plantar reflex (extensor, flexor) is tested. The classic Babinski's reflex (the great toe extends and the other toes fan apart) is highly specific for a corticospinal tract lesion. A normal jaw jerk and hyperreflexic arms and legs suggest a cervical lesion affecting the corticospinal tract, usually cervical stenosis. Anal tone, anal wink reflex, or both are reduced or absent in spinal cord injury but are preserved in ascending paralysis due to Guillain-Barre syndrome. Abdominal reflexes are absent below the level of spinal cord injury. A cremasteric reflex can test the integrity of the upper lumbar cord and roots in males.

Evaluation also includes testing for back tenderness to percussion (present with vertebral inflammation, some vertebral tumors, and epidural abscess), straight leg raising (painful with sciatica), and checking for scapular winging (suggesting weakness of the shoulder girdle muscles).

General examination: If patients have no objective motor weakness, the general examination is particularly important; in such patients, nonneuromuscular disorders should be sought.

Signs of respiratory distress (eg, tachypnea, weak inspiration) are noted. The skin is examined for jaundice, pallor, rash, and striae. Other important findings during inspection include the moon facies of Cushing's syndrome and the parotid enlargement, smooth hairless skin, ascites, and vascular spiders of chronic alcohol use. The neck, axillae, and inguinal area should be palpated for adenopathy; any thyromegaly is noted.

Heart and lungs are auscultated for crackles, wheezes, prolonged expiration, murmurs, and gallops. The abdomen is palpated for masses, including, if spinal cord dysfunction is possible, a grossly enlarged bladder. A rectal examination is done to check for heme-positive stool. Joint range of motion is assessed.

If tick paralysis is suspected, the skin, particularly the scalp, should be thoroughly inspected for ticks.

Red flags: The following findings are of particular concern:

• Weakness that becomes severe over a few days or less

• Dyspnea

• Inability to raise the head against gravity

• Bulbar symptoms (eg, difficulty chewing, talking, and swallowing)

• Loss of ambulation

Interpretation of findings: The history helps differentiate weakness from fatigue, defines the time course of the illness, and gives clues to the anatomic pattern of weakness. Weakness and fatigue tend to cause different symptoms:

• **Weakness:** Patients typically complain that they cannot do specific tasks. They may also report limb heaviness or stiffness. Weakness usually has a particular pattern in time, anatomy, or both.

• **Fatigue:** Fatigue reported as "weakness" tends to have no temporal pattern (eg, "tired all of the time") or anatomic pattern (eg, "weak everywhere"); complaints center more on being tired than on being unable to do specific tasks.

The **temporal pattern** of symptoms is useful.

• Weakness that becomes severe within minutes or less is usually caused by severe trauma or stroke; in stroke, weakness is usually unilateral and can be mild or severe. Sudden weakness, numbness, and severe pain localized to a limb are more likely caused by local arterial occlusion and limb ischemia, which can be differentiated by vascular assessment (eg, pulse, color, temperature, capillary refill, differences in Doppler-measured limb BPs). Spinal cord compression can also cause paralysis that evolves over minutes (but usually over hours or days) and is readily distinguished by incontinence and clinical findings of a discrete cord sensory and motor level.

• Weakness that progresses steadily over hours to days may be caused by acute or subacute disorders (eg, spinal cord compression, transverse myelitis, spinal cord ischemia or hemorrhage, Guillain-Barre syndrome, sometimes muscle wasting caused by a critical illness, rhabdomyolysis, botulism, organophosphate poisoning).

• Weakness that progresses over weeks to months may be caused by subacute or chronic disorders (eg, cervical myelopathy, most inherited and acquired polyneuropathies, myasthenia gravis, motor neuron disorders, acquired myopathies, most tumors).

• Weakness that fluctuates from day to day may be caused by multiple sclerosis and sometimes metabolic myopathies.

• Weakness that fluctuates over the course of a day may be caused by myasthenia gravis, Eaton-Lambert syndrome, or periodic paralysis.

The **anatomic pattern** of weakness is characterized by specific motor tasks that are difficult to do. Anatomic patterns suggest certain diagnoses:

- Proximal muscle weakness impairs reaching upward (eg, combing hair, lifting objects over the head), ascending stairs, or getting up from a sitting position; this pattern is typical of myopathies.

- Distal muscle weakness impairs tasks such as stepping over a curb, holding a cup, writing, buttoning, or using a key; this pattern is typical of polyneuropathies and myotonic dystrophy. Many disorders (eg, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, myasthenia gravis, radiculopathies, Eaton-Lambert syndrome) cause proximal and distal weakness, but one pattern may be more prominent at first.

- Bulbar weakness can cause facial weakness, dysarthria, and dysphagia, with or without impairment of ocular movements; these manifestations are typical of certain neuromuscular disorders, such as myasthenia gravis, Eaton-Lambert syndrome, or botulism, but also certain motor neuron disorders, such as ALS or progressive supranuclear bulbar palsy.

Physical examination further helps localize the lesion. First, general patterns are discerned:

- Weakness primarily of proximal muscles suggests myopathy.

- Weakness accompanied by hyperreflexia and increased muscle tone suggests upper motor neuron (corticospinal or other motor tract) dysfunction, particularly if an extensor plantar (Babinski's) reflex is present.

- Disproportionate impairment of fine finger dexterity (eg, fine pincer movements, playing the piano) with relatively preserved grip strength indicates selective disruption of the corticospinal (pyramidal) tract.

- Complete paralysis accompanied by absent reflexes and severely depressed muscle tone (flaccidity) occurs in sudden, severe spinal cord injury (spinal shock).

- Weakness accompanied by hyporeflexia, decreased muscle tone (with or without fasciculations), and chronic muscle atrophy suggests lower motor neuron dysfunction.

- Weakness that is most noticeable in muscles innervated by the longest nerves (ie, distal more than proximal, legs more than arms), particularly with loss of distal sensation, suggests lower motor neuron dysfunction due to peripheral polyneuropathy.

- Absence of neurologic abnormalities (ie, normal reflexes, no muscle wasting or fasciculations, normal strength or poor effort during strength testing) or poor effort in patients with tiredness or with weakness that has no temporal or anatomic pattern suggests fatigue rather than true muscular weakness. However, if weakness is intermittent and is absent at the time of examination, abnormalities may be missed.

Additional findings can help localize the lesion more precisely. For example, weakness accompanied by upper motor signs plus other signs such as aphasia, mental status abnormalities, or other cortical dysfunction suggests a brain lesion. Unilateral upper motor neuron signs (spasticity, hyperreflexia, extensor plantar response) and weakness involving an arm and a leg on the same side of the body suggest a contralateral hemispheric lesion, most often a stroke. Upper or lower motor neuron signs (or both) plus loss of sensation below a segmental spinal cord level and loss of bowel or bladder control (or both) suggest a spinal cord lesion. Weakness with lower motor neuron signs may result from a disorder affecting one or more peripheral nerves; such a disorder has very specific patterns of weakness (eg, wrist drop in radial nerve injury). When the brachial or pelvic plexus is damaged, motor, sensory, and reflex deficits are often patchy and do not follow any one peripheral nerve pattern.

Determination of a specific causative disorder: Sometimes combinations of findings suggest a cause (see
Table 168-3).

If **no symptoms or signs of true weakness** (eg, characteristic anatomic and temporal pattern, objective signs) are present and patients complain only of overall weakness, fatigue, or lack of energy,

clinicians should consider nonneurologic disorders. However, among elderly patients who feel too weak to walk, determining the contribution of muscle weakness may be difficult because gait dysfunction is often multifactorial (see Geriatrics Essentials on p. 1606). Patients with many disorders may be functionally limited but lack true loss of muscle strength. For example, cardiopulmonary dysfunction or anemia can cause fatigue due to dyspnea or exercise intolerance. Joint dysfunction (eg, due to arthritis) or muscle pain (eg, due to polymyalgia rheumatica or fibromyalgia) may make doing physical tasks difficult. These and other physical disorders that cause complaints of weakness (eg, influenza, infectious mononucleosis, renal failure) typically are already diagnosed or are suggested by findings during the history, physical examination, or both.

[**Table 168-3.** Findings Related to Weakness Suggesting a Specific Disorder]

In general, if history and physical examination do not detect abnormalities suggesting physical disorders, these disorders are unlikely; disorders that cause constant, generalized fatigue with no physiologic temporal or anatomic pattern (eg, depression, chronic fatigue syndrome) should be considered.

Testing: Testing may be unnecessary in patients with fatigue rather than weakness. Although many tests can be done if patients have true muscular weakness, such testing is often only adjunctive.

If **no true weakness** is present, other clinical findings (eg, dyspnea, pallor, jaundice, heart murmur), if present, are used to guide testing.

If patients have no abnormal clinical findings, test results are unlikely to be abnormal. In such cases, testing practices vary widely. If done, initial tests usually include some combination of CBC, electrolytes, glucose, Ca, Mg, kidney and liver function tests, thyroid-stimulating hormone (TSH), ESR, and hepatitis C serologic testing.

If **sudden or severe general weakness or any respiratory symptoms** are present, forced vital capacity and maximal inspiratory force must be tested to assess risk of acute ventilatory failure. Patients with vital capacity < 15 mL/kg or inspiratory force < 20 cm H_2O are at increased risk.

If **true weakness** is present (and usually after risk of acute ventilatory failure is assessed), initial testing typically focuses on determining the mechanism of weakness. Unless the cause is obvious, routine laboratory tests (CBC, electrolytes, glucose, Ca, Mg, kidney and liver function tests, TSH, ESR, hepatitis C serologic testing) are usually done.

If **brain upper motor neuron dysfunction** is suspected as the cause of weakness, the key test is MRI. CT is used when MRI testing is not possible (eg, in patients with a cardiac pacemaker).

If **myelopathy** is suspected, MRI can detect lesions in the spinal cord. It also detects other causes of paralysis that may mimic myelopathy, including lesions of the cauda equina, spinal roots, and brachial and pelvic plexuses. CT myelography may be used when MRI testing is not available. Other tests are done (see Table 168-2). CSF analysis may be unnecessary for some disorders diagnosed during imaging (eg, epidural tumor) and is contraindicated if CSF block (eg, due to epidural spinal cord compression) is suspected.

If **polyneuropathies, myopathies, or neuromuscular junction disorders** are suspected, the key tests that help differentiate these mechanisms of weakness are electrodiagnostic studies (electromyography and nerve conduction velocity studies).

After nerve injury, changes in nerve conductance and muscle denervation can take up to a few weeks to develop, so electrodiagnostic studies may not help when the disorder is acute. However, these studies can help differentiate among certain acute disorders, such as acute demyelinating neuropathy (eg, Guillain-Barre syndrome), acute botulism, and other acute neuromuscular junction disorders.

If myopathy is suspected (suggested by muscle weakness, muscle cramping, and pain), muscle enzymes (eg, CK, aldolase, LDH) may be measured. Elevated levels are consistent with myopathy but can also be high in neuropathies (reflecting muscle atrophy) and very high in ischemic rhabdomyolysis. Also, levels

may not be high in all myopathies. Regular crack cocaine use can also cause chronically moderately elevated CK levels (mean value, 400 IU/L).

Clinicians can use MRI to identify muscle inflammation, as occurs in inflammatory myopathies. Muscle biopsy may be necessary ultimately to diagnose myopathy. MRI or electromyography can help find a suitable site for muscle biopsy. However, needlestick artifact can mimic muscle pathology and must be avoided; thus, biopsy should never be done in the same muscle tested by electromyography.

If **motor neuron disorders** (eg, ALS) are suspected, tests include electromyography and nerve conduction velocity studies to confirm the diagnosis and exclude treatable disorders that mimic motor neuron disorders (eg, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block). Brain MRI may show degeneration of the corticospinal tracts when ALS is advanced. Spinal cord MRI (or CT myelography) is done routinely to rule out spinal cord compression or other myelopathies (see Table 168-2).

Testing for specific disorders may be needed:

• If findings suggest myasthenia gravis, edrophonium test and acetylcholine receptor antibody levels

• If findings suggest vasculitis, autoantibody testing

• If family history suggests a hereditary disorder, genetic testing

• If findings suggest polyneuropathy, other tests (see Table 168-2)

• If myopathy is unexplained by drugs, metabolic, or endocrine disorders, possibly muscle biopsy

Treatment

Causes are treated. For patients with life-threatening, acute weakness, ventilatory support may be needed. Physical and occupational therapy can help people adapt to permanent weakness and minimize loss of function.

Geriatrics Essentials

Some decrease in deep tendon reflexes is normal with aging, but asymmetry or absence of these reflexes with augmentation is abnormal.

Because the elderly are more likely to have preexisting sarcopenia, bed rest can cause debilitating muscle wasting rapidly, sometimes after only several days.

The elderly take more drugs and are more susceptible to drug-induced myopathies, neuropathies, and fatigue; thus, drugs are a common cause of weakness in the elderly.

Feeling too weak to walk often has multiple causes. Factors may include muscle weakness (eg, caused by stroke, use of certain drugs, myelopathy due to cervical spondylosis, or muscle atrophy), but also hydrocephalus, parkinsonism, painful arthritis, and age-related loss of neural networks mediating postural stability (vestibular system, proprioceptive pathways), coordination (cerebellum, basal ganglia), vision, and praxis (frontal lobe). Evaluation should focus on reversible factors.

Physical therapy and rehabilitation are generally helpful no matter what the etiology of the weakness is.

Key Points

• True loss of muscle strength must be distinguished from a feeling of fatigue.

• Fatigue with no anatomic or temporal pattern of weakness in patients with a normal physical examination may reflect chronic fatigue syndrome, an as yet undiscovered systemic illness (eg, severe

anemia, hypothyroidism, Addison's disease), a psychologic problem (eg, depression), or an adverse drug effect.

- Initial evaluation of true muscle weakness focuses on determining whether weakness is caused by dysfunction of the brain, spinal cord, plexuses, peripheral nerves, neuromuscular junction, or muscles.

- Hyperreflexia and increased muscle tone (spasticity), particularly if Babinski's reflex is present, suggest an upper motor neuron (eg, corticospinal tract) lesion in the brain or spinal cord; MRI is usually required.

- Hyporeflexia, decreased muscle tone, muscle atrophy, and muscle fasciculations suggest a lower motor neuron lesion.

- Hyporeflexia and predominantly distal muscle weakness, particularly with distal sensory deficits or paresthesias, suggest polyneuropathy.

- Difficulty climbing stairs, combing hair, and standing up with predominantly proximal muscle weakness and intact sensation suggests myopathy.

- Physical therapy is usually helpful in improving strength no matter what the cause is.

Chapter 169. Neurotransmission

Introduction

A neuron generates and propagates an action potential along its axon, then transmits this signal across a synapse by releasing neurotransmitters, which trigger a reaction in another neuron or an effector cell (eg, muscle cells, most exocrine and endocrine cells). The signal may stimulate or inhibit the receiving cell, depending on the neurotransmitter and receptor involved.

In the CNS, interconnections are complex. An impulse from one neuron to another may pass from axon to cell body, axon to dendrite (a neuron's receiving branches), cell body to cell body, or dendrite to dendrite. A neuron can simultaneously receive many impulses—excitatory and inhibitory—from other neurons and integrate simultaneous impulses into various patterns of firing.

Propagation: Action potential propagation along an axon is electrical, caused by the exchanges of Na^+ and K^+ ions across the axonal membrane. A particular neuron generates the same action potential after each stimulus, conducting it at a fixed velocity along the axon. Velocity depends on axonal diameter and degree of myelination and ranges from 1 to 4 m/sec in small unmyelinated fibers to 75 m/sec in large myelinated ones. Propagation speed is higher in myelinated fibers because the myelin cover has regular gaps (nodes of Ranvier) where the axon is exposed. The electrical impulse jumps from one node to the next, skipping the myelinated section of the axon. Thus, disorders that alter the myelin cover (eg, multiple sclerosis) interfere with impulse propagation, causing various neurologic symptoms.

Transmission: Impulse transmission is chemical, caused by release of specific neurotransmitters from the nerve ending (terminal). Neurotransmitters diffuse across the synaptic cleft and bind briefly to specific receptors on the adjoining neuron or effector cell. Depending on the receptor, the response may be excitatory or inhibitory.

One type of synapse, the electrical synapse, does not involve neurotransmitters; ion channels directly connect the cytoplasm of the presynaptic and postsynaptic neurons. This type of transmission is the fastest.

The nerve cell body produces enzymes that synthesize most neurotransmitters, which are stored in vesicles at the nerve terminal (see Fig. 169-1). The amount in one vesicle (usually several thousand molecules) is a quantum. A membrane action potential arriving at the terminal opens axonal Ca channels; Ca inflow releases neurotransmitter molecules from many vesicles by fusing the vesicle membranes to the nerve terminal membrane. Membrane fusion generates an opening through which the molecules are expelled into the synaptic cleft via exocytosis.

The amount of neurotransmitters in the terminal is typically independent of nerve activity and kept relatively constant by modifying uptake of neurotransmitter precursors or the activity of enzymes involved in neurotransmitter synthesis or destruction. Stimulation of presynaptic receptors can decrease presynaptic neurotransmitter synthesis, and blockade can increase it.

The neurotransmitter-receptor interaction must be terminated quickly to allow rapid, repeated activation of receptors. One of the following can happen to neurotransmitters that have interacted with receptors:

- They can be quickly pumped back into the presynaptic nerve terminals by active, ATP-dependent processes (reuptake).

- They can be destroyed by enzymes near the receptors.

- They can diffuse into the surrounding area and be removed.

Neurotransmitters taken up by the nerve terminals are repackaged in vesicles for reuse.

Receptors: Neurotransmitter receptors are protein complexes that span the cell membrane. Their nature determines whether a given neurotransmitter is excitatory or inhibitory. Receptors that are continuously stimulated by neurotransmitters or drugs become desensitized (downregulated); those that are not stimulated by their neurotransmitter or are chronically blocked by drugs become supersensitive (upregulated). Downregulation or upregulation of receptors strongly influences the development of tolerance and physical dependence. These concepts are particularly important in organ or tissue transplantation, in which denervation deprives receptors of their neurotransmitter. Withdrawal symptoms can be explained at least in part by a rebound phenomenon due to altered receptor affinity or density.

Most neurotransmitters interact primarily with postsynaptic receptors, but some receptors are located on presynaptic neurons, providing fine control of neurotransmitter release.

[Fig. 169-1. Neurotransmission.]

One family of receptors, termed ionotropic receptors (eg, *N*-methyl-D-glutamate, kinate-quisqualate, nicotinic acetylcholine, glycine, and γ-aminobutyric acid [GABA] receptors), consist of ion channels that open when bound to the neurotransmitter and effect a very rapid response. In the other family, termed metabotropic receptors (eg, serotonin, α- and β-adrenergic, and dopaminergic receptors), neurotransmitters interact with G proteins and activate another molecule (2nd messenger such as cAMP) that catalyzes a chain of events through protein phosphorylation Ca mobilization, or both; cellular changes mediated by 2nd messengers are slower and permit finer tuning of the rapid ionotropic neurotransmitter response. Far more neurotransmitters activate specific receptors than 2nd messengers.

Major Neurotransmitters and Receptors

At least 100 substances can act as neurotransmitters; about 18 are of major importance. Several occur in slightly different forms.

Glutamate and aspartate: These amino acids are the major excitatory neurotransmitters in the CNS. They occur in the cortex, cerebellum, and spinal cord. In neurons, synthesis of nitric oxide (NO) increases in response to glutamate. Excess glutamate can be toxic, increasing intracellular Ca, free radicals, and proteinase activity. These neurotransmitters may contribute to tolerance to opioid therapy and mediate hyperalgesia.

Glutamate receptors are classified as NMDA (*N*-methyl-D-aspartate) receptors and non-NMDA receptors. Phencyclidine (PCP, also known as angel dust) and memantine (used to treat Alzheimer's disease) bind to NMDA receptors.

GABA: GABA is the major inhibitory neurotransmitter in the brain. It is an amino acid derived from glutamate, which is decarboxylated by glutamate decarboxylase. After interaction with its receptors, GABA is actively pumped back into nerve terminals and metabolized. Glycine, which resembles GABA in its action, occurs principally in interneurons (Renshaw cells) of the spinal cord and in circuits that relax antagonist muscles.

GABA receptors are classified as $GABA_A$ (activating chloride channels) and $GABA_B$ (potentiating cAMP formation). $GABA_A$ receptors are the site of action for several neuroactive drugs, including benzodiazepines, barbiturates, picrotoxin, and muscimol. $GABA_B$ receptors are activated by baclofen, used to treat muscle spasms (eg, in multiple sclerosis).

Serotonin: Serotonin (5-hydroxytryptamine, or 5-HT) is generated by the raphe nucleus and midline neurons of the pons and upper brain stem. Tryptophan is hydroxylated by tryptophan hydroxylase to 5-hydroxytryptophan, then decarboxylated to serotonin. Serotonin levels are controlled by the uptake of tryptophan and intraneuronal monoamine oxidase (MAO), which breaks down serotonin. Ultimately, serotonin is excreted in the urine as 5-hydroxyindoacetic acid or 5-HIAA.

Serotoninergic (5-HT) receptors (with at least 15 subtypes) are classified as $5\text{-}HT_1$ (with 4 subtypes), $5\text{-}HT_2$, and $5\text{-}HT_3$. Selective serotonin receptor agonists (eg, sumatriptan) can abort migraines.

Acetylcholine: Acetylcholine is the major neurotransmitter of the bulbospinal motor neurons, autonomic preganglionic fibers, postganglionic cholinergic (parasympathetic) fibers, and many neurons in the CNS (eg, basal ganglia, motor cortex). It is synthesized from choline and acetyl coenzyme A by choline acetyltransferase, and its action is rapidly terminated via local hydrolysis to choline and acetate by acetylcholinesterase. Acetylcholine levels are regulated by choline acetyltransferase and by choline uptake. Levels of this neurotransmitter are decreased in patients with Alzheimer's disease.

Cholinergic receptors are classified as nicotinic N_1 (in the adrenal medulla and autonomic ganglia) or N_2 (in skeletal muscle) or muscarinic M_1 through M_5 (widely distributed in the CNS). M_1 occurs in the autonomic nervous system, striatum, cortex, and hippocampus; M_2 occurs in the autonomic nervous system, heart, intestinal smooth muscle, hindbrain, and cerebellum.

Dopamine: Dopamine interacts with receptors on some peripheral nerve fibers and many central neurons (eg, in the substantia nigra, midbrain, ventral tegmental area, and hypothalamus). The amino acid tyrosine is taken up by dopaminergic neurons and converted by tyrosine hydroxylase to 3,4-dihydroxyphenylalanine (dopa), which is decarboxylated by aromatic-L-amino-acid decarboxylase to dopamine. After release and interaction with receptors, dopamine is actively pumped back (reuptake) into the nerve terminal. Tyrosine hydroxylase and MAO (which breaks down dopamine) regulate dopamine levels in nerve terminals.

Dopaminergic receptors are classified as D_1 through D_5. D_3 and D_4 receptors play a role in thought control (limiting the negative symptoms of schizophrenia); D_2 receptor activation controls the extrapyramidal system. However, receptor affinity does not predict functional response (intrinsic activity); eg, ropinirole, which has high affinity for the D_3 receptor, has intrinsic activity via activation of D_2 receptors.

Norepinephrine: Norepinephrine is the neurotransmitter of most postganglionic sympathetic fibers and many central neurons (eg, in the locus caeruleus and hypothalamus). The precursor tyrosine is converted to dopamine, which is hydroxylated by dopamine β-hydroxylase to norepinephrine. After release and interaction with receptors, some norepinephrine is degraded by catechol *O*-methyltransferase (COMT), and the remainder is actively taken back into the nerve terminal, where it is degraded by MAO. Tyrosine hydroxylase, dopamine β-hydroxylase, and MAO regulate intraneuronal norepinephrine levels.

Adrenergic receptors are classified as α_1 (postsynaptic in the sympathetic system), α_2 (presynaptic in the sympathetic system and postsynaptic in the brain), β_1 (in the heart), or β_2 (in other sympathetically innervated structures).

Endorphins and enkephalins: Endorphins and enkephalins are opioids. Endorphins are large polypeptides that activate many central neurons (eg, in the hypothalamus, amygdala, thalamus, and locus caeruleus). The cell body contains a large polypeptide called proopiomelanocortin, the precursor of α-, β-, and γ-endorphins. This polypeptide is transported down the axon and cleaved into fragments; one is β-endorphin, contained in neurons that project to the periaqueductal gray matter, limbic structures, and major catecholamine-containing neurons in the brain. After release and interaction with receptors, β-endorphin is hydrolyzed by peptidases.

Met-enkephalin and leu-enkephalin are small polypeptides present in many central neurons (eg, in the globus pallidus, thalamus, caudate, and central gray matter). Their precursor, proenkephalin, is formed in the cell body, then split by specific peptidases into the active peptides. These substances are also localized in the spinal cord, where they modulate pain signals. The neurotransmitters of pain signals in the posterior horn of the spinal cord are glutamate and substance P. Enkephalins decrease the amount of neurotransmitter released and hyperpolarize (make more negative) the postsynaptic membrane, reducing the generation of action potentials and pain perception at the level of the postcentral gyrus. After release and interaction with peptidergic receptors, enkephalins are hydrolyzed into smaller, inactive peptides and amino acids. Rapid inactivation of exogenous enkephalins prevents these substances from being clinically useful. More stable molecules (eg, morphine) are used as analgesics instead.

Endorphin-enkephalin (opioid) receptors are classified as μ_1 and μ_2 (affecting sensorimotor integration and analgesia), δ_1 and δ_2 (affecting motor integration, cognitive function, and analgesia), and κ_1, κ_2, and κ_3 (affecting water balance regulation, analgesia, and food intake). σ-Receptors, currently classified as nonopioid and mostly localized in the hippocampus, bind PCP. New data suggest the presence of many more receptor subtypes, with pharmacologic implications. Components of the molecular precursor to the receptor protein can be rearranged during receptor synthesis to produce several receptor variants (eg, 27 splice variants of the μ opioid receptor). Also, 2 receptors can combine (dimerize) to form a new receptor.

Other neurotransmitters: Dynorphins are a group of 7 peptides with similar amino acid sequences. They, like enkephalins, are opioids.

Substance P, a peptide, occurs in central neurons (in the habenula, substantia nigra, basal ganglia, medulla, and hypothalamus) and is highly concentrated in the dorsal root ganglia. Its release is triggered by intense afferent painful stimuli. It modulates the neural response to pain and mood; it modulates nausea and vomiting through the activation of NK1A receptors that are localized in the brain stem.

Nitric oxide (NO) is a labile gas that mediates many neuronal processes. It is generated from arginine by NO synthase. Neurotransmitters that increase intracellular Ca^{++} (eg, substance P, glutamate, acetylcholine) stimulate NO synthesis in neurons that express NO synthetase. NO may be an intracellular messenger; it may diffuse out of a cell into a 2nd neuron and produce physiologic responses (eg, long-term potentiation [strengthening of certain presynaptic and postsynaptic responses—a form of learning]) or enhance glutamate (NMDA-receptor-mediated) neurotoxicity (eg, in Parkinson's disease, stroke, or Alzheimer's disease).

Substances with less firmly established roles in neurotransmission include histamine, vasopressin, vasoactive intestinal peptide, carnosine, bradykinin, cholecystokinin, bombesin, somatostatin, corticotropin releasing factor, neurotensin, and possibly adenosine.

Disorders Associated With Defects in Neurotransmission

Disorders or substances that alter the production, release, reception, breakdown, or reuptake of neurotransmitters or that change the number and affinity of receptors can cause neurologic or psychiatric symptoms and cause disease (see Table 169-1). Drugs that modify neurotransmission can alleviate many of these disorders (eg, Parkinson's disease, depression).

[**Table 169-1.** Examples of Disorders Associated with Defects in Neurotransmission]

Chapter 170. Autonomic Nervous System

Introduction

The autonomic nervous system (ANS) regulates physiologic processes. Regulation occurs without conscious control, ie, autonomously. The 2 major divisions are the sympathetic and parasympathetic systems.

Disorders of the ANS cause autonomic insufficiency or failure and can affect any system of the body.

Anatomy

The ANS receives input from parts of the CNS that process and integrate stimuli from the body and external environment. These parts include the hypothalamus, nucleus of the solitary tract, reticular formation, amygdala, hippocampus, and olfactory cortex.

The sympathetic and parasympathetic systems each consist of 2 sets of nerve bodies: one set (called preganglionic) in the CNS, with connections to another set in ganglia outside the CNS. Efferent fibers from the ganglia (postganglionic fibers) lead to effector organs (see Fig. 170-1).

Sympathetic: The preganglionic cell bodies of the sympathetic system are located in the intermediolateral horn of the spinal cord between T1 and L2 or L3. The sympathetic ganglia are adjacent to the spine and consist of the vertebral (sympathetic chain) and prevertebral ganglia, including the superior cervical, celiac, superior mesenteric, inferior mesenteric, and aorticorenal ganglia. Long fibers run from these ganglia to effector organs, including the smooth muscle of blood vessels, viscera, lungs, scalp (piloerector muscles), and pupils; the heart; and glands (sweat, salivary, and digestive).

Parasympathetic: The preganglionic cell bodies of the parasympathetic system are located in the brain stem and sacral portion of the spinal cord. Preganglionic fibers exit the brain stem with the 3rd, 7th, 9th, and 10th (vagus) cranial nerves and exit the spinal cord at S2 and S3; the vagus nerve contains about 75% of all parasympathetic fibers. Parasympathetic ganglia (eg, ciliary, sphenopalatine, otic, pelvic, and vagal ganglia) are located within the effector organs, and postganglionic fibers are only 1 or 2 mm long. Thus, the parasympathetic system can produce specific, localized responses in effector organs, such as blood vessels of the head, neck, and thoraco-abdominal viscera; lacrimal and salivary glands; smooth muscle of glands and viscera (eg, liver, spleen, colon, kidneys, bladder, genitals); and ocular muscles.

Physiology

The ANS controls BP, heart rate, body temperature, weight, digestion, metabolism, fluid and electrolyte balance, sweating, urination, defecation, sexual response, and other processes. Many organs are controlled primarily by either the sympathetic or parasympathetic system, although they may receive input from both; occasionally, functions are reciprocal (eg, sympathetic input increases heart rate; parasympathetic decreases it).

The sympathetic nervous system is catabolic; it activates fight-or-flight responses. The parasympathetic nervous system is anabolic; it conserves and restores (see Table 170-1).

Two major neurotransmitters in the ANS are

- **Acetylcholine:** Fibers that secrete acetylcholine (cholinergic fibers) include all preganglionic fibers, all postganglionic parasympathetic fibers, and some postganglionic sympathetic fibers (those that innervate piloerectors, sweat glands, and blood vessels).

- **Norepinephrine:** Fibers that secrete norepinephrine (adrenergic fibers) include most postganglionic sympathetic fibers. Sweat glands on the palms and soles also respond to adrenergic stimulation to some degree.

There are different subtypes of adrenergic receptors (see p. 1609) and cholinergic receptors (see p. 1608), which vary by location.

Etiology

Disorders causing autonomic insufficiency or failure can originate in the peripheral or central nervous system and may be primary or secondary to other disorders.

The **most common causes** of autonomic insufficiency are

• Peripheral neuropathies

• Aging

• Parkinson's disease

Other causes include

• Autoimmune autonomic neuropathy

• Multiple system atrophy

• Spinal cord disorders

• Drugs

• Disorders of the neuromuscular junction (eg, botulism, Lambert-Eaton syndrome)

[**Fig. 170-1.** The autonomic nervous system.]

[**Table 170-1.** Divisions of the Autonomic Nervous System]

Evaluation

History: Symptoms suggesting autonomic insufficiency include

• Orthostatic hypotension

• Heat intolerance

• Loss of bladder and bowel control

• Erectile dysfunction (an early symptom)

Other possible symptoms include dry eyes and dry mouth, but they are less specific.

Physical examination: Important parts of the examination include the following:

• Postural BP and heart rate: In a normally hydrated patient, a sustained (eg, > 1 min) decrease of ≥ 20 mm Hg in systolic BP or a decrease of ≥ 10 mm Hg in diastolic BP with standing suggests autonomic insufficiency. Heart rate change with respiration and standing should be noted; absence of physiologic sinus arrhythmia and failure of heart rate to increase with standing indicate autonomic insufficiency. In contrast, patients with postural tachycardia syndrome, a benign disorder, typically have postural tachycardia without hypotension (see p. 2035).

• Eye examination: Miosis and mild ptosis (Horner's syndrome) suggest a sympathetic lesion. A dilated, unreactive pupil (Adie's pupil) suggests a parasympathetic lesion.

• GU and rectal reflexes: Abnormal GU and rectal reflexes may indicate ANS deficits. Testing includes the cremasteric reflex (normally, stroking the upper inner thigh results in retraction of the testes), anal wink reflex (normally, stroking perianal skin results in contraction of the anal sphincter), and bulbocavernosus reflex (normally, squeezing the glans penis or clitoris results in contraction of the anal sphincter).

Laboratory testing: If patients have symptoms and signs suggesting autonomic insufficiency, sudomotor, cardiovagal, and adrenergic testing is usually done to help determine severity and distribution of the insufficiency.

Sudomotor testing includes the following:

• Quantitative sudomotor axon-reflex test: This test evaluates integrity of postganglionic neurons using iontophoresis; electrodes filled with acetylcholine are placed on the legs and wrist to stimulate sweat glands, and the volume of sweat is then measured. The test can detect decreased or absent sweat production.

• Thermoregulatory sweat test: This test evaluates both preganglionic and postganglionic pathways. After a dye is applied to the skin, patients enter a closed compartment that is heated to cause maximal sweating. Sweating causes the dye to change color, so that areas of anhidrosis and hypohidrosis are apparent and can be calculated as a percentage of BSA.

Cardiovagal testing evaluates heart rate response (via ECG rhythm strip) to deep breathing and to the Valsalva maneuver. If the ANS is intact, heart rate varies with these maneuvers; normal responses to deep breathing and the Valsalva ratio vary by age.

Adrenergic testing evaluates response of beat-to-beat BP to the following:

• Head-up tilt: Blood is shifted to dependent parts, causing reflex responses in BP and heart rate. This test helps differentiate autonomic neuropathies from postural tachycardia syndrome.

• Valsalva maneuver: This maneuver increases intrathoracic pressure and reduces venous return, causing BP changes and reflex vasoconstriction.

With the head-up tilt test and Valsalva maneuvers, the pattern of responses is an index of adrenergic function.

Plasma norepinephrine levels can be measured with patients supine and then after they stand for > 5 min. Normally, levels increase after standing. If patients have autonomic insufficiency, levels may not increase with standing and may be low in the supine position, particularly in postganglionic disorders (eg, autonomic neuropathy, pure autonomic failure).

Autonomic Neuropathies

Autonomic neuropathies are peripheral nerve disorders with disproportionate involvement of autonomic fibers.

The best known autonomic neuropathies are those accompanying peripheral neuropathy due to diabetes, amyloidosis, or autoimmune disorders. Autoimmune autonomic neuropathy is an idiopathic disorder that often develops after a viral infection; onset may be subacute. Autonomic insufficiency is usually a late manifestation in alcoholic neuropathy.

Common symptoms of autonomic neuropathies include orthostatic hypotension, neurogenic bladder, erectile dysfunction, gastroparesis, and intractable constipation. When somatic fibers are involved, sensory loss in a stocking-and-glove distribution and distal weakness may occur (see also Ch. 185).

Diagnosis

• Clinical evaluation

Diagnosis is based on demonstration of autonomic failure (see p. 1617) and of a specific cause of neuropathy (eg, diabetes, amyloidosis). Autoimmune autonomic neuropathy may be suspected after a viral infection. Ganglionic anti-acetylcholine receptor antibody A_3 is present in about one half of patients with autoimmune autonomic neuropathy and is occasionally present in patients with other autonomic neuropathies.

Treatment

Underlying disorders are treated. Autoimmune autonomic neuropathy may respond to immunotherapy; plasma exchange or IV γ-globulin can be used for more severe cases.

Horner's Syndrome

Horner's syndrome is ptosis, miosis, and anhidrosis due to dysfunction of cervical sympathetic output.

Etiology

Horner's syndrome results when the cervical sympathetic pathway running from the hypothalamus to the eye is disrupted. The causative lesion may be primary (including congenital) or secondary to another disorder. Lesions are usually divided into

• Central (eg, brain stem ischemia, syringomyelia, brain tumor)

• Peripheral (eg, Pancoast's tumor, cervical adenopathy, neck and skull injuries, aortic or carotid dissection, thoracic aortic aneurysm)

Peripheral lesions may be preganglionic or postganglionic in origin.

Symptoms and Signs

Symptoms include ptosis, miosis, anhidrosis, and hyperemia of the affected side. In the congenital form, the iris does not become pigmented and remains blue-gray.

Diagnosis

• Cocaine eye drop test

• MRI or CT to diagnose cause

Liquid cocaine 10% can be applied to the affected eye; poor pupillary dilation after 30 min indicates Horner's syndrome. If results are positive, 1% hydroxyamphetamine solution or 5% *N*-methyl hydroxyamphetamine can be applied to the eye 48 h later to determine whether the lesion is preganglionic (if the pupil dilates) or postganglionic (if the pupil does not dilate). Patients with Horner's syndrome require MRI or CT of the brain, spinal cord, chest, or neck, depending on clinical suspicion.

Treatment

The cause, if identified, is treated; there is no treatment for primary Horner's syndrome.

Multiple System Atrophy

Multiple system atrophy is a relentlessly progressive neurodegenerative disorder causing pyramidal, cerebellar, and autonomic dysfunction. It includes 3 disorders previously thought to be distinct: olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome. Symptoms include hypotension, urinary retention, constipation, ataxia, rigidity, and postural

instability. Diagnosis is clinical. Treatment is symptomatic, with volume expansion, compression garments, and vasoconstrictor drugs.

Multiple system atrophy affects about twice as many men as women. Mean age at onset is about 53 yr; after symptoms appear, patients live about 9 to 10 yr.

Etiology

Etiology is unknown, but neuronal degeneration occurs in several areas of the brain; the area and amount damaged determine initial symptoms. A characteristic finding is cytoplasmic inclusion bodies containing α-synuclein within oligodendroglial cells.

Symptoms and Signs

Initial symptoms vary but include a combination of parkinsonism unresponsive to levodopa, cerebellar abnormalities, and symptoms due to autonomic insufficiency.

Parkinsonian symptoms: These symptoms predominate in striatonigral degeneration. They include rigidity, bradykinesia, postural instability, and jerky postural tremor. Highpitched, quavering dysarthria is common. In contrast to Parkinson's disease, multiple system atrophy usually does not cause resting tremor and dyskinesia, and symptoms respond poorly and transiently to levodopa.

Cerebellar abnormalities: These abnormalities predominate in olivopontocerebellar atrophy. They include ataxia, dysmetria, dysdiadochokinesia (difficulty performing rapidly alternating movements), poor coordination, and abnormal eye movements.

Autonomic symptoms: Typically, autonomic insufficiency causes orthostatic hypotension (symptomatic fall in BP when a person stands, often with syncope—see p. 2035), urinary retention or incontinence, constipation, and erectile dysfunction.

Other autonomic symptoms, which may occur early or late, include decreased sweating, difficulty breathing and swallowing, fecal incontinence, and decreased tearing and salivation. REM sleep behavior disorder (eg, speech or skeletal muscle movement during REM sleep) and respiratory stridor are common. Patients are often unaware of REM sleep behavior disorder. Patients may have nocturnal polyuria; contributing factors may include a circadian decrease in arginine vasopressin and treatments used to increase blood volume.

Diagnosis

- Clinical evaluation (parkinsonism or cerebellar symptoms that respond poorly to levodopa plus autonomic failure)

- MRI

Diagnosis is suspected clinically, based on the combination of autonomic failure and parkinsonism or cerebellar symptoms. Similar symptoms may result from Parkinson's disease, Lewy body dementia, pure autonomic failure, autonomic neuropathies, progressive supranuclear palsy, multiple cerebral infarcts, or drug-induced parkinsonism.

No diagnostic test is definitive, but MRI abnormalities in the striatum, pons, and cerebellum strongly suggest the disorder. Multiple system atrophy can be diagnosed antemortem based on these findings plus symptoms of generalized autonomic failure and lack of response to levodopa.

Treatment

- Supportive care

There is no specific treatment, but symptoms are managed as follows:

- Orthostatic hypotension: Treatment includes intravascular volume expansion with salt and water supplementation and sometimes fludrocortisone 0.1 to 0.4 mg po once/day. Use of compression garments for the lower body (eg, abdominal binder, Jobst stockings) and α-adrenoreceptor stimulation with midodrine 10 mg po tid may help. However, midodrine also increases peripheral vascular resistance and supine BP, which may be problematic. Raising the head of the bed about 10 cm reduces nocturnal polyuria and supine hypertension and may reduce morning orthostatic hypotension.

- Parkinsonism: Levodopa/carbidopa 25/100 mg po at bedtime or pergolide 0.1 mg po once/day, titrated upward to 0.25 to 1.0 mg tid, may be tried to relieve rigidity and other parkinsonian symptoms, but these drugs are usually ineffective or provide modest benefit.

- Urinary incontinence: If the cause is detrusor hyperreflexia, oxybutynin chloride 5 mg po tid or tolterodine 2 mg po bid may be used.

- Urinary retention: Many patients must self-catheterize their bladder.

- Constipation: A high-fiber diet and stool softeners can be used; for refractory cases, enemas may be necessary.

- Erectile dysfunction: Drugs such as sildenafil 50 mg po prn and various physical means can be used (see p. 2347).

Pure Autonomic Failure

Pure autonomic failure results from neuronal loss in autonomic ganglia, causing orthostatic hypotension and other autonomic symptoms.

Pure autonomic failure, previously called idiopathic orthostatic hypotension or Bradbury-Eggleston syndrome, denotes generalized autonomic failure without CNS involvement. This disorder differs from multiple system atrophy because it lacks central or preganglionic involvement. Pure autonomic failure affects more women, tends to begin during a person's 40s or 50s, and does not result in death.

Etiology is usually unknown. Some cases are due to a synucleinopathy (see p. 1765); occasionally, the cause is an autoimmune autonomic neuropathy.

The main symptom is orthostatic hypotension; there may be other autonomic symptoms, such as decreased sweating, heat intolerance, urinary retention, bladder spasms (possibly causing incontinence), erectile dysfunction, fecal incontinence or constipation, and pupillary abnormalities.

Diagnosis

- Clinical evaluation

Diagnosis is by exclusion. The norepinephrine level is usually < 100 pg/mL supine and does not increase with standing. Postural tachycardia syndrome can be differentiated because with standing, it does not usually cause hypotension, the norepinephrine level increases, and heart rate increases by > 30 beats/min or to 120 beats/min within 10 min.

Treatment

Treatment is symptomatic:

- Orthostatic hypotension: Vasopressors and support hose

- Constipation: High-fiber diet and stool softeners

- Bladder spasms: Bladder antispasmodics
- Urinary retention: Possibly self-catheterization of the bladder
- Sweating abnormalities: Avoidance of hot conditions

Chapter 171. Pain

Introduction

Pain is the most common reason patients seek medical care. Pain has sensory and emotional components and is often classified as acute or chronic. Acute pain is frequently associated with anxiety and hyperactivity of the sympathetic nervous system (eg, tachycardia, increased respiratory rate and BP, diaphoresis, dilated pupils). Chronic pain does not involve sympathetic hyperactivity but may be associated with vegetative signs (eg, fatigue, loss of libido, loss of appetite) and depressed mood. People vary considerably in their tolerance for pain.

Pathophysiology

Acute pain, which usually occurs in response to tissue injury, results from activation of peripheral pain receptors and their specific A delta and C sensory nerve fibers (nociceptors). Chronic pain (see p. 1629) related to ongoing tissue injury is presumably caused by persistent activation of these fibers. Chronic pain may also result from ongoing damage to or dysfunction of the peripheral or central nervous system (which causes neuropathic pain) (see p. 1632).

Nociceptive pain may be somatic or visceral. Somatic pain receptors are located in skin, subcutaneous tissues, fascia, other connective tissues, periosteum, endosteum, and joint capsules. Stimulation of these receptors usually produces sharp or dull localized pain, but burning is not uncommon if the skin or subcutaneous tissues are involved. Visceral pain receptors are located in most viscera and the surrounding connective tissue. Visceral pain due to obstruction of a hollow organ is poorly localized, deep, and cramping and may be referred to remote cutaneous sites. Visceral pain due to injury of organ capsules or other deep connective tissues may be more localized and sharp.

Although pain of predominantly psychologic origin is far less common than nociceptive or neuropathic pain, psychologic factors commonly contribute to chronic pain and may contribute to pain-related disability. Pain thought to be caused predominantly by psychologic factors is sometimes called psychogenic pain; however, psychophysiologic pain is a more accurate term because the pain results from interaction of physiologic and psychologic phenomena. This type of pain can be categorized in terms of defined somato-form disorders (eg, chronic pain disorders, somatization disorders, hypochondriasis —see p. 1573) in the *Diagnostic and Statistical Manual of Mental Disorders* , Fourth Edition, Text Revision (DSM-IV-TR).

Many pain syndromes are multifactorial. For example, chronic low back pain and most cancer pain syndromes have a prominent nociceptive component but may also involve neuropathic pain (due to nerve damage).

Pain transmission and modulation: Pain fibers enter the spinal cord at the dorsal root ganglia and synapse in the dorsal horn. From there, fibers cross to the other side and travel up the lateral columns to the thalamus and then to the cerebral cortex.

Repetitive stimulation (eg, from a prolonged painful condition) can sensitize neurons in the dorsal horn of the spinal cord so that a lesser peripheral stimulus causes pain (wind-up phenomenon). Peripheral nerves and nerves at other levels of the CNS may also be sensitized, producing long-term synaptic changes in cortical receptive fields (remodeling) that maintain exaggerated pain perception.

Substances released when tissue is injured, including those involved in the inflammatory cascade, can sensitize peripheral nociceptors. These substances include vasoactive peptides (eg, calcitonin gene-related protein, substance P, neurokinin A) and other mediators (eg, prostaglandin E_2, serotonin, bradykinin, epinephrine).

The pain signal is modulated at multiple points in both segmental and descending pathways by many neurochemical mediators, including endorphins (eg, enkephalin) and monoamines (eg, serotonin, norepinephrine). These mediators interact in poorly understood ways to exaggerate or reduce the

perception of and response to pain. They mediate the potential benefit of CNS-active drugs (eg, opioids, antidepressants, anticonvulsants, membrane stabilizers) that interact with specific receptors and neurochemicals in the treatment of chronic pain.

Psychologic factors are important modulators. They not only affect verbal expression of pain (ie, whether patients appear stoic or sensitive) but also generate neural output that modulates neurotransmission along pain pathways. Psychologic reaction to protracted pain interacts with other CNS factors to induce long-term changes in pain perception.

Evaluation

Clinicians should evaluate the cause, severity, and nature of the pain and its effect on activities and psychologic well-being. Evaluation of the cause of acute pain (eg, back pain, chest pain—see elsewhere in THE MANUAL) differs from that of chronic pain (see p. 1630).

The history should include the following information about the pain:

• Quality (eg, burning, cramping, aching, deep, superficial, boring, shooting)

• Severity

• Location

• Radiation pattern

• Duration

• Timing (including pattern and degree of fluctuation and frequency of remissions)

• Exacerbating and relieving factors

The patient's level of function should be assessed, focusing on activities of daily living (eg, dressing, bathing), employment, avocations, and personal relationships (including sexual).

The patient's perception of pain can represent more than the disorder's intrinsic physiologic processes. What pain means to the patient should be determined, with emphasis on psychologic issues, depression, and anxiety. Reporting pain is more socially acceptable than reporting anxiety or depression, and appropriate therapy often depends on sorting out these divergent perceptions. Pain and suffering should also be distinguished, especially in cancer patients (see p. 1075); suffering may be due as much to loss of function and fear of impending death as to pain. Whether secondary gain (external, incidental benefits of a disorder—eg, time off, disability payments) contributes to pain or pain-related disability should be considered. The patient should be asked whether litigation is ongoing or financial compensation for injury will be sought. A personal or family history of chronic pain can often illuminate the current problem. Whether family members perpetuate chronic pain (eg, by constantly asking about the patient's health) should be considered.

Patients and sometimes family members and caregivers should be asked about the use, efficacy, and adverse effects of prescription and OTC drugs and other treatments and about alcohol and recreational or illicit drug use.

Pain severity: Pain severity should be assessed before and after potentially painful interventions. In verbal patients, self-report is the gold standard, and external signs of pain or distress (eg, crying, wincing, rocking) are secondary. For patients who have difficulty communicating and for young children, nonverbal indicators (behavioral and sometimes physiologic) may need to be the primary source of information.

Formal measures (see Fig. 171-1) include verbal category scales (eg, mild, moderate, severe), numeric scales, and the Visual Analog Scale (VAS). For the numeric scale, patients are asked to rate their pain from 0 to 10 (0 = no pain;

10 = "the worst pain ever"). For the VAS, patients make a hash mark representing their degree of pain on an unmarked 10-cm line with the left side labeled "no pain" and the right side labeled "unbearable pain." The pain score is distance in mm from the left

[Fig. 171-1. Some pain scales for quantifying pain as it is occurring.]

end of the line. Children and patients with limited literacy or known developmental problems may select from images of faces ranging from smiling to contorted with pain or from fruits of varying sizes to convey their perception of pain severity. When measuring pain, the examiner should specify a time period (eg, "on average during the past week").

Demented and aphasic patients: Assessing pain in patients with disorders affecting cognition, speech, or language (eg, dementia, aphasia) can be difficult. Pain is suggested by facial grimacing, frowning, or repetitive eye blinking. Sometimes caregivers can describe behaviors that suggest pain (eg, sudden social withdrawal, irritability, grimacing). Pain should be considered in patients who have difficulty communicating and who inexplicably change their behavior. Many patients who have difficulty communicating can communicate meaningfully when an appropriate pain scale is used. For example, the Function Pain Scale has been validated and can be used in nursing home patients who have Mini-Mental State Examination scores of ≥ 17.

Patients receiving neuromuscular blockade: No validated instruments are available to assess pain when neuromuscular blockade is used to facilitate mechanical ventilation. If the patient is given a sedative, the dose can be adjusted until there is no evidence of consciousness. In such cases, specific analgesics are not needed. If, however, the patient is sedated but continues to have evidence of consciousness (eg, blinking, some eye movement response to command), pain treatment should be considered based on the degree of pain usually caused by the condition (eg, burns, trauma). If a potentially painful procedure (eg, turning a bedbound patient) is required, pretreatment with the selected analgesic or anesthetic should be given.

Treatment of Pain

Nonopioid and opioid analgesics are the main drugs used to treat pain. Antidepressants, anticonvulsants, and other CNS-active drugs may also be used for chronic or neuropathic pain and are first-line therapy for some conditions. Neuraxial infusion, nerve stimulation, injection therapies, and neural blockade can help selected patients. Cognitive-behavioral interventions (eg, incremental gains in function; changes in relationships in the home; systematic use of relaxation techniques, hypnosis, or biofeedback; graduated exercise) may reduce pain and painrelated disability and help patients cope.

Nonopioid Analgesics

Acetaminophen and NSAIDs are often effective for mild to moderate pain (see Table 171-1). Of these, only ketorolac can be given parenterally. Nonopioids do not cause physical dependence or tolerance.

Acetaminophen has no anti-inflammatory or antiplatelet effects and does not cause gastric irritation.

NSAIDs include nonselective COX (COX-1 and COX-2) inhibitors and selective COX-2 inhibitors (coxibs); all are effective analgesics. Aspirin is the least expensive but has prolonged antiplatelet effects. Coxibs have lowest risk of ulcer formation and GI upset. However, when a coxib is used with low-dose aspirin, it may have no GI benefit over other NSAIDs. Recent studies suggest that inhibition of COX-2, which occurs with both nonselective COX inhibitors and coxibs, is associated with a prothrombotic effect that can increase risk of MI, stroke, and claudication. This effect appears to be drug-related, as well as dose- and duration-related. Although there is some evidence that the risk is very low with some of the nonselective COX inhibitors (eg, ibuprofen, naproxen) and coxibs (celecoxib), it is prudent to consider the potential for prothrombotic effects as a risk of all NSAID therapy.

If an NSAID is likely to be used only short-term, significant adverse effects are unlikely, regardless of the drug used. Some clinicians use a coxib first whenever therapy is likely to be long-term (eg, months)

because the risk of GI adverse effects is lower; others limit coxib use to patients predisposed to GI adverse effects (eg, the elderly, patients taking corticosteroids, those with a history of peptic ulcer disease or GI upset due to other NSAIDs) and those who are not doing well with nonselective NSAIDs or who have a history of intolerance to them. Although data are still limited, the prothrombotic risk suggests that all NSAIDs should be used cautiously in patients with clinically significant atherosclerosis or multiple cardiovascular risk factors. All NSAIDs should be used cautiously in patients with renal insufficiency; coxibs are not renal-sparing.

If initial recommended doses provide inadequate analgesia, a higher dose is given, up to the conventional safe maximum dose. If analgesia remains inadequate, the drug should be stopped. If pain is not severe, another NSAID may be tried because response varies from drug to drug. It is prudent during long-term NSAID therapy to monitor for occult blood in stool and changes in CBC, electrolytes, and hepatic and renal function.

Opioid Analgesics

"Opioid" is a generic term for natural or synthetic substances that bind to specific opioid receptors in the CNS, producing an agonist action. Opioids are also called narcotics. Some opioids used for analgesia have both agonist and antagonist actions. Potential for abuse among those with a known history of abuse or addiction may be less with agonist-antagonists than with pure agonists, but agonist-antagonist drugs have a ceiling effect for analgesia and induce a withdrawal syndrome in patients already physically dependent on opioids. In general, acute pain is best treated with short-acting pure agonist drugs, and chronic pain is

[**Table 171-1.** Nonopioid Analgesics]

best treated with longer-acting pure agonist drugs (see Tables 171-2 and 171-3).

Opioid analgesics are useful in managing severe acute or chronic pain. They are often underused, resulting in needless pain and suffering because clinicians often underestimate the required dosage, overestimate the duration of action and risk of adverse effects, and have unreasonable concerns about addiction (see p. 1512). Physical dependence (development of withdrawal symptoms when a drug is stopped) should be assumed to exist in all patients treated with opioids for more than a few days. However, addiction (loss of control, compulsive use, craving and use despite harm) is very rare in patients with no history of substance abuse. Before opioid therapy is initiated, clinicians should ask about risk factors for abuse and addiction. These risk factors include prior alcohol or drug abuse, a family history of alcohol or drug abuse, and a prior major psychiatric disorder. If risk factors are present, treatment may still be appropriate; however, the clinician should use more controls to prevent abuse (eg, small prescriptions, frequent visits, no refills for "lost" prescriptions) or should refer the patient to a pain specialist or an addiction medicine specialist experienced in pain management.

Route of administration: Almost any route can be used. The oral or transdermal route is preferred for long-term use; both are effective

[**Table 171-2.** Opioid Analgesics]

and provide stable blood levels. Modified-release oral and transdermal forms allow less frequent dosing, which is particularly important for providing overnight relief. Formulations of fentanyl are now available for delivery through the oral mucosa. Lozenges are used for sedation in children and as treatment of breakthrough pain. Effervescent tablets are available for breakthrough pain. Breakthrough pain has been targeted by these formulations because they have a relatively more rapid onset than the oral route; other rapid-onset, transmucosal

[**Table 171-3.** Equianalgesic Doses of Opioid Analgesics*]

formulations of fentanyl and other drugs are in development.

The IV route provides the most rapid onset and thus the easiest titration, but duration of analgesia is short. Large, rapid fluctuations in blood levels (bolus effect) can lead to toxicity at peak levels early in the dosing interval or later to breakthrough pain at trough levels. Continuous IV infusion, sometimes with patient-controlled supplemental doses, eliminates this effect but requires an expensive pump; this approach is used most often for postoperative pain.

The IM route provides analgesia longer than IV but is painful, and absorption can be erratic; it is not recommended. Long-term continuous sc infusion can be used, particularly for cancer pain.

Intraspinal opioids (eg, morphine 5 to 10 mg epidurally or 0.5 to 1 mg intrathecally for acute pain) can provide relief, which is prolonged when a hydrophilic drug like morphine is used; they are typically used postoperatively. Implanted infusion devices can provide long-term neuraxial infusion. These devices can also be used with other drugs (eg, local anesthetics, clonidine, ziconotide).

Dosing and titration: Initial dose is modified according to the patient's response; it is increased incrementally until analgesia is satisfactory or adverse effects limit treatment. Sedation and respiratory rate are monitored when opioids are given parenterally to relatively opioid-naive patients. The elderly are more sensitive to opioids and are predisposed to adverse effects; opioid-naive elderly patients typically require lower doses than younger patients. Neonates, especially when premature, are also sensitive to opioids, because they lack adequate metabolic pathways to eliminate them.

For moderate, transient pain, an opioid may be given prn. For severe or ongoing pain, doses should be given regularly, without waiting for severe pain; supplemental doses are given as needed when treating cancer pain and are typically considered case by case when treating chronic noncancer pain. A common error is prescribing short-acting drugs at long intervals, allowing breakthrough pain.

For patient-controlled analgesia, a bolus dose (in a postoperative setting, typically morphine 1 mg q 6 min) is provided when patients push a button; a baseline infusion (eg, morphine 0.5 to 1 mg/h) may or may not be given. The physician controls the amount and interval of the bolus. Patients with prior opioid exposure or with chronic pain require a higher bolus and baseline infusion dose; the infusion dose is further adjusted based on response.

Patients with dementia cannot use patient-controlled analgesia, nor can young children; however, adolescents often can.

During long-term treatment, the effective opioid dose can remain constant for prolonged periods. Some patients need intermittent dose escalation, typically in the setting of physical changes that suggest an increase in the pain (eg, progressive neoplasm). Fear of tolerance should not inhibit appropriate early, aggressive use of an opioid. If a previously adequate dose becomes inadequate, that dose must usually be increased by 30 to 100% to control pain.

Nonopioid analgesics (eg, acetaminophen, NSAIDs) are often given concomitantly. Products containing both drugs are convenient, but the nonopioid may limit upward titration of the opioid dose.

Adverse effects: In opioid-naive patients, adverse effects common at the start of therapy include sedation, mental clouding, constipation, nausea, vomiting, and itching. Respiratory depression is serious but is rare when opioids are given at appropriate doses. Because steady-state plasma levels are not approached until 4 to 5 half-lives have passed, drugs with a long half-life (particularly levorphanol and methadone) have a risk of delayed toxicity as plasma levels rise. Modified-release opioids typically require several days to approach steady-state levels.

In the elderly, opioids tend to have more adverse effects (commonly, constipation and sedation or mental clouding). Opioids may cause urinary retention in men with benign prostatic hyperplasia.

Although tolerance to opioid-induced sedation, mental clouding, and nausea usually develops within days, tolerance to opioid-induced constipation and urinary retention usually occurs much more slowly. Any adverse effect may be persistent in some patients and this is much more likely with constipation.

Opioids should be used cautiously in patients with certain disorders:

- Hepatic disorders because drug metabolism is delayed, particularly with modified-release preparations
- COPD because respiratory depression is a risk
- Some neurologic disorders, such as dementia and encephalopathy, because delirium is a risk
- Severe renal insufficiency because metabolites may accumulate and cause problems; accumulation is least likely with fentanyl and methadone

Constipation is common among patients who take opioids for more than a few days. For prevention in predisposed patients (eg, the elderly), dietary fiber and fluids should be increased, and a stimulant laxative (eg, senna—see p. 87) should be given. Persisting constipation can be managed with Mg citrate 90 mL po q 2 to 3 days, lactulose 15 mL po bid, or propylethylene glycol powder (dose is adjusted as needed). Some patients require regular enemas.

While sedated after taking an opioid, patients should not drive and should take precautions to prevent falls and other accidents. If sedation impairs quality of life, certain stimulant drugs may be given intermittently (eg, before a family gathering or other event that requires alertness) or, to some patients, regularly. Drugs that can be effective are methylphenidate (initially, 5 to 10 mg po bid), dextroamphetamine (initially, 2.5 to 10 mg po bid), or modafinil (initially, 100 to 200 mg po once/day). These drugs are typically given in the morning and as needed later. The maximum dose of methylphenidate seldom exceeds 60 mg/day. For some patients, caffeine-containing beverages provide enough stimulation. Stimulants may also potentiate analgesia.

Nausea can be treated with hydroxyzine 25 to 50 mg po q 6 h, metoclopramide 10 to 20 mg po q 6 h, or an antiemetic phenothiazine (eg, prochlorperazine 10 mg po or 25 mg rectally q 6 h).

Respiratory depression is rare with conventional doses and with long-term use. If it occurs acutely, ventilatory assistance may be needed until the opioid's effect can be reversed by an opioid antagonist.

For urinary retention, double voiding or using Crede's method during voiding may help; some patients benefit from adding an α-adrenergic blocker such as tamsulosin 0.4 mg po once/day (starting dose).

Opioids can cause neuroendocrine effects, typically reversible hypogonadism. Symptoms may include fatigue, loss of libido, infertility due to low levels of sex hormones, and, in women, amenorrhea.

Opioid antagonists: Opioid antagonists are opioid-like substances that bind to opioid receptors but produce little or no agonist activity. They are used mainly to reverse symptoms of opioid overdose, particularly respiratory depression.

Naloxone acts in < 1 min when given IV and slightly less rapidly when given IM. It can also be given sublingually or endotracheally. Duration of action is about 60 to 120 min. However, opioid-induced respiratory depression usually lasts longer than the duration of antagonism; thus, *repeated doses of naloxone and close monitoring are necessary*. The dose for acute opioid overdosage is 0.4 mg IV q 2 to 3 min prn. For patients receiving long-term opioid therapy, naloxone should be used only to reverse respiratory depression and must be given more cautiously to avoid precipitating withdrawal or recurrent pain. A reasonable regimen is 1 mL of a dilute solution (0.4 mg in 10 mL saline) IV q 1 to 2 min, titrated to adequate respirations (not alertness). Nalmefene is similar to naloxone, but its duration of action is about 4 to 8 h. Nalmefene is occasionally used to ensure prolonged opioid reversal.

Naltrexone, an orally bioavailable opioid antagonist, is given as adjunctive therapy in opioid and alcohol addiction. It is long-acting and generally well tolerated.

Adjuvant Analgesic Drugs

Many drugs are used as adjuvant analgesics, including anticonvulsants (eg, pregabalin, gabapentin) and antidepressants (eg, tricyclics, duloxetine, venlafaxine, bupropion), and many others (see Table 171-4). These drugs have many uses, most notably to relieve pain with a neuropathic component. Gabapentin is the most widely used drug for such purposes. The dose often needs to be high, up to 1200 mg tid or sometimes higher. Pregabalin is similar to gabapentin but has more stable pharmacokinetics; some patients who do not respond well to gabapentin do respond to pregabalin and visa versa. Duloxetine is a new mixed mechanism (serotonin and norepinephrine) reuptake inhibitor, which has good evidence of analgesic efficacy in diabetic neuropathic pain and fibromyalgia.

Topical drugs are also widely used. Capsaicin cream, topical NSAIDS, other compounded creams (eg, local anesthetics), and a lidocaine 5% patch have little risk of adverse effects; they should be considered for many types of pain.

Neural Blockade

Interrupting nerve transmission in peripheral or central pain pathways via drugs or physical methods provides short-term and sometimes long-term relief. Neuroablation (pathway destruction is used rarely; it is typically reserved for patients with an advanced disorders and a short life expectancy.

Local anesthetic drugs (eg, lidocaine) can be given IV, intrathecally, intrapleurally, transdermally, sc, or epidurally. Epidural analgesia using local anesthetics or opioids is particularly useful for some types of postoperative pain. Long-term epidural drug administration is occasionally used for patients with localized pain and a short life expectancy. Generally, for long-term neuraxial infusion, an intrathecal route via an implanted pump is preferred.

Neuroablation involves interrupting a nociceptive pathway surgically or using radio-frequency energy to produce a lesion. The procedure is used mainly for cancer pain. Somatic pain is more responsive than visceral pain. Neuroablation of the ascending spinothalamic tract (cordotomy) is usually used; it provides relief for several years, although numbness and dysesthesias develop. Neuroablation of the dorsal roots (rhizotomy) is used when a specific dermatome can be identified.

Neuromodulation

Stimulation of neural tissues may decrease pain, presumably by activating endogenous pain modulatory pathways. The most common method is transcutaneous electrical nerve stimulation (TENS), which applies a small current to the skin. Also, electrodes may be implanted along peripheral nerves or along the dorsal columns in the epidural space. Stimulation of brain structures (deep brain stimulation and motor cortex stimulation) has also been used, but evidence of benefit is slight.

Geriatrics Essentials

In the elderly, the most common causes of pain are musculoskeletal disorders. However, pain is often chronic and multifactorial, and the causes may not be clear.

NSAIDs: Risk of ulcers and GI bleeding due to NSAIDs for people > 65 is 3 to 4 times higher than that for middle-aged people. Risk depends on drug dose and duration of therapy. Elderly patients at high risk of GI adverse effects may benefit from concomitant use of cytoprotective drugs (usually, a proton pump inhibitor; occasionally, the prostaglandin misoprostol).

The newly recognized risk of cardiovascular toxicity, which presumably occurs with nonselective COX-1 and COX-2 inhibitors and with selective COX-2 inhibitors (coxibs), is particularly relevant to the elderly, who are more likely to have cardiovascular risk factors (eg, a history of MI or cerebrovascular or peripheral vascular disease). These drugs should be prescribed cautiously for such patients.

Both nonselective and selective NSAIDs can impair renal function and cause Na and water retention; they should be used cautiously in the elderly, particularly in those who have a renal or hepatic disorder, heart failure, or hypovolemia. Rarely, NSAIDs cause cognitive impairment and personality changes in the elderly. Indomethacin causes more confusion in the elderly than other NSAIDs and should be avoided.

Given the overall greater risk of serious toxicity in the elderly, low doses of NSAIDs should be used if possible, and using short-term therapy or interrupted therapy to confirm effectiveness should be considered.

Opioids: In the elderly, opioids have a longer half-life and possibly a greater analgesic effect than in younger patients. Opioid agonist-antagonists often have psychotomimetic effects (eg, delirium) in the elderly and should usually be avoided. Opioids can contribute to constipation and urinary retention in patients of any age, but the effects tend to be more problematic in the elderly.

Chronic Pain

(See also Fibromyalgia on p. 375.)

Chronic pain is pain that persists or recurs for > 3 mo, persists > 1 mo after resolution of an acute tissue injury, or accompanies a nonhealing lesion. Causes include chronic disorders (eg, cancer, arthritis, diabetes) and injuries (eg, herniated disk, torn ligament), and many primary pain disorders (eg, neuropathic pain, fibromyalgia, chronic headache). Various drugs and psychologic treatments are used.

Unresolved, long-lasting disorders (eg, cancer, RA, herniated disk) that produce ongoing nociceptive stimuli may account completely for chronic pain. Alternatively, injury, even mild injury, may lead to long-lasting changes (sensitization) in the nervous system—from peripheral receptors to the cerebral cortex—that may produce persistent pain in the absence of ongoing nociceptive stimuli. With sensitization, discomfort that is due to a nearly resolved disorder and might otherwise be perceived as mild or trivial is instead perceived as significant pain. Psychologic factors may also amplify persistent pain. Thus, chronic pain commonly appears out of proportion to identifiable physical processes. In some cases (eg, chronic back pain after injury), the original precipitant of pain is obvious; in others (eg, chronic headache, atypical facial pain, chronic abdominal pain), the precipitant is remote or occult.

In most patients, physical processes are undeniably involved in sustaining chronic pain and are sometimes (eg, in cancer pain) the main factor. However, even in these patients, psychologic factors usually also play a role. Patients who have to continually prove that they are sick to obtain medical care, insurance coverage, or work relief may unconsciously reinforce their pain perceptions, particularly when litigation is involved. This response differs from malingering, which is conscious exaggeration of symptoms for secondary gain (eg, time off, disability payments). Various factors in the patient's environment (eg, family members, friends) may reinforce behaviors that perpetuate chronic pain.

Chronic pain can lead to psychologic problems. Constant, unremitting pain limits activities and may cause depression and anxiety, interrupt sleep, and interfere with almost all activities. Distinguishing cause from effect is often difficult.

Symptoms and Signs

Chronic pain often leads to vegetative signs (eg, lassitude, sleep disturbance, decreased appetite, loss of taste for food, weight loss, diminished libido, constipation), which develop gradually; depression may develop. Patients may become inactive, withdraw socially, and become preoccupied with physical health. Psychologic and social impairment may be severe, causing virtual lack of function.

Some patients, particularly those without a clear-cut ongoing cause, have a history of failed medical and surgical treatments, multiple (and duplicative) diagnostic tests, use of many drugs (sometimes involving abuse or addiction), and inappropriate use of health care.

Diagnosis

• Evaluation for organic cause initially and if symptoms change

An organic cause should always be sought—even if a prominent psychologic contribution to the pain is

likely. Physical processes associated with the pain should be evaluated appropriately and characterized. However, once a full evaluation is done, repeating tests in the absence of new findings is not useful. The best approach is often to stop testing and focus on relieving pain and restoring function.

The effect of pain on the patient's life should be evaluated; evaluation by an occupational therapist may be necessary. Formal psychiatric evaluation should be considered if a coexisting psychiatric disorder (eg, major depression) is suspected as cause or effect.

Treatment

• Often multimodal therapy (eg, analgesics, physical methods, psychologic treatments)

Specific causes should be treated. Early, aggressive treatment of acute pain is always preferable and may limit or prevent sensitization and remodeling and hence prevent progression to chronic pain.

Drugs or physical methods may be used. Psychologic and behavioral treatments are usually helpful. Many patients who have marked functional impairment or who do not respond to a reasonable attempt at management by their physician benefit from the multidisciplinary approach available at a pain clinic.

Many patients prefer to have their pain treated at home, even though an institution may offer more advanced modalities of pain management. Also, pain control may be compromised by certain practices in institutions; for example, they restrict visiting hours, use of televisions and radios (which provide useful distraction), and use of heating pads (for fear of thermal injury).

Drugs: Analgesics include NSAIDs, opioids, and adjuvant analgesics (eg, antidepressants, anticonvulsants—see p. 1628 and Table 171-4). One or more drugs may be appropriate.

[**Table 171-4.** Drugs for Neuropathic Pain]

Adjuvant analgesics are most commonly used for neuropathic pain. For persistent, moderate-to-severe pain that impairs function, opioids should be considered after determining the following:

• What conventional treatment practice is

• Whether other treatments are reasonable

• Whether the patient has an unusually high risk of adverse effects from an opioid

• Whether the patient is likely to be a responsible drug user

Prescription drug abuse may be a problem, and physicians should not offer long-term opioid therapy unless they can assess risk of abuse, monitor patients appropriately, and respond reasonably to problematic drug use. As pain lessens, patients usually need help reducing use of opioids. If depression coexists with pain, antidepressants should be used.

Depending on the condition, trigger point injection, joint or spinal injections, nerve blocks, or neuraxial infusion may be appropriate.

Physical methods: Many patients benefit from physical therapy or occupational therapy. Spray-and-stretch techniques can relieve myofascial trigger points. Some patients require an orthosis. Spinal cord stimulation may be appropriate.

Psychologic treatments: Behavioral treatments can improve patient function, even without reducing pain. Patients should keep a diary of daily activities to pinpoint areas amenable to change. The physician should make specific recommendations for gradually increasing physical activity and social engagement. Activities should be prescribed in gradually increasing units of time; pain should not, if at all possible, be allowed to abort the commitment to greater function. When activities are increased in this way, reports of pain often decrease.

Various cognitive techniques of pain control (eg, relaxation training, distraction techniques, hypnosis, biofeedback) may be useful. Patients may be taught to use distraction by guided imagery (organized fantasy evoking calm and comfort—eg, imagining resting on a beach or lying in a hammock). Other cognitive-behavioral techniques (eg, self-hypnosis) may require training by specialists.

Behavior of family members or fellow workers that reinforces pain behavior (eg, constant inquiries about the patient's health or insistence that the patient do no chores) should be discouraged. The physician should avoid reinforcing pain behavior, discourage maladaptive behaviors, applaud progress, and provide pain treatment while emphasizing return of function.

Neuropathic Pain

Neuropathic pain results from damage to or dysfunction of the peripheral or central nervous system, rather than stimulation of pain receptors. Diagnosis is suggested by pain out of proportion to tissue injury, dysesthesia (eg, burning, tingling), and signs of nerve injury detected during neurologic examination. Although neuropathic pain responds to opioids, treatment is often with adjuvant drugs (eg, antidepressants, anticonvulsants, baclofen, topical drugs).

Pain can develop after injury to any level of the nervous system, peripheral or central; the sympathetic nervous system may be involved (causing sympathetically maintained pain). Specific syndromes include postherpetic neuralgia (see p. 1420), root avulsions, painful traumatic mononeuropathy, painful polyneuropathy (particularly due to diabetes), central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system), postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, phantom pain), and complex regional pain syndrome (reflex sympathetic dystrophy and causalgia—see p. 1633).

Etiology

Peripheral nerve injury or dysfunction can result in neuropathic pain. Examples are mononeuropathies (eg, carpal tunnel syndrome, radiculopathy), plexopathies (typically caused by nerve compression, as by a neuroma, tumor, or herniated disk), and polyneuropathies (typically caused by various metabolic neuropathies—see Table 185-1 on p. 1785). Mechanisms presumably vary and may involve an increased number of Na channels on regenerating nerves.

Central neuropathic pain syndromes appear to involve reorganization of central somatosensory processing; the main categories are deafferentation pain and sympathetically maintained pain. Both are complex and, although presumably related, differ substantially.

Deafferentation pain is due to partial or complete interruption of peripheral or central afferent neural activity. Examples are postherpetic neuralgia, central pain (pain after CNS injury), and phantom pain (pain felt in the region of an amputated body part). Mechanisms are unknown but may involve sensitization of central neurons, with lower activation thresholds and expansion of receptive fields.

Sympathetically maintained pain depends on efferent sympathetic activity. Complex regional pain syndrome sometimes involves sympathetically maintained pain. Other types of neuropathic pain may have a sympathetically maintained component. Mechanisms probably involve abnormal sympathetic-somatic nerve connections (ephapses), local inflammatory changes, and changes in the spinal cord.

Symptoms and Signs

Dysesthesias (spontaneous or evoked burning pain, often with a superimposed lancinating component) are typical, but pain may also be deep and aching. Other sensations—eg, hyperesthesia, hyperalgesia, allodynia (pain due to a nonnoxious stimulus), and hyperpathia (particularly unpleasant, exaggerated pain response)—may also occur. Symptoms are long-lasting, typically persisting after resolution of the primary cause (if one was present) because the CNS has been sensitized and remodeled.

Diagnosis

• Clinical evaluation

Neuropathic pain is suggested by its typical symptoms when nerve injury is known or suspected. The cause (eg, amputation, diabetes) may be readily apparent. If not, the diagnosis often can be assumed based on the description. Pain that is ameliorated by sympathetic nerve block is sympathetically maintained pain.

Treatment

• Multimodal therapy (eg, psychologic treatments, physical methods, antidepressants or anticonvulsants, sometimes surgery)

Without concern for diagnosis, rehabilitation, and psychosocial issues, treatment has a limited chance of success. For peripheral nerve lesions, mobilization is needed to prevent trophic changes, disuse atrophy, and joint ankylosis. Surgery may be needed to alleviate compression. Psychologic factors must be constantly considered from the start of treatment. Anxiety and depression must be treated appropriately. When dysfunction is entrenched, patients may benefit from the comprehensive approach provided by a pain clinic.

Several classes of drugs are moderately effective (see Table 171-4), but complete or near-complete relief is unlikely. Antidepressants and anticonvulsants are most commonly used. Evidence of efficacy is strong for several antidepressants and anticonvulsants.

Opioid analgesics can provide some relief but are less effective than for nociceptive pain; adverse effects may prevent adequate analgesia. Topical drugs and a lidocaine-containing patch may be effective for peripheral syndromes. Sympathetic blockade is usually ineffective except for some patients with complex regional pain syndrome.

Complex Regional Pain Syndrome

(Reflex Sympathetic Dystrophy and Causalgia)

Complex regional pain syndrome (CRPS) is chronic neuropathic pain that follows soft-tissue or bone injury (type I) or nerve injury (type II) and lasts longer and is more severe than expected for the original tissue damage. Other manifestations include autonomic changes (eg, sweating, vasomotor abnormalities), motor changes (eg, weakness, dystonia), and trophic changes (eg, skin or bone atrophy, hair loss, joint contractures). Diagnosis is clinical. Treatment includes drugs, physical therapy, and sympathetic blockade.

CRPS type I was previously known as reflex sympathetic dystrophy, and type II as causalgia. Both types occur most often in young adults and are 2 or 3 times more common among women.

Etiology

CRPS type I typically follows an injury (usually of a hand or foot), most commonly after crush injuries, especially in a lower limb. It may follow amputation, acute MI, stroke, or cancer (eg, lung, breast, ovary, CNS); no precipitant is apparent in about 10% of patients. CRPS type II is similar to type I but involves overt damage to a peripheral nerve.

Pathophysiology

Pathophysiology is unclear, but peripheral nociceptor and central sensitization and release of neuropeptides (substance P, calcitonin gene-related peptide) help maintain pain and inflammation. The sympathetic nervous system is more involved in CRPS than in other neuropathic pain syndromes: Central sympathetic activity is increased, and peripheral nociceptors are sensitized to norepinephrine (a

sympathetic neurotransmitter); these changes may lead to sweating abnormalities and poor blood flow due to vasoconstriction. Nonetheless, only some patients respond to sympathetic manipulation (ie, central or peripheral sympathetic blockade).

Symptoms and Signs

Symptoms vary greatly and do not follow a pattern; they include sensory, focal autonomic (vasomotor or sudomotor), and motor abnormalities.

Pain—burning or aching—is common. It does not follow the distribution of a single peripheral nerve; it may worsen with changes in environment or emotional stress. Allodynia and hyperalgesia may occur. Pain often causes patients to limit use of an extremity.

Cutaneous vasomotor changes (eg, red, mottled, or ashen color; increased or decreased temperature) and sudomotor abnormalities (dry or hyperhidrotic skin) may be present. Edema may be considerable and locally confined. Other symptoms include trophic abnormalities (eg, shiny, atrophic skin; cracking or excess growth of nails; bone atrophy; hair loss) and motor abnormalities (weakness, tremors, spasm, dystonia with fingers fixed in flexion or equinovarus position of foot). Range of motion is often limited, sometimes leading to joint contractures. Symptoms may interfere with fitting a prosthesis after amputation.

Psychologic distress (eg, depression, anxiety, anger) is common, fostered by the poorly understood cause, lack of effective therapy, and prolonged course.

Diagnosis

• Clinical evaluation

The following clinical criteria must be present to establish the diagnosis of CRPS:

• Occurrence of pain (usually burning)

• Allodynia or hyperalgesia

• Focal autonomic dysregulation (vasomotor or sudomotor abnormalities)

• No evidence of another disorder that could explain the symptoms

If another disorder is present, CRPS should be considered possible or probable.

Other symptoms and findings may support the diagnosis: edema, trophic abnormalities, or a change in temperature of the affected area. Thermography may be used to document the temperature change if clinical evaluation is equivocal and if this finding would help establish the diagnosis. Bone changes (eg, demineralization on x-ray, increased uptake on a triple-phase radionuclide bone scan) may be detected and are usually evaluated only if the diagnosis is equivocal. However, imaging tests may also be abnormal after trauma in patients without CRPS.

Sympathetic nerve block (cervical stellate ganglion or lumbar) can be used for diagnosis and treatment. However, false-positive and false-negative results are common because not all CRPS pain is sympathetically maintained and nerve block may also affect nonsympathetic fibers. In another test of sympathetic involvement, a patient is given IV infusions of saline (placebo) or phentolamine 1 mg/kg over 10 min while pain scores are recorded; a decrease in pain after phentolamine but not placebo indicates sympathetically maintained pain.

Prognosis

Prognosis varies and is difficult to predict. CRPS may remit or remain stable for years; in a few patients, it progresses, spreading to other areas of the body.

Treatment

- Multimodal therapy (eg, drugs, physical therapy, sympathetic blockade, psychologic treatments, neuromodulation)

Treatment is complex and often unsatisfactory, particularly if begun late. It includes drugs, physical therapy, sympathetic blockade, psychologic treatments, and neuromodulation. Few controlled trials have been done.

Many of the drugs used for neuropathic pain, including tricyclic antidepressants, anticonvulsants, and corticosteroids (see Table 171-4), may be tried; none is known to be superior. Long-term treatment with opioid analgesics may be useful for selected patients.

In some patients with sympathetically maintained pain, regional sympathetic blockade relieves pain, making physical therapy possible. Oral analgesics (NSAIDs, opioids, and various adjuvant analgesics) may also relieve pain sufficiently to allow rehabilitation.

For neuromodulation, implanted spinal cord stimulators are being increasingly used. Transcutaneous electrical nerve stimulation (TENS), applied at multiple locations with different stimulation parameters, should be given a long trial. Other methods of neuromodulation include brisk rubbing of the affected part (counterirritation) and acupuncture. No one form of neuromodulation is known to be more effective than another, and a poor response to one form does not mean a poor response to another.

Neuraxial infusion with opioids, anesthetics, and clonidine may help, and intrathecal baclofen has reduced dystonia in a few patients.

Physical therapy is essential. Goals include strengthening, increased range of motion, and vocational rehabilitation.

Chapter 172. Function and Dysfunction of the Cerebral Lobes

Introduction

The cerebrum is divided by a longitudinal fissure into 2 hemispheres, each containing 5 discrete lobes. The frontal, temporal, parietal, and occipital lobes cover the brain's surface; the insula is hidden under the Sylvian fissure (see Fig. 172-1). Although specific functions are attributed to each lobe, most activities require coordination of multiple areas in both hemispheres. For example, although the occipital lobe is essential to visual processing, parts of the parietal, temporal, and frontal lobes on both sides also process complex visual stimuli.

Function is extensively lateralized. Visual, tactile, and motor activities of the left side of the body are directed predominantly by the right hemisphere and vice versa. Certain complex functions involve both hemispheres but are directed predominantly by one (cerebral dominance). For example, the left hemisphere is typically dominant for language, and the right is dominant for spatial attention.

The cerebral cortex contains the primary sensory and motor areas as well as multiple association areas. The primary sensory areas receive somesthetic, auditory, visual, olfactory, and gustatory stimuli from specialized sensory organs and peripheral receptors. Sensory stimuli are further processed in association areas that relate to one or more senses. The primary motor cortex generates volitional body movements; motor association areas help plan and execute complex motor activity. Some cortical areas are heteromodal. They are not restricted to any single motor or sensory function but receive convergent information from multiple sensory and motor areas of the brain. Heteromodal association areas in the frontal, temporal, and parietal lobes integrate sensory data, motor feedback, and other information with instinctual and acquired memories. This integration facilitates learning and creates thought, expression, and behavior.

Frontal lobes: The frontal lobes are anterior to the central sulcus. They are essential for planning and executing learned and purposeful behaviors; they are also the site of many inhibitory functions. There are several functionally distinct areas in the frontal lobes:

- The primary motor cortex is the most posterior part of the precentral gyrus. The primary motor cortex on one side controls all moving parts on the contralateral side of the body (shown on a spatial map called a homunculus—see Fig. 172-2); 90% of motor fibers from each hemisphere cross the midline in the brain stem. Thus, damage to the motor cortex of one hemisphere causes weakness or paralysis mainly on the contralateral side of the body.

[**Fig. 172-1.** Areas of the brain.]

[**Fig. 172-2.** Homunculus.]

- The medial frontal cortex (sometimes called the medial prefrontal area) is important in arousal and motivation. If lesions in this area are large and extend to the most anterior part of the cortex (frontal pole), patients sometimes become abulic (apathetic, inattentive, and markedly slow to respond).

- The orbital frontal cortex (sometimes called the orbital prefrontal area—see Fig. 172-1) helps modulate social behaviors. Patients with orbital frontal lesions can become emotionally labile, indifferent to the implications of their actions, or both. They may be alternately euphoric, facetious, vulgar, and indifferent to social nuances. Bilateral acute trauma to this area may make patients boisterously talkative, restless, and socially intrusive. With aging and in many types of dementia, disinhibition and abnormal behaviors can develop; these changes probably result from degeneration of the frontal lobe, particularly the orbital frontal cortex.

- The left posteroinferior frontal cortex (sometimes called Broca's area or the posteroinferior prefrontal area—see Fig. 172-1) controls expressive language function. Lesions in this area cause expressive aphasia (impaired expression of words—see p. 1640).

- The dorsolateral frontal cortex (sometimes called the dorsolateral prefrontal area) manipulates very recently acquired information—a function called working memory. Lesions in this area can impair the ability to retain information and process it in real time (eg, to spell words backwards or to alternate between letters and numbers sequentially).

Parietal lobes: Several areas in the parietal lobes have specific functions.

- The primary somatosensory cortex, located in the postrolandic area (postcentral gyrus) in the anterior parietal lobes, integrates somesthetic stimuli for recognition and recall of form, texture, and weight. The primary somatosensory cortex on one side receives all somatosensory input from the contralateral side of the body (see Fig. 172-2). Lesions of the anterior parietal lobe can cause difficulty recognizing objects by touch (astereognosis).

- Areas posterolateral to the postcentral gyrus generate visual-spatial relationships and integrate these perceptions with other sensations to create awareness of trajectories of moving objects. These areas also mediate proprioception (awareness of the position of body parts in space).

- Parts of the midparietal lobe of the dominant hemisphere are involved in abilities such as calculation, writing, left-right orientation, and finger recognition. Lesions in the angular gyrus can cause deficits in writing, calculating, left-right disorientation, and finger-naming (Gerstmann's syndrome).

- The nondominant parietal lobe integrates the contralateral side of the body with its environment, enabling people to be aware of this environmental space, and is important for abilities such as drawing. Acute injury to the nondominant parietal lobe may cause neglect of the contralateral side (usually the left), resulting in decreased awareness of that part of the body, its environment, and any associated injury to that side (anosognosia). For example, patients with large right parietal lesions may deny the existence of left-sided paralysis. Patients with smaller lesions may lose the ability to do learned motor tasks (eg, dressing, other well-learned activities)—a spatial-manual deficit called apraxia.

Temporal lobes: The temporal lobes are integral to auditory perception, receptive components of language, visual memory, declarative (factual) memory, and emotion. Patients with right temporal lobe lesions commonly lose the ability to interpret nonverbal auditory stimuli (eg, music). Left temporal lobe lesions interfere greatly with the recognition, memory, and formation of language.

Patients with epileptogenic foci in the medial limbic-emotional parts of the temporal lobe commonly have complex partial seizures, characterized by uncontrollable feelings and autonomic, cognitive, or emotional dysfunction. Occasionally, such patients have personality changes, characterized by humorlessness, philosophic religiosity, and obsessiveness.

Occipital lobes: The occipital lobes contain the primary visual cortex and visual association areas. Lesions in the primary visual cortex lead to a form of central blindness called Anton's syndrome; patients become unable to recognize objects by sight and are generally unaware of their deficits. Seizures in the occipital lobe can cause visual hallucinations, often consisting of lines or meshes of color superimposed on the contralateral visual field.

Insula: The insula integrates sensory and autonomic information from the viscera. It plays a role in certain language functions, as evidenced by aphasia in patients with some insular lesions. The insula processes aspects of pain and temperature sensation and possibly taste.

Pathophysiology

Cerebral dysfunction may be focal or global. Focal and global processes may also affect subcortical systems, altering arousal (eg, causing stupor or coma) or integration of thought (eg, causing delirium).

Focal dysfunction usually results from structural abnormalities (eg, tumors, stroke, trauma, malformations, gliosis, demyelination). Manifestations depend on the lesion's location, size, and development rate. Lesions that are < 2 cm in diameter or that develop very slowly may be asymptomatic.

Larger lesions, rapidly developing lesions (over weeks or months rather than years), and lesions that simultaneously affect both hemispheres are more likely to become symptomatic. Focal lesions in white matter can interrupt the connectivity between brain areas and cause the disconnection syndrome (inability to do a task that requires coordinated activity of ≥ 2 brain regions, despite retention of basic functions of each region).

Global dysfunction is caused by toxicmetabolic disorders or sometimes by diffuse inflammation, vasculopathy, major trauma, or disseminated cancer; these disorders affect multiple dimensions of cerebral function.

Recovery: Recovery from brain injury depends in part on the plasticity (ability of an area of the brain to alter its function) of the remaining cerebrum, a capacity that varies from person to person and is affected by age and general health. Plasticity is most prominent in the developing brain. For example, if the dominant hemisphere language areas are severely damaged before age 8 yr, the opposite hemisphere can often assume near-normal language function. Although capacity for recovery from brain injury is considerable after the first decade of life, severe damage more often results in permanent deficits. Gross reorganization of brain function after injury in adults is uncommon, although plasticity remains operative in certain specific areas of the brain throughout life.

Cerebral dysfunction syndromes: Specific syndromes include agnosia, amnesia, aphasia, and apraxia. Psychiatric conditions (eg, depression, psychosis, anxiety disorders) sometimes include similar elements.

Diagnosis

In general, diagnosis is clinical, often assisted by neuropsychologic testing. Diagnosis of the cause usually requires laboratory tests (blood and sometimes CSF analysis) and brain imaging, either structural (CT, MRI) or functional (PET, single-photon emission CT).

Agnosia

Agnosia is inability to identify an object using one or more of the senses. Diagnosis is clinical, often including neuropsychologic testing, with brain imaging (eg, CT, MRI) to identify the cause. Prognosis depends on the nature and extent of damage and patient age. There is no specific treatment, but occupational therapy may help patients compensate.

Agnosias are uncommon. They result from damage to (eg, by infarct, tumor, trauma) or degeneration of areas of the brain that integrate perception, memory, and identification.

Discrete brain lesions can cause different forms of agnosia, which may involve any sense. Typically, only one sense is affected. Examples are hearing (auditory agnosia, the inability to identify objects through sound such as a ringing telephone), taste (gustatory agnosia), smell (olfactory agnosia), touch (tactile agnosia), and sight (visual agnosia).

Other forms of agnosia involve very specific and complex processes within one sense. For example, prosopagnosia is inability to identify well-known faces, including those of close friends, or to otherwise distinguish individual objects among a class of objects, despite the ability to identify generic facial features and objects.

Anosognosia often accompanies damage to the right, nondominant parietal lobe. Patients deny their deficit, insisting that nothing is wrong even when one side of their body is completely paralyzed. When shown the paralyzed body part, patients may deny that it is theirs. In an often related phenomenon, patients ignore the paralyzed or desensitized body parts (hemi-inattention) or the space around them (hemineglect). Hemineglect most often involves the left side of the body.

Occipitotemporal lesions may cause an inability to recognize familiar places (environmental agnosia), visual disturbances (visual agnosia), or color blindness (achromatopsia). Right-sided temporal lesions may cause an inability to interpret sounds (auditory agnosia) or impaired music perception (amusia).

Diagnosis

• Bedside and neuropsychologic testing

• Brain imaging

At bedside, patients are asked to identify common objects through sight, touch, or another sense. If hemineglect is suspected, patients are asked to identify the paralyzed parts of their body or objects in their hemivisual fields. Physical examination is done to detect primary deficits in individual senses or communication that may interfere with testing for agnosias. For example, if light touch is defective, patients may not sense an object even when cortical function is intact. Also, aphasias may interfere with patient's expression. Neuropsychologic testing may help identify more subtle agnosias.

Brain imaging (eg, CT or MRI with or without angiographic protocols) is required to characterize a central lesion (eg, infarct, hemorrhage, mass) and to check for atrophy suggesting a degenerative disorder.

Prognosis

Recovery may be influenced by size and location of lesions, degree of impairment, and patient age. Most recovery occurs within the first 3 mo but may continue to a variable degree up to a year.

Treatment

There is no specific treatment. Rehabilitation with speech or occupational therapists can help patients learn to compensate for their deficits.

Amnesias

Amnesia is partial or total inability to recall past experiences. It may result from traumatic brain injury, degeneration, metabolic disorders, seizure disorders, or psychologic disturbances. Diagnosis is clinical but often includes neuropsychologic testing and brain imaging (eg, CT, MRI). Treatment is directed at the cause.

Processing of memories involves registration (taking in new information), encoding (forming associations, time stamps, and other processes necessary for retrieval), and retrieval. Deficits in any of these steps can cause amnesia. Amnesia, by definition, results from impairment of memory functions, not impairment of other functions (eg, attention, motivation, reasoning, language), which may cause similar symptoms.

Amnesia can be classified as follows:

• Retrograde: Amnesia for events *before* the causative event

• Anterograde: Inability to store new memories *after* the causative event

• Global: Amnesia for information related to all senses and past times

• Sense-specific: Amnesia for events processed by one sense—eg, an agnosia

Amnesia may be transient (as occurs after brain trauma), fixed (as occurs after a serious event such as encephalitis, global ischemia, or cardiac arrest), or progressive (as occurs with degenerative dementias, such as Alzheimer's disease).

Memory deficits more commonly involve facts (declarative memory) and, less commonly, skills (procedural memory).

Etiology

Amnesia can result from diffuse cerebral impairment, bilateral lesions, or multifocal injuries that impair memory-storage areas in the cerebral hemispheres. Predominant pathways for declarative memory are located along the medial parahippocampal region and hippocampus as well as in the inferomedial temporal lobes, orbital surface of the frontal lobes (basal forebrain), and diencephalon (which contains the thalamus and hypothalamus). Of these structures, the hippocampal gyri, hypothalamus, nuclei of the basal forebrain, and dorsomedial thalamic nuclei are critical. The amygdaloid nucleus contributes emotional amplifications to memory. The thalamic intralaminar nuclei and brain stem reticular formation stimulate the imprinting of memories. Bilateral damage to the mediodorsal nuclei of the thalamus severely impairs recent memory and the ability to form new memories; the most common causes are

- Thiamin deficiency
- Hypothalamic tumors
- Vertebrobasilar ischemia

Other causes of amnesia include the following:

- Bilateral damage to the medial temporal lobes (especially the hippocampus)
- Degenerative dementias
- Severe brain trauma
- Global brain anoxia or ischemia
- Alcoholic-nutritional disorders (eg, Wernicke's encephalopathy, Korsakoff's psychosis—see pp. 1522 and 1523)
- Various drug intoxications (eg, chronic solvent sniffing, amphotericin B or lithium toxicity)

Posttraumatic amnesias for the periods immediately before and after concussion or more severe head trauma seem to result from medial temporal lobe injury. More severe injuries may affect larger areas of memory storage and recall, as can many diffuse cerebral disorders that cause dementia.

Psychologic disturbances of memory result from extreme psychologic trauma or stress (see p. 1503).

With aging, many people gradually develop noticeable problems with memory, often first for names, then for events, and occasionally for spatial relationships. This widely experienced so-called benign senescent forgetfulness has no proven relationship to dementia, although some similarities are hard to overlook. People who have a subjective memory problem, who perform worse on objective memory tests, but who otherwise have intact cognition and daily function may have amnestic mild cognitive impairment (amnestic MCI). People with amnestic MCI are more likely to develop Alzheimer's disease than agematched people without memory problems.

Diagnosis

- Bedside testing

Simple bedside tests (eg, 3-item recall, location of objects previously hidden in the room) and formal tests (eg, word list learning tests such as the California Verbal Learning Test and the Buschke Selective Reminding Test) can help identify verbal memory loss. Assessment of nonverbal memory is more difficult but may include recall of visual designs or a series of tones. Clinical findings usually suggest causes and any necessary tests.

Treatment

- Treatment directed at the cause

Any underlying disorder or psychologic cause must be treated. However, some patients with acute amnesia improve spontaneously. Certain disorders that cause amnesia (eg, Alzheimer's disease, Korsakoff's psychosis, herpes encephalitis) can be treated; however, treatment of the underlying disorder may or may not lessen the amnesia. If it does not, no specific measures can hasten recovery or improve the outcome.

Transient Global Amnesia

Transient global amnesia is disturbed memory typically caused by vascular or ischemic lesions in the brain. Diagnosis is primarily clinical but includes laboratory tests and CT, MRI, or both to evaluate central circulation. The amnesia typically remits spontaneously but may recur. There is no specific treatment, but underlying abnormalities are corrected.

Transient global amnesia is typically caused by ischemia (eg, due to atherosclerosis, thrombosis, or thromboembolism) that transiently affects the posteromedial thalamus or hippocampus bilaterally, but this amnesia can be caused by seizure activity or migraines.

A distinct benign form of transient global amnesia can follow excessive alcohol ingestion, moderately large sedative doses of barbiturates, use of several illicit drugs, or sometimes relatively small doses of benzodiazepines (especially midazolam and triazolam).

Symptoms and Signs

Patients present with acute global amnesic confusion that usually lasts 6 to 12 h but may last from 30 min to 24 h (rarely). Patients have a retrograde memory deficit that can extend back for several years; they are often disoriented to time and place but usually not to personal identity. Anterograde memory is less disturbed. Many patients are anxious or agitated and may repeatedly ask questions about transpiring events. Language function, attention, visual-spatial skills, and social skills are retained. Impairments gradually resolve as the episode subsides.

The benign transient amnesia after substance ingestion is distinct because it is selectively retrograde (ie, for events during and preceding intoxication), relates specifically to drug-accompanied events, does not cause confusion (once acute intoxication resolves), and recurs only if similar amounts of the same drug are ingested.

Diagnosis

• Primarily clinical evaluation

• Brain imaging

Diagnosis is primarily clinical. Neurologic examination typically does not detect any abnormalities other than disturbed memory. Brain ischemia must be ruled out (see p. 1648). Laboratory tests should include CBC, coagulation tests, and evaluation for hypercoagulable states. CT, MRI, or both, with or without angiographic protocols, are done. EEG usually shows nonspecific abnormalities and is unnecessary unless a seizure is suspected or episodes recur.

Prognosis

Prognosis is good. Symptoms typically last < 24 h. As the disorder resolves, the amnesia lessens, but memory for events during the attack may be lost. Usually, episodes do not recur, unless the cause is seizures or migraines. Overall lifetime recurrence rate is about 5 to 25%.

Treatment

No specific treatment is indicated. However, underlying ischemia (see p. 1649) or seizure (see p. 1692) should be treated.

Aphasia

Aphasia is language dysfunction that may involve impaired comprehension or expression of words or nonverbal equivalents of words. It results from dysfunction of the language centers in the cerebral cortex and basal ganglia or of the white matter pathways that connect them. Diagnosis is clinical, often including neuropsychologic testing, with brain imaging (CT, MRI) to identify cause. Prognosis depends on the cause and extent of damage and on patient age. There is no specific treatment, but speech therapy may promote recovery.

Language function resides predominantly in the following:

- Posterosuperior temporal lobe, which contains Wernicke's area
- Adjacent inferior parietal lobe
- Posteroinferior part of the frontal lobe just anterior to the motor cortex, which contains Broca's area
- Subcortical connection between those regions—usually in the left hemisphere, even in left-handed people

Damage to any part of this roughly triangular area (eg, by infarct, tumor, trauma, or degeneration) interferes with some aspect of language function. Prosody (quality of rhythm and emphasis that adds meaning to speech) is usually influenced by both hemispheres but is sometimes affected by dysfunction of the nondominant hemisphere alone.

Aphasia is distinct from developmental disorders of language and from dysfunction of the motor pathways and muscles that produce speech (dysarthria). It is broadly divided into receptive and expressive aphasia.

- **Receptive (sensory, fluent, or Wernicke's) aphasia:** Patients cannot comprehend words or recognize auditory, visual, or tactile symbols. It is caused by a disorder of the posterosuperior temporal gyrus of the language-dominant hemisphere (Wernicke's area). Often, alexia (loss of the ability to read words) is also present.

- **Expressive (motor, nonfluent, or Broca's) aphasia:** The ability to create words is impaired, but comprehension and ability to conceptualize are relatively preserved. It is due to a disorder that affects the dominant left frontal or frontoparietal area, including Broca's area. It often causes agraphia (loss of the ability to write) and impairs oral reading.

There are other types of aphasia (see Table 172-1), which may overlap considerably. No aphasia classification system is ideal. Describing the types of deficits is often the most precise way to describe a particular aphasia.

Symptoms and Signs

Wernicke's aphasia: Patients speak normal words fluently, often including meaningless phonemes, but do not know their meaning or relationships. The result is a jumble of words or "word salad." Patients are typically unaware that their speech is incomprehensible to others. A right visual field cut commonly accompanies Wernicke's aphasia because the visual pathway is near the affected area.

[**Table 172-1.** Types of Aphasia]

Broca's aphasia: Patients can comprehend and conceptualize relatively well, but their ability to form words is impaired. Usually, the impairment affects speech production and writing (agraphia, dysgraphia), greatly frustrating patients' attempts to communicate. Broca's aphasia may include anomia (inability to name objects) and impaired prosody.

Diagnosis

• Exclusion of other communication problems

• Bedside and neuropsychologic testing

• Brain imaging

Verbal interaction can typically identify gross aphasias. However, the clinician should try to differentiate aphasias from communication problems that stem from severe dysarthria, impaired hearing, vision (eg, when assessing reading), or motor writing ability.

Initially, Wernicke's aphasia may be mistaken for delirium. However, Wernicke's aphasia is a pure language disturbance without other features of delirium (eg, fluctuating level of consciousness, hallucinations, inattention).

Testing to identify specific deficits should include assessment of the following:

• **Spontaneous speech:** Speech is assessed for fluency, number of words spoken, ability to initiate speech, presence of spontaneous errors, word-finding pauses, hesitations, and prosody.

• **Naming:** Patients are asked to name objects. Those who have difficulty naming often use circumlocutions (eg, "what you use to tell time" for "clock").

• **Repetition:** Patients are asked to repeat grammatically complex phrases (eg, "no ifs, ands, or buts").

• **Comprehension:** Patients are asked to point to objects named by the clinician, carry out one-step and multistep commands, and answer simple and complex yes-or-no questions.

• **Reading and writing:** Patients are asked to write spontaneously and to read aloud. Reading comprehension, spelling, and writing in response to dictation are assessed.

Formal cognitive testing by a neuropsychologist or speech and language therapist may detect finer levels of dysfunction and assist in planning treatment and assessing potential for recovery. Various formal tests for diagnosing aphasia (eg, Boston Diagnostic Aphasia Examination, Western Aphasia Battery, Boston Naming Test, Token Test, Action Naming Test) are available.

Brain imaging (eg, CT, MRI; with or without angiographic protocols) is required to characterize the lesion (eg, infarct, hemorrhage, mass). Further tests are done to determine the etiology of the lesion (eg, stroke, seizure disorder) as indicated (see pp. 1648 and 1690).

Prognosis

Recovery is influenced by cause, size and location of lesions, extent of language impairment, and, to a lesser degree, the age, education, and general health of the patient. Children < 8 yr often regain language function after severe damage to either hemisphere. After that age, most recovery occurs within the first 3 mo, but improvement continues to a variable degree up to a year.

Treatment

• Speech therapy

• Augmentative communication devices

Effectiveness of treatment is unclear, but most clinicians think that treatment by qualified speech therapists helps and that patients treated soon after onset improve the most. Patients who cannot recover basic language skills and caregivers of such patients are sometimes able to convey messages with augmentative communication devices (eg, a book or communication board that contains pictures or symbols of a patient's daily needs, computer-based devices).

Apraxia

Apraxia is inability to execute purposeful, previously learned motor tasks, despite physical ability and willingness, as a result of brain damage. Diagnosis is clinical, often including neuropsychologic testing, with brain imaging (eg, CT, MRI) to identify cause. Prognosis depends on the cause and extent of damage and patient age. There is no specific treatment, but physical and occupational therapy may modestly improve functioning and patient safety.

Apraxia results from brain damage (eg, by infarct, tumor, or trauma) or degeneration, usually in the parietal lobes or their connections, which retain memories of learned movement patterns. Less commonly, apraxia results from damage to other areas of the brain, such as the premotor cortex (the part of the frontal lobe anterior to the motor cortex), other parts of the frontal lobe, or the corpus callosum, or from diffuse damage related to degenerative dementias.

Symptoms and Signs

Patients cannot conceptualize or do learned complex motor tasks despite an ability to do the individual component movements. For example, patients with constructional apraxia may be unable to copy a simple geometric shape despite being able to see and recognize the stimulus, hold and use a pen, and understand the task. Typically, patients do not recognize their deficits.

Diagnosis

• Bedside and neuropsychologic testing

• Brain imaging

Tests include asking patients to do or imitate common learned tasks (eg, saluting, stopping or starting to walk, combing hair, striking and blowing out a match, opening a lock with a key, using a screwdriver or scissors, taking a deep breath and holding it). Strength and range of motion must be assessed to exclude motor weakness and musculoskeletal abnormalities as the cause of symptoms. Neuropsychologic testing or assessment by a physical or occupational therapist may help identify more subtle apraxias.

Caregivers should be asked about the patient's ability to do activities of daily living, especially those that involve household tools (eg, correct and safe use of eating utensils, toothbrush, kitchen utensils to prepare a meal, hammer, and scissors) and writing.

Brain imaging (eg, CT, MRI; with or without angiographic protocols) is required to diagnose and characterize central lesions (eg, infarct, hemorrhage, mass, focal atrophy).

Prognosis

In general, patients become dependent, requiring help with activities of daily living and at least some degree of supervision. Patients with stroke may have a stable course and even improve somewhat.

Treatment

• Physical and occupational therapy

There is no specific medical treatment. Drugs that slow the symptomatic progression of dementia do not appear beneficial. Physical and occupational therapy may modestly improve functioning but is more often useful for making the environment safer and for providing devices that help patients circumvent the primary deficit.

Chapter 173. Stroke

Introduction

(Cerebrovascular Accident)

Strokes are a heterogeneous group of disorders involving sudden, focal interruption of cerebral blood flow that causes neurologic deficit. Strokes can be ischemic (80%), typically resulting from thrombosis or embolism, or hemorrhagic (20%), resulting from vascular rupture (eg, subarachnoid or intracerebral hemorrhage). Stroke symptoms lasting < 1 h are termed a transient ischemic attack (TIA). Strokes damage brain tissue; TIAs often do not, and when damage occurs, it is less extensive than that due to strokes. In Western countries, stroke is the 3rd most common cause of death and the most common cause of neurologic disability.

Strokes involve the arteries of the brain (see Fig. 173-1), either the anterior circulation (branches of the internal carotid artery) or the posterior circulation (branches of the vertebral and basilar arteries).

Risk factors: Risk factors include the following:

• Prior stroke

• Older age

• Family history of stroke

• Alcoholism

• Male sex

• Hypertension

• Cigarette smoking

• Hypercholesterolemia

• Diabetes

• Use of certain drugs (eg, cocaine, amphetamines)

Certain risk factors predispose to a particular type of stroke (eg, hypercoagulability predisposes to thrombotic stroke, atrial fibrillation to embolic stroke, and intracranial aneurysms to subarachnoid hemorrhage).

Symptoms and Signs

Initial symptoms occur suddenly. Generally, they include numbness, weakness, or paralysis of the contralateral limbs and the face; aphasia;

[**Fig. 173-1.** Arteries of the brain.]

confusion; visual disturbances in one or both eyes (eg, transient monocular blindness); dizziness or loss of balance and coordination; and headache.

Neurologic deficits reflect the area of brain involved (see Table 173-1). Anterior circulation stroke typically causes unilateral symptoms. Posterior circulation stroke can cause unilateral or bilateral deficits and is more likely to affect consciousness, especially when the basilar artery is involved.

Other manifestations, rather than neurologic deficits, often suggest the type of stroke. For example, sudden, severe headache suggests subarachnoid hemorrhage. Impaired consciousness or coma, often accompanied by headache, nausea, and vomiting, suggests increased intracranial pressure (see p. 1815), which can occur 48 to 72 h after large ischemic strokes and earlier with many hemorrhagic strokes; fatal brain herniation may result (see p. 1656).

Complications: Stroke complications can include sleep problems, confusion, depression, incontinence, atelectasis, pneumonia, and swallowing dysfunction, which can lead to aspiration, dehydration, or undernutrition. Immobility can lead to thromboembolic disease, deconditioning, sarcopenia, UTIs, pressure ulcers, and contractures. Daily functioning (including the ability to walk, see, feel, remember, think, and speak) may be decreased.

Evaluation

Evaluation aims to establish whether stroke has occurred, whether it is ischemic or hemorrhagic, and whether immediate treatment is required.

Stroke is suspected in patients with any of the following:

• Sudden neurologic deficits compatible with brain damage in an arterial territory

• A particularly sudden, severe headache

• Sudden, unexplained coma

• Sudden impairment of consciousness

If stroke is suspected, immediate neuroimaging is required to differentiate hemorrhagic from ischemic stroke and to detect signs of

[**Table 173-1.** Selected Stroke Syndromes]

increased intracranial pressure. CT is sensitive for intracranial blood but may be normal or show only subtle changes during the first hours of symptoms after anterior circulation ischemic stroke. CT also misses some small posterior circulation strokes and up to 3% of subarachnoid hemorrhages. MRI is sensitive for intracranial blood and may detect signs of ischemic stroke missed by CT, but CT can usually be done more rapidly. If CT does not confirm clinically suspected stroke, diffusion-weighted MRI can usually detect ischemic stroke (see p. 1648). If consciousness is impaired and lateralizing signs are absent or equivocal, further tests to check for other causes are done (see p. 1656).

After the stroke is identified as ischemic or hemorrhagic, tests are done to determine the cause. Patients are also evaluated for coexisting acute general disorders (eg, infection, dehydration, hypoxia, hyperglycemia, hypertension). Patients are asked about depression, which commonly occurs after stroke. A dysphagia team evaluates swallowing; sometimes a barium swallow study is necessary.

Treatment

• Stabilization

• Supportive measures and treatment of complications

Stabilization may need to precede complete evaluation. Comatose or obtunded patients (eg, Glasgow Coma Score ≤ 8) may require airway support (see p. 2279). If increased intracranial pressure is suspected, intracranial pressure monitoring (see p. 2246) and measures to reduce cerebral edema (see p. 3225) may be necessary. Specific acute treatments vary by type of stroke.

Providing supportive care, correcting coexisting abnormalities (eg, fever, hypoxia, dehydration,

hyperglycemia, sometimes hypertension), and preventing and treating complications are vital during the acute phase and convalescence (see Table 173-2); these measures clearly improve clinical outcomes. During convalescence, measures to prevent aspiration, deep venous thrombosis, UTIs, pressure ulcers, and undernutrition may be necessary. Passive exercises, particularly of paralyzed limbs, and breathing exercises are started early to prevent contractures, atelectasis, and pneumonia. Most patients require occupational and physical therapy (see p. 3462) to maximize functional recovery. Some need additional therapies (eg, speech therapy, feeding restrictions). Depression after stroke may require antidepressants; many patients benefit from counseling. For rehabilitation, an interdisciplinary approach is best. Modifying risk factors through lifestyle changes (eg, stopping cigarette smoking) and drug therapy (eg, for hypertension) can help delay or prevent subsequent strokes.

[**Table 173-2.** Strategies to Prevent and Treat Stroke Complications]

Ischemic Stroke

Ischemic stroke is sudden neurologic deficits that result from focal cerebral ischemia associated with permanent brain infarction (eg, positive diffusion-weighted MRI). Common causes are (from most to least common) nonthrombotic occlusion of small, deep cortical arteries (lacunar infarction); cardiogenic embolism; arterial thrombosis that decreases cerebral blood flow; and artery-to-artery embolism. Diagnosis is clinical, but CT or MRI is done to exclude hemorrhage and confirm the presence and extent of stroke. Thrombolytic therapy may be useful acutely in certain patients. Depending on the cause of stroke, carotid endarterectomy, antiplatelet drugs, or warfarin may help reduce risk of subsequent strokes.

Etiology

Ischemia usually results from thrombi or emboli. Even infarcts classified as lacunar based on clinical criteria (morphology, size, and location) often involve small thrombi or emboli.

Thrombosis: Atheromas, particularly if ulcerated, predispose to thrombi. Atheromas can occur in any major cerebral artery and are common at areas of turbulent flow, particularly at the carotid bifurcation. Partial or complete thrombotic occlusion occurs most often at the main trunk of the middle cerebral artery and its branches but is also common in the large arteries at the base of the brain, in deep perforating arteries, and in small cortical branches. The basilar artery and the segment of the internal carotid artery between the cavernous sinus and supraclinoid process are often occluded.

Less common causes of thrombosis include vascular inflammation secondary to disorders such as acute or chronic meningitis, vasculitic disorders, and syphilis; dissection of intracranial arteries or the aorta; hypercoagulability disorders (eg, antiphospholipid syndrome, hyperhomocysteinemia); hyperviscosity disorders (eg, polycythemia, thrombocytosis, hemoglobinopathies, plasma cell disorders); and rare disorders (eg, moyamoya disease, Binswanger's disease). Older oral contraceptive formulations increase risk of thrombosis.

Embolism: Emboli may lodge anywhere in the cerebral arterial tree. Emboli may originate as cardiac thrombi, especially in the following conditions:

- Atrial fibrillation
- Rheumatic heart disease (usually mitral stenosis)
- Post-MI
- Vegetations on heart valves in bacterial or marantic endocarditis
- Prosthetic heart valves

Other sources include clots that form after open-heart surgery and atheromas in neck arteries or in the

aortic arch. Rarely, emboli consist of fat (from fractured long bones), air (in decompression sickness), or venous clots that pass from the right to the left side of the heart through a patent foramen ovale with shunt (paradoxical emboli). Emboli may dislodge spontaneously or after invasive cardiovascular procedures (eg, catheterization). Rarely, thrombosis of the subclavian artery results in embolic stroke in the vertebral artery or its branches.

Lacunar infarcts: Ischemic stroke can also result from lacunar infarcts. These small (≤ 1.5 cm) infarcts result from nonatherothrombotic obstruction of small, perforating arteries that supply deep cortical structures; the usual cause is lipohyalinosis (degeneration of the media of small arteries and replacement by lipids and collagen). Whether emboli cause lacunar infarcts is controversial. Lacunar infarcts tend to occur in elderly patients with diabetes or poorly controlled hypertension.

Other causes: Less commonly, ischemic stroke results from vasospasm (eg, during migraine, after subarachnoid hemorrhage, after use of sympathomimetic drugs such as cocaine or amphetamines) or venous sinus thrombosis (eg, during intracranial infection, postoperatively, peripartum, secondary to a hypercoagulation disorder).

Pathophysiology

Inadequate blood flow in a single brain artery can often be compensated for by an efficient collateral system, particularly between the carotid and vertebral arteries via anastomoses at the circle of Willis and, to a lesser extent, between major arteries supplying the cerebral hemispheres. However, normal variations in the circle of Willis and in the caliber of various collateral vessels, atherosclerosis, and other acquired arterial lesions can interfere with collateral flow, increasing the chance that blockage of one artery will cause brain ischemia.

Some neurons die when perfusion is < 5% of normal for > 5 min; however, the extent of damage depends on the severity of ischemia. If it is mild, damage proceeds slowly; thus, even if perfusion is 40% of normal, 3 to 6 h may elapse before brain tissue is completely lost. However, if severe ischemia (ie, decrease in perfusion) persists > 15 to 30 min, all of the affected tissue dies (infarction). Damage occurs more rapidly during hyperthermia and more slowly during hypothermia. If tissues are ischemic but not yet irreversibly damaged, promptly restoring blood flow may reduce or reverse injury. For example, intervention may be able to salvage the moderately ischemic areas (penumbras) that often surround areas of severe ischemia (these areas exist because of collateral flow).

Mechanisms of ischemic injury include edema, microvascular thrombosis, programmed cell death (apoptosis), and infarction with cell necrosis. Inflammatory mediators (eg, IL-1B, tumor necrosis factor-α) contribute to edema and microvascular thrombosis. Edema, if severe or extensive, can increase intracranial pressure. Many factors may contribute to necrotic cell death; they include loss of ATP stores, loss of ionic homeostasis (including intracellular Ca accumulation), lipid peroxidative damage to cell membranes by free radicals (an iron-mediated process), excitatory neurotoxins (eg, glutamate), and intracellular acidosis due to accumulation of lactate.

Symptoms and Signs

Symptoms and signs depend on the part of brain affected. Patterns of neurologic deficits often suggest the affected artery (see Table 173-1), but correlation is often inexact.

Deficits may become maximal within several minutes of onset, typically in embolic stroke. Less often, deficits evolve slowly, usually over 24 to 48 h (called evolving stroke or stroke in evolution), typically in thrombotic stroke. In most evolving strokes, unilateral neurologic dysfunction (often beginning in one arm, then spreading ipsilaterally) extends without causing headache, pain, or fever. Progression is usually stepwise, interrupted by periods of stability. A stroke is considered submaximal when, after it is complete, there is residual function in the affected area, suggesting viable tissue at risk of damage.

Embolic strokes often occur during the day; headache may precede neurologic deficits. Thrombi tend to occur during the night and thus are first noticed on awakening. Lacunar infarcts may produce one of the classic lacunar syndromes (eg, pure motor hemiparesis, pure sensory hemianesthesia, ataxic

hemiparesis, dysarthria-clumsy hand syndrome); signs of cortical dysfunction (eg, aphasia) are absent. Multiple lacunar infarcts may result in multi-infarct dementia.

Deterioration during the first 48 to 72 h after onset of symptoms, particularly progressively impaired consciousness, results more often from cerebral edema than from extension of the infarct. Unless the infarct is large or extensive, function commonly improves within the first few days; further improvement occurs gradually for up to 1 yr.

Diagnosis

• Primarily clinical evaluation

• Neuroimaging and bedside glucose testing

• Evaluation to identify the cause

Diagnosis is suggested by sudden neurologic deficits referable to a specific arterial territory. Ischemic stroke must be distinguished from other causes of similar focal deficits (eg, hypoglycemia; postictal [Todd's] paralysis; hemorrhagic stroke; rarely, migraine). Headache, coma or stupor, and vomiting are more likely with hemorrhagic stroke.

Although diagnosis is clinical, neuroimaging and bedside glucose testing are mandatory. CT is done first to exclude intracerebral hemorrhage, subdural or epidural hematoma, and a rapidly growing, bleeding, or suddenly symptomatic tumor. CT evidence of even large anterior circulation ischemic stroke may be subtle during the first few hours; changes may include effacement of sulci or the insular cortical ribbon, loss of the gray-white junction between cortex and white matter, and a dense middle cerebral artery sign. After 24 h of ischemia, medium-sized to large infarcts are usually visible as hypodensities; small infarcts (eg, lacunar infarcts) may be visible only with MRI. Diffusion-weighted MRI (highly sensitive for early ischemia) can be done immediately after CT initial neuroimaging.

Distinction between lacunar, embolic, and thrombotic stroke based on history, examination, and neuroimaging is not always reliable, so tests to identify common or treatable causes and risk factors for all of these types of strokes are routinely done. These tests typically include carotid duplex ultrasonography, ECG, transesophageal echocardiography, and various blood tests (CBC, platelet count, PT/PTT, fasting blood glucose, lipid profile, homocysteine, ESR, and, for at-risk patients, syphilis serology). Troponin I level is measured to detect concomitant MI. Magnetic resonance or CT angiography is also often done. Other tests (eg, antiphospholipid antibodies) are done if certain disorders are suspected clinically.

Prognosis

Stroke severity and progression are often assessed using standardized measures such as the National Institutes of Health Stroke Scale (see Table 173-3); the score on this scale correlates with extent of functional impairment and prognosis. During the first days, progression and outcome can be difficult to predict. Older age, impaired consciousness, aphasia, and brain stem signs suggest a poor prognosis. Early improvement and younger age suggest a favorable prognosis.

About 50% of patients with moderate or severe hemiplegia and most with milder deficits have a clear sensorium and eventually can take care of their basic needs and walk

[**Table 173-3.** The National Institutes of Health Stroke Scale*]

adequately. Complete neurologic recovery occurs in about 10%. Use of the affected limb is usually limited, and most deficits that remain after 12 mo are permanent. Subsequent strokes often occur, and each tends to worsen neurologic function. About 20% of patients die in the hospital; mortality rate increases with age.

Treatment

• General stroke treatments

• Acute antihypertensive therapy only in certain circumstances

• Antiplatelet therapy

• Occasionally for acute treatment, tPA or thrombolysis-in-situ

• Sometimes anticoagulation

• Long-term control of risk factors

• Sometimes carotid endarterectomy

Acute: Guidelines for early management of stroke are available from the Stroke Council of the American Heart Association/American Stroke Association. Patients with acute ischemic strokes are usually hospitalized. Supportive measures (see p. 1646) may be needed during initial evaluation and stabilization.

Perfusion of an ischemic brain area may require a high BP because autoregulation is lost; thus, BP should not be decreased except in the following situations:

• BP is > 220 mm Hg systolic or > 120 mm Hg diastolic on 2 successive readings > 15 min apart.

• There are signs of other end-organ damage (eg, aortic dissection, acute MI, pulmonary edema, hypertensive encephalopathy, retinal hemorrhages, acute renal failure).

• Use of recombinant tissue plasminogen activator (tPA) is likely.

If indicated, nicardipine 2.5 mg/h IV is given initially; dose is increased by 2.5 mg/h q 5 min to a maximum of 15 mg/h as needed to decrease systolic BP by 10 to 15%. Alternatively, IV labetalol can be used.

Patients with presumed thrombi or emboli may be treated with tPA, thrombolysis-in-situ, antiplatelet drugs, and/or anticoagulants. Most patients are not candidates for thrombolytic therapy; they should be given an antiplatelet drug (usually aspirin 325 mg po) when they are admitted to the hospital. Contraindications to antiplatelet drugs include aspirin-or NSAID-induced asthma or urticaria, other hypersensitivity to aspirin or to tartrazine, acute GI bleeding, G6PD deficiency, and use of warfarin.

Recombinant tPA is used for patients with acute ischemic stroke of < 3 h duration and no contraindications to tPA (see Table 174-4). Although tPA can cause fatal or other symptomatic brain hemorrhage, patients treated with tPA strictly following protocol have a higher likelihood of functional neurologic recovery. Thus, only physicians experienced in stroke management should use tPA to treat patients with acute stroke; inexperienced physicians are more likely to violate protocols, resulting in more brain hemorrhages and deaths. tPA must be given within 3 h of symptom onset—a difficult requirement. Because the precise time of symptom onset may not be known, clinicians must start timing from the moment the patient was last observed to be well. Before treatment with tPA, brain hemorrhage must be excluded by CT, and systolic BP must be <185 mm Hg and diastolic BP <110 mm Hg; antihypertensive drugs may be given as above. Dose of tPA is 0.9 mg/kg IV (maximum dose 90 mg); 10% is given by rapid IV injection, and the remainder by constant infusion over 60 min. Vital signs are closely monitored for 24 h after treatment, and BP is maintained below the target levels listed above. Any bleeding complications are aggressively managed. Anticoagulants and antiplatelet drugs are not used within 24 h of treatment with tPA.

[**Table 173-4.** Exclusion Criteria for Use of Tissue Plasminogen Activator in Stroke*]

Thrombolysis-in-situ (angiographically directed intra-arterial thrombolysis) of a thrombus or embolus can sometimes be used for major strokes if symptoms have begun > 3 h but < 6 h ago, particularly for

strokes due to large occlusions in the middle cerebral artery. Clots in the basilar artery may be intra-arterially lysed up to 12 h after stroke onset, sometimes even later depending on the clinical circumstances. This treatment, although standard of care in some large stroke centers, is often unavailable in other hospitals.

Anticoagulation with heparin or low molecular weight heparin is used for stroke caused by cerebral venous thrombosis and is sometimes used for emboli due to atrial fibrillation and when stroke due to presumed progressive thrombosis continues to evolve despite use of antiplatelet drugs and cannot be treated any other way (eg, with tPA or invasive methods). Warfarin is begun simultaneously with heparin. Before anticoagulation, hemorrhage must be excluded by CT. Constant weight-based heparin infusion (see
Fig. 194-2 on p. 1916) is used to increase PTT to 1.5 to 2 times baseline values until warfarin has increased the INR to 2 to 3 (3 in hypercoagulable disorders). Because warfarin predisposes to bleeding and is continued after hospital discharge, its use should be restricted to patients likely to comply with dosage and monitoring requirements and not prone to falls.

Long term: Supportive care is continued during convalescence. Controlling general medical risk factors (especially hyperglycemia and fever) can limit brain damage after stroke, leading to better functional outcomes.

Carotid endarterectomy is indicated for patients with recent nondisabling, submaximal stroke attributed to an ipsilateral carotid obstruction of 70 to 99% of the arterial lumen or to an ulcerated plaque if life expectancy is at least 5 yr. In other symptomatic patients (eg, patients with TIAs), endarterectomy with antiplatelet therapy is indicated for carotid obstruction of ≥ 60% with or without ulceration if life expectancy is at least 5 yr. The procedure should be done by surgeons who have a morbidity and mortality rate of < 3% with the procedure in the hospital where it will be done. If carotid stenosis is asymptomatic, endarterectomy is beneficial only when done by very experienced surgeons, and that benefit is likely to be small. For many patients, carotid stenting with an emboli-protection device (a type of filter) is as effective as surgery.

Oral antiplatelet drugs are used to prevent subsequent strokes (secondary prevention). Aspirin 81 or 325 mg once/day, clopidogrel 75 mg once/day, or the combination product aspirin 25 mg/extended-release dipyridamole 200 mg bid may be used. In patients taking warfarin, antiplatelet drugs additively increase risk of bleeding and are thus usually avoided; however, aspirin is occasionally used simultaneously with warfarin in certain high-risk patients. The combination of clopidogrel and aspirin is avoided because it has no advantage over aspirin alone in secondary stroke prevention and results in more bleeding complications.

Transient Ischemic Attack

A transient ischemic attack (TIA) is focal brain ischemia that causes sudden neurologic deficits and is not associated with permanent brain infarction (eg, negative results on diffusion-weighted MRI). Diagnosis is clinical. Carotid endarterectomy, antiplatelet drugs, and warfarin decrease risk of stroke after certain types of TIA.

TIA is similar to ischemic stroke except that symptoms last < 1 h; most TIAs last < 5 min. Infarction is very unlikely if deficits resolve within 1 h. Deficits that resolve spontaneously within 1 to 24 h have been shown on diffusion-weighted MRI and other studies to often be accompanied by infarction and are thus no longer considered TIAs. TIAs are most common among the middle-aged and elderly. TIAs markedly increase risk of stroke, beginning in the first 24 h.

Etiology

Most TIAs are caused by emboli, usually from carotid or vertebral arteries, although most of the causes of ischemic stroke (see p. 1647) can also result in TIAs. Uncommonly, TIAs result from impaired perfusion due to severe hypoxemia, reduced O_2-carrying capacity of blood (eg, profound anemia, carbon monoxide poisoning), or increased blood viscosity (eg, severe polycythemia), particularly in brain arteries with preexisting stenosis. Systemic hypotension does not usually cause cerebral ischemia unless it is severe

or arterial stenosis preexists because autoregulation maintains brain blood flow at near-normal levels over a wide range of systemic BPs.

In subclavian steal syndrome, a subclavian artery stenosed proximal to the origin of the vertebral artery "steals" blood from the vertebral artery (in which blood flow reverses) to supply the arm during exertion, causing signs of vertebrobasilar ischemia.

Occasionally, TIAs occur in children with a severe cardiovascular disorder that produces emboli or a very high Hct.

Symptoms and Signs

Neurologic deficits are similar to those of strokes (see Table 173-1). Transient monocular blindness (amaurosis fugax), which usually lasts < 5 min, may occur when the ophthalmic artery is affected. Symptoms begin suddenly, usually last 2 to 30 min, then resolve completely. Patients may have several TIAs daily or only 2 or 3 over several years. Symptoms are usually similar in successive carotid attacks but vary somewhat in successive vertebrobasilar attacks.

Diagnosis

• Resolution of stroke-like symptoms within 1 h

• Neuroimaging

• Evaluation to identify the cause

Diagnosis is made retrospectively when sudden neurologic deficits referable to ischemia in an arterial territory resolve within 1 h. Isolated peripheral facial nerve palsy, loss of consciousness, or impaired consciousness does not suggest TIA. TIAs must be distinguished from other causes of similar symptoms (eg, hypoglycemia, migraine aura, postictal [Todd's] paralysis). Because an infarct, a small hemorrhage, and even a mass lesion cannot be excluded clinically, neuroimaging is required. Usually, CT is the study most likely to be immediately available. However, CT may not identify infarcts for > 24 h. MRI usually detects evolving infarction within hours. Diffusion-weighted MRI is the most accurate imaging test to rule out an infarct in patients with presumed TIA but is not always available.

The cause of a TIA is sought as for that of ischemic strokes, including tests for carotid stenosis, cardiac sources of emboli, atrial fibrillation, and hematologic abnormalities and screening for stroke risk factors. Because risk of subsequent ischemic stroke is high and immediate, evaluation proceeds rapidly, usually on an inpatient basis. It is not clear which patients, if any, can be safely discharged from the emergency department.

Treatment

• Prevention of strokes

Treatment is aimed at preventing strokes; antiplatelet drugs are used (see p. 1651). Carotid endarterectomy or arterial angioplasty plus stenting can be useful for some patients, particularly those who have no neurologic deficits but who are at high risk of stroke. Warfarin is indicated if cardiac sources of emboli are present. Modifying stroke risk factors, when possible, may prevent stroke.

Intracerebral Hemorrhage

Intracerebral hemorrhage is focal bleeding from a blood vessel in the brain parenchyma. The cause is usually hypertension. Typical symptoms include focal neurologic deficits, often with abrupt onset of headache, nausea, and impairment of consciousness. Diagnosis is by CT or MRI. Treatment includes BP control, supportive measures, and, for some patients, surgical evacuation.

Most intracerebral hemorrhages occur in the basal ganglia, cerebral lobes, cerebellum, or pons. Intracerebral hemorrhage may also occur in other parts of the brain stem or in the midbrain.

Etiology

Intracerebral hemorrhage usually results from rupture of an arteriosclerotic small artery that has been weakened, primarily by chronic arterial hypertension. Such hemorrhages are usually large, single, and catastrophic. Use of cocaine or, occasionally, other sympathomimetic drugs can cause transient severe hypertension leading to hemorrhage. Less often, intracerebral hemorrhage results from congenital aneurysm, arteriovenous or other vascular malformation (see Sidebar 173-1), trauma (see p. 3220), mycotic aneurysm, brain infarct (hemorrhagic infarction), primary or metastatic brain tumor, excessive anticoagulation, blood dyscrasia, or a bleeding or vasculitic disorder.

Lobar intracerebral hemorrhages (hematomas in the cerebral lobes, outside the basal ganglia) usually result from angiopathy due to amyloid deposition in cerebral arteries (cerebral amyloid angiopathy), which affects primarily the elderly. Lobar hemorrhages may be multiple and recurrent.

Pathophysiology

Blood from an intracerebral hemorrhage accumulates as a mass that can dissect through and compress adjacent brain tissues, causing neuronal dysfunction. Large hematomas increase intracranial pressure. Pressure from supratentorial hematomas and the accompanying edema may cause transtentorial brain herniation (see Fig. 174-1 on p. 1657), compressing the brain stem and often causing secondary hemorrhages in the midbrain and pons. If the hemorrhage ruptures into the ventricular system (intraventricular hemorrhage), blood may cause acute hydrocephalus. Cerebellar hematomas can expand to block the 4th ventricle, also causing acute hydrocephalus, or they can dissect into the brain stem. Cerebellar hematomas that are > 3 cm in diameter may cause midline shift or herniation. Herniation, midbrain or pontine hemorrhage, intraventricular hemorrhage, acute hydrocephalus, or dissection into the brain stem can impair consciousness and cause coma and death.

Symptoms and Signs

Symptoms typically begin with sudden headache, often during activity. However, headache may be mild or absent in the elderly. Loss of consciousness is common, often within seconds or a few minutes. Nausea, vomiting, delirium, and focal or generalized seizures are also common. Neurologic deficits are usually sudden and progressive. Large hemorrhages, when located in the hemispheres, cause hemiparesis; when located in the posterior fossa, they cause cerebellar or brain stem deficits (eg, conjugate eye deviation or ophthalmoplegia, stertorous breathing, pinpoint pupils, coma). Large hemorrhages are fatal within a few days in about one half of patients. In survivors, consciousness returns and neurologic deficits gradually diminish to various degrees as the extravasated blood is resorbed. Some patients have surprisingly few neurologic deficits because hemorrhage is less destructive to brain tissue than infarction.

Sidebar 173-1 Vascular Lesions in the Brain

Common brain vascular lesions include arteriovenous malformations and aneurysms.

Arteriovenous malformations (AVMs): AVMs are tangled, dilated blood vessels in which arteries flow directly into veins. AVMs occur most often at the junction of cerebral arteries, usually within the parenchyma of the frontal-parietal region, frontal lobe, lateral cerebellum, or overlying occipital lobe. AVMs can bleed or directly compress brain tissue; seizures or ischemia may result.

Neuroimaging may detect them incidentally; contrast or noncontrast CT can usually detect AVMs > 1 cm, but the diagnosis is confirmed with MRI. Occasionally, a cranial bruit suggests an AVM. Conventional angiography is required for definitive diagnosis and determination of whether the lesion is operable.

Superficial AVMs > 3 cm in diameter are usually obliterated by a combination of microsurgery,

radiosurgery, and endovascular surgery. AVMs that are deep or < 3 cm in diameter are treated with stereotactic radiosurgery, endovascular therapy (eg, preresection embolization or thrombosis via an intra-arterial catheter), or coagulation with focused proton beams.

Aneurysms: Aneurysms are focal dilations in arteries. They occur in about 5% of people. Common contributing factors may include arteriosclerosis, hypertension, and hereditary connective tissue disorders (eg, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, autosomal dominant polycystic kidney syndrome). Occasionally, septic emboli cause mycotic aneurysms. Brain aneurysms are most often < 2.5 cm in diameter and saccular (noncircumferential); sometimes they have one or more small, thin-walled, outpouchings (berry aneurysm). Most aneurysms occur along the middle or anterior cerebral arteries or the communicating branches of the circle of Willis, particularly at arterial bifurcations. Mycotic aneurysms usually develop distal to the first bifurcation of the arterial branches of the circle of Willis.

Many aneurysms are asymptomatic, but a few cause symptoms by compressing adjacent structures. Ocular palsies, diplopia, squint, or orbital pain may indicate pressure on the 3rd, 4th, 5th, or 6th cranial nerves. Visual loss and a bitemporal field defect may indicate pressure on the optic chiasm. Aneurysms may bleed into the subarachnoid space, causing subarachnoid hemorrhage. Aneurysms occasionally cause sentinel (warning) headaches before rupture; subarachnoid bleeding may accompany sentinel headaches. Rupture causes a sudden severe headache called a thunderclap headache.

Neuroimaging may detect aneurysms incidentally.

Diagnosis requires angiography, CT angiography, or magnetic resonance angiography.

If < 7 mm, asymptomatic aneurysms in the anterior circulation rarely rupture and do not warrant the risks of immediate treatment. They can be monitored with serial imaging. If aneurysms are larger, are in the posterior circulation, or cause symptoms due to bleeding or to compression of neural structures, endovascular therapy, if feasible, is required.

Small hemorrhages may cause focal deficits without impairment of consciousness and with minimal or no headache and nausea. Small hemorrhages may mimic ischemic stroke.

Diagnosis

• Neuroimaging

• Bedside glucose measurement

Diagnosis is suggested by sudden onset of headache, focal neurologic deficits, and impaired consciousness, particularly in patients with risk factors. Intracerebral hemorrhage must be distinguished from ischemic stroke, subarachnoid hemorrhage, and other causes of acute neurologic deficits (eg, seizure, hypoglycemia).

Immediate CT or MRI and bedside blood glucose measurement are necessary. Neuroimaging is usually diagnostic. If neuroimaging shows no hemorrhage but subarachnoid hemorrhage is suspected clinically, lumbar puncture is necessary.

Treatment

• Supportive measures

• Sometimes surgical evacuation (eg, for many cerebellar hematomas > 3 cm)

Treatment includes supportive measures and control of general medical risk factors. Anticoagulants and antiplatelet drugs are contraindicated. If patients have used anticoagulants, the effects are reversed when possible by giving fresh frozen plasma, vitamin K, or platelet transfusions as indicated. Hypertension should be treated only if mean arterial pressure is > 130 mm Hg or systolic BP is > 185 mm Hg.

Nicardipine 2.5 mg/h IV is given initially; dose is increased by 2.5 mg/h q 5 min to a maximum of 15 mg/h as needed to decrease systolic BP by 10 to 15%.

Cerebellar hemisphere hematomas that are > 3 cm in diameter may cause midline shift or herniation, so surgical evacuation is often lifesaving. Early evacuation of large lobar cerebral hematomas may also be lifesaving, but rebleeding occurs frequently, sometimes increasing neurologic deficits. Early evacuation of deep cerebral hematomas is seldom indicated because surgical mortality is high and neurologic deficits are usually severe.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage is sudden bleeding into the subarachnoid space. The most common cause of spontaneous bleeding is a ruptured aneurysm. Symptoms include sudden, severe headache, usually with loss or impairment of consciousness. Secondary vasospasm (causing focal brain ischemia), meningismus, and hydrocephalus (causing persistent headache and obtundation) are common. Diagnosis is by CT or MRI; if neuroimaging is normal, diagnosis is by CSF analysis. Treatment is with supportive measures and neurosurgery or endovascular measures, preferably in a referral center.

Etiology

Subarachnoid hemorrhage is bleeding between the arachnoid and pia mater. In general, head trauma is the most common cause, but traumatic subarachnoid hemorrhage is usually considered a separate disorder (see p. 3218). Spontaneous (primary) subarachnoid hemorrhage usually results from ruptured aneurysms. A congenital intracranial saccular or berry aneurysm is the cause in about 85% of patients. Bleeding may stop spontaneously. Aneurysmal hemorrhage may occur at any age but is most common from age 40 to 65. Less common causes are mycotic aneurysms, arteriovenous malformations, and bleeding disorders.

Pathophysiology

Blood in the subarachnoid space causes a chemical meningitis that commonly increases intracranial pressure for days or a few weeks. Secondary vasospasm may cause focal brain ischemia; about 25% of patients develop signs of a transient ischemic attack (TIA) or ischemic stroke. Brain edema is maximal and risk of vasospasm and subsequent infarction (called angry brain) is highest between 72 h and 10 days. Secondary acute hydrocephalus is also common. A 2nd rupture (rebleeding) sometimes occurs, most often within about 7 days.

Symptoms and Signs

Headache is usually severe, peaking within seconds. Loss of consciousness may follow, usually immediately but sometimes not for several hours. Severe neurologic deficits may develop and become irreversible within minutes or a few hours. Sensorium may be impaired, and patients may become restless. Seizures are possible. Usually, the neck is not stiff initially unless the cerebellar tonsils herniate. However, within 24 h, chemical meningitis causes moderate to marked meningismus, vomiting, and sometimes bilateral extensor plantar responses. Heart or respiratory rate is often abnormal. Fever, continued headaches, and confusion are common during the first 5 to 10 days. Secondary hydrocephalus may cause headache, obtundation, and motor deficits that persist for weeks. Rebleeding may cause recurrent or new symptoms.

Diagnosis

• Usually noncontrast CT and, if negative, lumbar puncture

Diagnosis is suggested by characteristic symptoms. Testing should proceed as rapidly as possible, before damage becomes irreversible. Noncontrast CT is > 90% sensitive. MRI is comparably sensitive but less likely to be immediately available. False-negative results occur if volume of blood is small. If subarachnoid hemorrhage is suspected clinically but not identified on neuroimaging or if neuroimaging is not

immediately available, lumbar puncture is done. Lumbar puncture is contraindicated if increased intracranial pressure is suspected because the sudden decrease in CSF pressure may lessen the tamponade of a clot on the ruptured aneurysm, causing further bleeding.

CSF findings suggesting subarachnoid hemorrhage include numerous RBCs, xanthochromia, and increased pressure. RBCs in CSF may also be caused by traumatic lumbar puncture. Traumatic lumbar puncture is suspected if the RBC count decreases in tubes of CSF drawn sequentially during the same lumbar puncture. About 6 h or more after a subarachnoid hemorrhage, RBCs become crenated and lyse, resulting in a xanthochromic CSF supernatant and visible crenated RBCs (noted during microscopic CSF examination); these findings usually indicate that subarachnoid hemorrhage preceded the lumbar puncture. If there is still doubt, hemorrhage should be assumed, or the lumbar puncture should be repeated in 8 to 12 h.

In patients with subarachnoid hemorrhage, conventional cerebral angiography is done as soon as possible after the initial bleeding episode; alternatives include magnetic resonance angiography and CT angiography. All 4 arteries (2 carotid and 2 vertebral arteries) should be injected because up to 20% of patients (mostly women) have multiple aneurysms.

On ECG, subarachnoid hemorrhage may cause ST-segment elevation or depression. It can cause syncope, mimicking MI. Other possible ECG abnormalities include prolongation of the QRS or QT intervals and peaking or deep, symmetric inversion of T waves.

Prognosis

About 35% of patients die after the first aneurysmal subarachnoid hemorrhage; another 15% die within a few weeks because of a subsequent rupture. After 6 mo, a 2nd rupture occurs at a rate of about 3%/yr. In general, prognosis is grave with an aneurysm, better with an arteriovenous malformation, and best when 4-vessel angiography does not detect a lesion, presumably because the bleeding source is small and has sealed itself. Among survivors, neurologic damage is common, even when treatment is optimal.

Treatment

• Treatment in referral center

• Nicardipine if mean arterial pressure is > 130 mm Hg

• Nimodipine to prevent vasospasm

• Occlusion of causative aneurysms

Patients with subarachnoid hemorrhage should be treated in referral centers whenever possible.

Hypertension should be treated only if mean arterial pressure is > 130 mm Hg; euvolemia is maintained, and IV nicardipine is titrated as for intracerebral hemorrhage (see p. 1652). Bed rest is mandatory. Restlessness and headache are treated symptomatically. Stool softeners are given to prevent constipation, which can lead to straining. Anticoagulants and antiplatelet drugs are contraindicated.

Vasospasm is prevented by giving nimodipine 60 mg po q 4 h for 21 days to prevent vasospasm, but BP needs to be maintained in the desirable range (usually considered to be a mean arterial pressure of 70 to 130 mm Hg and a systolic pressure of 120 to 185 mm Hg). If clinical signs of acute hydrocephalus occur, ventricular drainage should be considered.

Aneurysms are occluded to reduce risk of rebleeding. Detachable endovascular coils can be inserted during angiography to occlude the aneurysm. Alternatively, if the aneurysm is accessible, surgery to clip the aneurysm or bypass its blood flow can be done, especially for patients with an evacuable hematoma or acute hydrocephalus. If patients are arousable, most vascular neurosurgeons operate within the first 24 h to minimize risk of rebleeding and risks due to angry brain. If > 24 h have elapsed, some neurosurgeons delay surgery until 10 days have passed; this approach decreases risks due to angry

brain but increases risk of rebleeding and overall mortality.

Chapter 174. Coma and Impaired Consciousness

Introduction

Coma is unresponsiveness from which the patient cannot be aroused. Similar, but less severe disturbances of consciousness may also occur. The mechanism involves dysfunction of both cerebral hemispheres or of the reticular activating system (also known as the ascending arousal system). Causes may be structural or nonstructural (eg, toxic or metabolic disturbances). Damage may be focal or diffuse. Diagnosis is clinical; identification of cause usually requires laboratory tests and neuroimaging. Treatment is immediate stabilization and specific management of the cause. For long-term coma, adjunctive treatment includes passive range-of-motion exercises, enteral feedings, and measures to prevent pressure ulcers.

Decreased or impaired consciousness or alertness refers to decreased responsiveness to external stimuli. Severe impairment includes

- **Coma:** The patient usually cannot be aroused, and the eyes do not open in response to any stimulation.

- **Stupor:** The patient can be awakened only by vigorous physical stimulation.

Less severely impaired levels of consciousness are often labeled as lethargy or, if more severe, obtundation. However, differentiation between less severely impaired levels is often imprecise; the label is less important than a precise clinical description (eg, "the best level of response is partial limb withdrawal to nail bed pressure"). Delirium differs because cognitive disturbances (in attention, cognition, and level of consciousness) fluctuate more; also, delirium is usually reversible (see p. 1669).

Pathophysiology

Maintaining alertness requires intact function of the cerebral hemispheres and preservation of arousal mechanisms in the reticular activating system (RAS—also known as the ascending arousal system)—an extensive network of nuclei and interconnecting fibers in the upper pons, midbrain, and posterior diencephalon. Therefore, the mechanism of impaired consciousness must involve both cerebral hemispheres or dysfunction of the RAS.

To impair consciousness, cerebral dysfunction must be bilateral; unilateral cerebral hemisphere disorders are not sufficient, although they may cause severe neurologic deficits. However, rarely, a unilateral massive hemispheric focal lesion (eg, left middle cerebral artery stroke) impairs consciousness if the contralateral hemisphere is already compromised.

Usually, RAS dysfunction results from a condition that has diffuse effects, such as toxic or metabolic disturbances (eg, hypoglycemia, hypoxia, uremia, drug overdose). RAS dysfunction can also be caused by focal ischemia (eg, certain upper brain stem infarcts), hemorrhage, or direct, mechanical disruption.

Any condition that increases intracranial pressure may decrease cerebral perfusion pressure, resulting in secondary brain ischemia. Secondary brain ischemia may affect the RAS or both cerebral hemispheres, impairing consciousness.

When brain damage is extensive, brain herniation (see Fig. 174-1 and Table 174-1) contributes to neurologic deterioration because it directly compresses brain tissue, increases intracranial pressure, and may lead to hydrocephalus.

Impaired consciousness may progress to coma and ultimately to brain death (see p. 1667).

Etiology

Coma or impaired consciousness may result from structural disorders, which typically cause focal

damage, or nonstructural disorders, which typically cause diffuse damage (see Table 174-2). But causes are usually thought of as structural or diffuse.

Psychiatric disorders (eg, psychogenic unresponsiveness) can mimic impaired consciousness but are usually distinguished from true impaired consciousness by neurologic examination.

Symptoms and Signs

Consciousness is decreased to varying degrees. Repeated stimuli arouse patients only briefly or not at all.

Depending on the cause, other symptoms develop (see Table 174-3):

- **Eye abnormalities:** Pupils may be dilated, pinpoint, or unequal. One or both pupils may be fixed in midposition. Eye movement may be dysconjugate or absent (oculomotor paresis). Homonymous hemianopia may be present. Other abnormalities include absence

[**Fig. 174-1.** Brain herniation.]

[**Table 174-1.** Effects of Brain Herniation]

of blinking in response to visual threat (almost touching the eye), as well as loss of the oculocephalic reflex (the eyes do not move in response to head rotation), the oculovestibular reflex (the eyes do not move in response to caloric stimulation), and corneal reflexes.

- **Autonomic dysfunction:** Patients may have abnormal breathing patterns (Cheyne-Stokes or Biot's respirations) or hypertension with bradycardia (Cushing's reflex). Abrupt respiratory and cardiac arrest may occur.

- **Motor dysfunction:** Abnormalities include flaccidity, hemiparesis, asterixis, multifocal myoclonus, decorticate posturing (elbow flexion and shoulder adduction with leg extension), and decerebrate posturing (limb extension and internal shoulder rotation).

- **Other symptoms:** If the brain stem is compromised, nausea, vomiting, meningismus, occipital headache, ataxia, and increasing somnolence can occur.

Diagnosis

- History

- General physical examination

- Neurologic examination, including eye examination

- Laboratory tests (eg, pulse oximetry, bedside glucose measurement, blood and urine tests)

- Immediate neuroimaging

- Sometimes measurement of intracranial pressure

- If diagnosis is unclear, lumbar puncture or EEG

Impaired consciousness is diagnosed if repeated stimuli arouse patients only briefly or not at all. If stimulation triggers primitive reflex movements (eg, decerebrate or decorticate posturing), impaired consciousness may be deepening into coma.

Diagnosis and initial stabilization (airway, breathing, and circulation) should occur simultaneously.

[**Table 174-2.** Common Causes of Coma or Impaired Consciousness]

[**Table 174-3.** Findings by Location*]

Glucose levels must be measured at bedside to identify low levels, which should be corrected immediately. If trauma is involved, the neck is immobilized until clinical history, physical examination, or imaging tests exclude an unstable injury and damage to the cervical spine.

History: Medical identification bracelets or the contents of a wallet or purse may provide clues (eg, hospital identification card, drugs). Relatives, paramedics, and police officers should be questioned about the environment in which the patient was found; containers that may have held food, alcohol, drugs, or poisons should be examined and saved for identification (eg, drug identification aided by a poison center) and possible chemical analysis. Relatives should be asked about the onset of the problem (eg, whether seizure, headache, vomiting, head trauma, or drug ingestion was observed), baseline mental status, recent infections, psychiatric problems and symptoms, drug history, substance use, previous illnesses, the last time the patient was normal, and any hunches they may have about what might be the cause (eg, possible occult overdose, possible occult head trauma due to recent intoxication). Medical records should be reviewed if available.

General physical examination: Physical examination should be focused and efficient and should include thorough examination of the head and face, skin, and extremities. Signs of head trauma include periorbital ecchymosis (raccoon eyes), ecchymosis behind the ear (Battle's sign), hemotympanum, instability of the maxilla, and CSF rhinorrhea and otorrhea. Scalp contusions and small bullet holes can be missed unless the head is carefully inspected. If unstable injury and cervical spine damage have been excluded, passive neck flexion is done; stiffness suggests subarachnoid hemorrhage or meningitis.

Fever, petechial or purpuric rash, hypotension, or severe extremity infections (eg, gangrene of one or more toes) may suggest sepsis or CNS infection. Needle marks may suggest drug overdose (eg, of opioids or insulin). A bitten tongue suggests seizure. Breath odor may suggest alcohol, other drug intoxication, or diabetic ketoacidosis.

Neurologic examination: The neurologic examination determines whether the brain stem is intact and where the lesion is located within the CNS (see p. 1587). The examination focuses on the following:

• Level of consciousness

• Eyes (see p. 1661)

• Motor function

• Deep tendon reflexes

Level of consciousness is evaluated by attempting to wake patients first with verbal commands, then with non-noxious stimuli, and finally with noxious stimuli (eg, pressure to the supraorbital ridge, nail bed, or sternum). The Glasgow Coma Scale (see Table 174-4) was developed to assess patients with head trauma. For head trauma, the score assigned by the scale is valuable prognostically. For coma or impaired consciousness of any cause, the scale is used because it is a relatively reliable, objective measure of the severity of unresponsiveness and can be used serially for monitoring. The scale assigns points based on responses to stimuli. Eye opening, facial grimacing, and purposeful withdrawal of limbs from a noxious stimulus indicate that consciousness is not greatly impaired. Asymmetric motor responses to pain or deep tendon reflexes may indicate a focal hemispheric lesion.

As impaired consciousness deepens into coma, noxious stimuli may trigger stereotypic reflex posturing. Decorticate posturing indicates hemispheric damage with preservation of motor centers in the upper

portion of the brain stem (eg, rubrospinal tract). Decerebrate posturing indicates that the upper brain stem motor centers, which facilitate flexion, have been damaged and that only the lower brain stem centers (eg, vestibulospinal tract, reticulospinal tract), which facilitate extension, are responding to sensory stimuli. Flaccidity without movement indicates that the lower brain stem is not affecting movement, regardless of whether the spinal cord is damaged. It is the worst possible motor response.

Asterixis and multifocal myoclonus suggest metabolic disorders such as uremia, hepatic encephalopathy, hypoxic encephalopathy, and drug toxicity.

Psychogenic unresponsiveness can be differentiated because, although voluntary motor response is typically absent, muscle tone and deep tendon reflexes remain normal, and all brain stem reflexes are preserved.

Eye examination: The following are evaluated:

• Pupillary responses

• Extraocular movements

• Fundi

• Other neuro-ophthalmic reflexes

Pupillary responses and extraocular movements provide information about brain stem function (see Table 174-5). One or both pupils usually become fixed early in coma due to structural lesions, but pupillary responses are often preserved until very late when coma is due to diffuse metabolic disorders (called toxic-metabolic encephalopathy), although responses may be sluggish.

[**Table 174-4.** Glasgow Coma Scale*]

The fundi should be examined for papilledema, hemorrhages, and exudates. Papilledema or hemorrhages may indicate increased intracranial pressure (ICP). Subhyaloid hemorrhage may indicate subarachnoid hemorrhage.

In an unresponsive patient, the oculocephalic reflex is tested by the doll's-eye maneuver: The eyes are observed while the head is passively rotated from side to side or flexed and extended. *This maneuver should not be attempted if cervical spine instability is suspected*.

[**Table 174-5.** Interpretation of Pupillary Response and Eye Movements]

• If the reflex is present, the maneuver causes the eyes to move in the opposite direction of head rotation, flexion, or extension, indicating that the oculovestibular pathways in the brain stem are intact. Thus, in a supine patient, the eyes continue to look straight up when the head is moved.

• If the reflex is absent, the eyes do not move and thus point in whatever direction the head is turned, indicating the oculovestibular pathways are disrupted. The reflex is also absent in most patients with psychogenic unresponsiveness.

If the patient is unconscious and the oculocephalic reflex is absent or the neck is immobilized, oculovestibular (cold caloric) testing is done. After integrity of the tympanic membrane is confirmed, the patient's head is elevated 30°, and with a syringe connected to a flexible catheter, the examiner irrigates the external auditory canal with 50 mL of ice water over a 30-sec period.

• If both eyes deviate toward the irrigated ear, the brain stem is functioning normally, suggesting mildly impaired consciousness.

• If nystagmus away from the irrigated ear also occurs, the patient is conscious and psychogenic unresponsiveness is likely. In conscious patients, 1 mL of ice water is often enough to induce ocular

deviation and nystagmus. Thus, if psychogenic unresponsiveness is suspected, a small amount of water should be used because cold caloric testing can induce severe vertigo, nausea, and vomiting in conscious patients.

- If the eyes do not move or movement is dysconjugate after irrigation, the integrity of the brain stem is uncertain and the coma is deeper. Prognosis may be less favorable.

Certain patterns of eye abnormalities and other findings may suggest brain herniation (see Fig. 174-1 and Table 174-1).

Respiratory patterns: The spontaneous respiratory rate and pattern should be documented unless emergency airway intervention is required. It may suggest a cause.

- Periodic cycling of breathing (Cheyne-Stokes or Biot's respirations—see p. 1827) may indicate dysfunction of both hemispheres or of the diencephalon.

- Hyperventilation (central neurogenic hyperventilation) with respiratory rates of > 40 breaths/min may indicate midbrain or upper pontine dysfunction.

- An inspiratory gasp with respiratory pauses of about 3 sec after full inspiration (apneustic breathing) typically indicates pontine or medullary lesions; this type of breathing often progresses to respiratory arrest.

Tests: Initially, pulse oximetry, fingerstick plasma glucose measurements, and cardiac monitoring are done. Blood tests should include a comprehensive metabolic panel (including at least serum electrolytes, BUN, creatinine, and Ca levels), CBC with differential and platelets, liver function tests, and ammonia level. ABGs are measured, and if carbon monoxide toxicity is suspected, carboxyhemoglobin level is measured. Blood and urine should be obtained for culture and routine toxicology screening; serum ethanol level is also measured. Additional toxicology tests (eg, additional toxicology screening, serum drug levels) are done based on clinical suspicion. ECG (12-lead) should be done.

If the cause is not immediately apparent, noncontrast head CT should be done as soon as possible to check for masses, hemorrhage, edema, and hydrocephalus. MRI can be done instead if immediately available. Contrast CT can be done if noncontrast CT is not diagnostic. MRI or contrast CT may detect isodense subdural hematomas, multiple metastases, sagittal sinus thrombosis, herpes encephalitis, or other causes missed by noncontrast CT. Chest x-ray should also be taken.

If coma is unexplained after neuroimaging and other tests, lumbar puncture is done to check opening pressure and exclude infection, subarachnoid hemorrhage, and other abnormalities. CSF analysis includes cell and differential counts, protein, glucose, Gram stain, cultures, and sometimes, based on clinical suspicion, specific tests (eg, cryptococcal antigen, Venereal Disease Research Laboratory [VDRL] tests, PCR for herpes simplex, visual or spectrophotometric determination of xanthochromia). In unconscious patients with or without focal neurologic deficits, cranial CT or MRI should be done before lumbar puncture to exclude an intracranial mass and obstructive hydrocephalus because if either is present, suddenly lowering CSF pressure by lumbar puncture could trigger brain herniation.

If increased ICP is suspected, pressure is measured. Hyperventilation should be considered under the care of an ICU specialist. Hyperventilation produces hypocapnia, which in turn decreases cerebral blood flow globally through vasoconstriction. Reduction in PCO_2 from 40 mm Hg to 30 mm Hg can reduce ICP about 30%. It is recommended to maintain PCO_2 at 25 mm Hg to 30 mm Hg as required with the initiation of other treatment modalities, but aggressive hypoventilation < 25 mm Hg should be avoided since this may reduce cerebral blood flow excessively and result in cerebral ischemia.

If pressure is increased, it is monitored continuously (see p. 2246).

If diagnosis remains uncertain, EEG may be done. In most comatose patients, EEG shows slowing and reductions in wave amplitude that are nonspecific but often occur in toxic-metabolic encephalopathy. However, in the rare patient with nonconvulsive status epilepticus, EEG shows spikes, sharp waves, or

spike and slow complexes.

Prognosis

Prognosis depends on the cause, duration, and depth of the impairment of consciousness. Prognosis is usually considered poor. However, if unresponsiveness lasts < 6 h, prognosis is more favorable.

After trauma, a Glasgow Coma Scale score of 3 to 5 may indicate fatal brain damage, especially if pupils are fixed or oculovestibular reflexes are absent. If pupils are unreactive or the motor response to noxious stimuli is absent or is only a reflex response 3 days after cardiac arrest, patients have virtually no chance of a good neurologic recovery. After coma, the early return of speech (even if incomprehensible), spontaneous eye movements, or ability to follow commands is a favorable prognostic sign. If the cause is a reversible condition (eg, sedative overdose, some metabolic disorders such as uremia), patients may lose all brain stem reflexes and all motor response and yet recover fully.

Treatment

• Immediate stabilization (airway, breathing, circulation)

• Supportive measures, including, when necessary, control of ICP

• Admission to an ICU

• Treatment of underlying disorder

Airway, breathing, and circulation must be ensured immediately. Hypotension must be corrected (see p. 2297). Patients are admitted to the ICU so that respiratory and neurologic status can be monitored.

Because some patients in coma are undernourished and susceptible to Wernicke encephalopathy, thiamin 100 mg IV or IM should be given routinely. If plasma glucose is low, patients should be given 50 mL of 50% dextrose. If opioid overdose is suspected, naloxone 2 mg IV is given. If trauma is involved, the neck is immobilized until damage to the cervical spine is ruled out.

Endotracheal intubation: Patients with infrequent, shallow, or stertorous respirations, low O_2 saturation (determined by pulse oximetry or ABG measurements), impaired airway reflexes, or severe unresponsiveness (including most patients with a Glasgow Coma Scale score ≤ 8) require endotracheal intubation to prevent aspiration and ensure adequate ventilation. If increased ICP is suspected, intubation should be done via rapid sequence oral intubation (using a paralytic drug) rather than via nasotracheal intubation (see Ch. 225); nasotracheal intubation in a patient who is breathing spontaneously causes more coughing and gagging, thus increasing ICP, which is already increased because of intracranial abnormalities.

To minimize the increase in ICP that may occur when the airway is manipulated, some clinicians recommend giving lidocaine 1.5 mg/kg IV 1 to 2 min before giving the paralytic. Patients are sedated before the paralytic is given. Etomidate is a good choice in hypotensive or trauma patients because it has minimal effects on BP; IV dose is 0.3 mg/kg for adults (or 20 mg for an average-sized adult) and 0.2 to 0.3 mg/kg for children. Alternatively, if hypotension is absent and unlikely and if propofol is readily available, propofol 0.2 to 1.5 mg/kg may be used. Succinylcholine 1.5 mg/kg IV is typically used as a paralytic. However, use of paralytics is minimized and, whenever possible, avoided because they can mask neurologic findings and changes.

Pulse oximetry and ABGs (if possible, end-tidal CO_2) should be used to assess adequacy of oxygenation and ventilation.

ICP control: If ICP is increased, intracranial and cerebral perfusion pressure should be monitored (see p. 2246), and pressures should be controlled. The goal is to maintain ICP at ≤ 20 mm Hg and cerebral perfusion pressure at 50 to 70 mm Hg. Cerebral venous drainage can be enhanced (thus lowering ICP) by elevating the head of the bed to 30° and by keeping the patient's head in a midline position.

Control of increased ICP involves several strategies:

- **Sedation:** Sedatives may be necessary to control agitation, excessive muscular activity (eg, due to delirium), or pain, which can increase ICP. Propofol is often used in adults (contraindicated in children) because onset and duration of action are quick; dose is 0.3 mg/kg/h by continuous IV infusion, titrated gradually up to 3 mg/kg/h as needed. An initial bolus is not used. The most common adverse effect is hypotension. Prolonged use at high doses can cause pancreatitis. Benzodiazepines (eg, midazolam, lorazepam) can also be used. Because sedatives can mask neurologic findings and changes, their use should be minimized and, whenever possible, avoided. Antipsychotics should be avoided if possible because they can delay recovery.

- **Hyperventilation:** Hyperventilation causes hypocapnia, which causes vasoconstriction, thus decreasing cerebral blood flow globally. Reduction in PCO_2 from 40 to 30 mm Hg can reduce ICP about 30%. Hyperventilation that reduces PCO_2 to 28 to 33 mm Hg decreases ICP for only about 30 min and is used by some clinicians as a temporary measure until other treatments take effect. Aggressive hypoventilation to < 25 mm Hg should be avoided because it may reduce cerebral blood flow excessively and result in cerebral ischemia. Other measures may be used to control increased ICP (see p. 3225).

- **Hydration:** Isotonic fluids are used. Providing free water through IV fluids (eg, 5% dextrose, 0.45% saline) can aggravate cerebral edema and should be avoided. Fluids may be restricted to some degree, but patients should be kept euvolemic. If patients have no signs of dehydration or fluid overload, IV fluids with normal saline can be started at 50 to 75 mL/h. The rate can be increased or decreased based on serum Na, osmolality, urine output, and signs of fluid retention (eg, edema).

- **Diuretics:** Serum osmolality should be kept at 295 to 320 mOsm/kg. Osmotic diuretics (eg, mannitol) may be given IV to lower ICP and maintain serum osmolality. They do not cross the blood-brain barrier. They pull water from brain tissue across an osmotic gradient into plasma, eventually leading to equilibrium. Effectiveness of these drugs decreases after a few hours. Thus, they should be reserved for patients whose condition is deteriorating or used preoperatively for patients with hematomas. Mannitol 20% solution is given 0.5 to 1 g/kg IV (2.5 to 5 mL/kg) over 15 to 30 min, then given as often as needed (usually q 6 to 8 h) in a dose ranging from 0.25 to 0.5 g/kg (1.25 to 2.5 mL/kg). Mannitol must be used cautiously in patients with severe coronary artery disease, heart failure, renal insufficiency, or pulmonary vascular congestion because mannitol rapidly expands intravascular volume. Because osmotic diuretics increase renal excretion of water relative to Na, prolonged use of mannitol may result in water depletion and hypernatremia. Furosemide 1 mg/kg IV can decrease total body water, particularly when transient hypervolemia associated with mannitol is to be avoided. Fluid and electrolyte balance should be monitored closely while osmotic diuretics are used. A 3% saline solution is being studied as another potential osmotic agent to control ICP.

- **BP control:** Systemic antihypertensives are needed only when hypertension is severe (> 180/95 mm Hg). How much BP is reduced depends on the clinical context. Systemic BP needs to be high enough to maintain cerebral perfusion pressure even when ICP increases. Hypertension can be managed by titrating a nicardipine drip (5 mg/h, increased by 2.5 mg q 5 min to a maximum of 15 mg/h) or by boluses of labetalol (10 mg IV over 1 to 2 min, repeated q 10 min to a maximum of 150 mg).

- **Corticosteroids:** These drugs are usually helpful for patients with a brain tumor or brain abscess, but they are ineffective for patients with head trauma, cerebral hemorrhage, ischemic stroke, or hypoxic brain damage after cardiac arrest. Corticosteroids increase plasma glucose; this increase may worsen the effects of cerebral ischemia. After an initial dose of dexamethasone 20 to 100 mg, 4 mg once/day appears to be effective while minimizing adverse effects.

If ICP continues to increase despite other measures to control it, the following may be used:

- **Pentobarbital coma:** Pentobarbital can reduce cerebral blood flow and metabolic demands. However, its use is controversial because the effect on clinical outcome is not consistently beneficial. Coma is induced by giving pentobarbital 10 mg/kg IV over 30 min, followed by 5 mg/kg/h for 3 h, then 1 mg/kg/h.

The dose may be adjusted to suppress bursts of EEG activity, which is continuously monitored. Hypotension is common and is managed by giving fluids and, if necessary, vasopressors. Other possible adverse effects include arrhythmias, myocardial depression, and impaired uptake or release of glutamate.

- **Decompressive craniotomy:** Craniotomy with duraplasty can be done to provide room for brain swelling. This procedure can prevent deaths, but overall functional outcome may not improve much. It may be most useful for large cerebral infarcts with impending herniation, particularly in patients < 50.

Long-term care: Patients require meticulous long-term care. Stimulants and opioids should be avoided. Enteral feeding is started with precautions to prevent aspiration (eg, elevation of the head of the bed); a percutaneous endoscopic jejunostomy tube is placed if necessary. Early, vigilant attention to skin care, including checking for breakdown especially at pressure points, is required to prevent pressure ulcers. Topical ointments to prevent desiccation of the eyes are beneficial. Passive range-of-motion exercises done by physical therapists and taping or dynamic flexion splitting of the extremities may prevent contractures. Measures are also taken to prevent UTIs and deep venous thrombosis.

Vegetative State

A vegetative state is absence of responsiveness and awareness due to overwhelming dysfunction of the cerebral hemispheres, with sufficient sparing of the diencephalon and brain stem to preserve autonomic and motor reflexes and sleep-wake cycles. Patients may have complex reflexes, including eye movements, yawning, and involuntary movements to noxious stimuli but show no awareness of self or environment. Diagnosis is clinical. Treatment is supportive. Prognosis with persistent deficits is bleak, and withdrawal of care should be discussed with family members.

The vegetative state is a chronic condition that preserves the ability to maintain BP, respiration, and cardiac function, but not cognitive function. Although medullary brainstem functions remain intact to support cardiorespiratory functions, the presence of midbrain or pontine reflexes may be variable.

A vegetative state occurs when the reticular activating system (RAS) remains functional (making wakefulness possible), but the cortex is severely damaged (eliminating cognitive function). The patient has no awareness of self and interacts with the environment only via reflexes. Hypothalamic and brain stem autonomic function are preserved and sufficient for survival if medical and nursing care is adequate. A vegetative state is considered persistent if it lasts > 1 mo.

The most common causes are traumatic brain injury and diffuse cerebral hypoxia. However, any disorder that results in brain damage can cause a vegetative state. Typically, a vegetative state occurs because the function of the brain stem and diencephalon resumes after coma, but cortical function does not.

Symptoms and Signs

Patients show no evidence of awareness of self or environment and cannot interact with other people. Purposeful responses to external stimuli are absent, as are language comprehension and expression.

Signs of an intact reticular formation (eg, eye opening) and an intact brain stem (eg, reactive pupils, oculocephalic reflex) are present. Sleep-wake cycles occur but do not necessarily reflect a specific circadian rhythm and are not associated with the environment. More complex brain stem reflexes, including yawning, chewing, swallowing, and, uncommonly, guttural vocalizations, are also present. Arousal and startle reflexes may be preserved; eg, loud sounds or blinking with bright lights may elicit eye opening. Eyes may water and produce tears. Patients may appear to smile or frown. Spontaneous roving eye movements—usually slow, of constant velocity, and without saccadic jerks—may be misinterpreted as volitional tracking and can be misinterpreted by family members as evidence of awareness.

Patients cannot react to visual threat and cannot follow commands. The limbs may move, but the only purposeful motor responses that occur are primitive (eg, grasping an object that contacts the hand). Pain usually elicits a motor response (typically decorticate or decerebrate posturing) but no purposeful

avoidance. Patients have fecal and urinary incontinence. Cranial nerve and spinal reflexes are typically preserved.

Diagnosis

• Clinical criteria after sufficient observation

• Sometimes functional brain imaging

A vegetative state is suggested by characteristic findings (eg, no purposeful activity or comprehension) plus signs of an intact reticular formation. Diagnosis is based on clinical criteria. However, neuroimaging is indicated to rule out treatable disorders.

The vegetative state must be distinguished from the minimally conscious state, which results from less severe but sometimes widespread cerebral damage. Fragments of awareness may be observed in patients in a minimally conscious state; they may reach for objects or visually fixate or speak a word or gesture in response to a command. Both states can be permanent or temporary, and the physical examination may not reliably distinguish one from the other. Sufficient observation is needed. If observation is too brief, evidence of awareness may be overlooked, resulting in a false-positive diagnosis.

CT or MRI can differentiate an ischemic infarct, an intracerebral hemorrhage, and a mass lesion involving the cortex or the brainstem. MR angiography can be used to visualize the cerebral vasculature following the exclusion of a cerebral hemorrhage. Additionally, diffusion-weighted MRI is becoming the desired imaging modality to follow ongoing ischemic changes in the brain. PET and SPECT provide an alternative method of imaging that assesses cerebral function rather than brain anatomy. If the diagnosis of persistent vegetative state is in doubt, PET or SPECT should be done. EEG is useful in assessing cortical dysfunction and identifying the presence of occult seizure activity.

Prognosis

Prognosis varies somewhat by cause and duration of the vegetative state. Prognosis may be better if the cause is a reversible metabolic condition (eg, toxic encephalopathy) than if the cause is neuronal death due to extensive hypoxia and ischemia or another injury. Also, younger patients may recover more motor function than older patients but not more cognition, behavior, or speech.

Recovery from a vegetative state is unlikely after 1 mo if brain damage is nontraumatic and after 12 mo if brain damage is traumatic. Even if some recovery occurs after these intervals, most patients are severely disabled. Rarely, improvement occurs late; after 5 yr, about 3% of patients recover the ability to communicate and comprehend, but even fewer can live independently; no patients regain normal function.

Most patients in a persistent vegetative state die within 6 mo of the original brain damage. The cause is usually pulmonary infection, UTI, or multiple organ failure, or death may be sudden and of unknown cause. For most of the rest, life expectancy is about 2 to 5 yr; a few patients live for decades.

Treatment

• Supportive care

There is no specific treatment, but supportive care should include the following:

• Preventing systemic complications due to immobilization (eg, pneumonia, UTI, thromboembolic disease)

• Providing good nutrition

• Preventing pressure ulcers

• Providing physical therapy to prevent limb contractures

Decisions about life-sustaining care should involve social services, the hospital ethics committee, and family members. Maintaining patients, especially those without advanced directives to guide decisions about terminating treatment (see p. 3471), in a prolonged vegetative state raises ethical and other (eg, resource utilization) questions.

Locked-In Syndrome

Locked-in syndrome is a state of wakefulness and awareness with quadriplegia and paralysis of the lower cranial nerves, resulting in inability to show facial expression, move, speak, or communicate, except by coded eye movements.

Locked-in syndrome typically results from a pontine hemorrhage or infarct that causes quadriplegia and disrupts and damages the lower cranial nerves and the centers that control horizontal gaze. Other disorders that produce severe widespread motor paralysis (eg, Guillain-Barre syndrome) are a less common cause.

Patients have intact cognitive function and are awake, with eye opening and normal sleepwake cycles. They can hear and see. However, they cannot move their lower face, chew, swallow, speak, breathe, move their limbs, or move their eyes laterally. Vertical eye movement is possible; patients can open and close their eyes or blink a specific number of times to answer questions.

Diagnosis

• Clinical evaluation

Diagnosis is primarily clinical. Because patients lack the motor responses (eg, withdrawal from painful stimuli) usually used to measure responsiveness, they may be mistakenly thought to be unconscious. Thus, all patients who cannot move should have their comprehension tested through requesting eye blinking or vertical eye movements.

Tests are chosen for the same indications as persistent vegetative state (see p. 1666). Brain imaging with CT or MRI is done and helps identify the pontine abnormality. PET or SPECT may be done if the diagnosis is in doubt. In patients with locked-in syndrome, EEG shows normal sleep-wake patterns.

Prognosis

Prognosis is usually dire. However, locked-in syndrome due to transient ischemia or a small stroke in the vertebrobasilar artery distribution may resolve completely. When the cause is partly reversible (eg, Guillain-Barre syndrome), recovery can occur over months but is seldom complete. Favorable prognostic features include early recovery of lateral eye movements and of evoked potentials in response to magnetic stimulation of the motor cortex. Irreversible or progressive disorders (eg, cancers that involve the posterior fossa and the pons) are usually fatal.

Treatment

• Supportive care

There is no specific treatment, but supportive care should include the following:

• Preventing systemic complications due to immobilization (eg, pneumonia, UTI, thromboembolic disease)

• Providing good nutrition

• Preventing pressure ulcers

• Providing physical therapy to prevent limb contractures

Speech therapists may help establish a communication code using eye blinks or movements. Because cognitive function is intact, patients should make their own health care decisions if communication can be established.

Brain Death

Brain death is loss of function of the entire cerebrum and brain stem, resulting in coma, no spontaneous respiration, and loss of all brain stem reflexes. Spinal reflexes, including deep tendon, plantar flexion, and withdrawal reflexes, may remain. Recovery does not occur.

The concept of brain death developed because ventilators and drugs can perpetuate cardiopulmonary and other body functions despite complete cessation of all cerebral activity. The concept that brain death (ie, total cessation of integrated brain function, especially that of the brain stem) constitutes a person's death has been accepted legally and culturally in most of the world.

Diagnosis

• Serial determination of clinical criteria

• Apnea testing

• Sometimes EEG, brain vascular imaging, or both

For a physician to declare brain death, a known structural or metabolic cause of brain damage must be present, and use of potentially anesthetizing or paralyzing drugs, especially self-administered, must be ruled out. Hypothermia < 32°C must be corrected, and if status epilepticus is suspected, EEG should be done. Sequential testing over 6 to 24 h is necessary (see Table 174-6). Examination includes assessment of pupil reactivity, oculovestibular and oculocephalic reflexes, corneal reflexes, and apnea testing. EEG or tests of brain perfusion may be used to confirm absence

[**Table 174-6.** Guidelines for Determining Brain Death (In Patients > 1 YR)]

of brain activity or brain blood flow and thus provide additional evidence to family members, but these tests are not required.

Prognosis

The diagnosis of brain death is equivalent to the person's death. No one who meets criteria for brain death recovers. After brain death is confirmed, all supporting cardiac and respiratory treatments are ended. Cessation of ventilatory support results in terminal arrhythmias. Spinal motor reflexes may occur during terminal apnea; they include arching of the back, neck turning, stiffening of the legs, and upper extremity flexion (the so-called Lazarus sign). Family members who wish to be present when the ventilator is shut off need to be warned of such reflex movements.

Chapter 175. Delirium and Dementia

Introduction

Delirium (sometimes called acute confusional state) and dementia are the most common causes of cognitive impairment, although affective disorders (eg, depression) can also disrupt cognition. Delirium and dementia are separate disorders but are sometimes difficult to distinguish. In both, cognition is disordered; however, dementia affects mainly memory, and delirium affects mainly attention.

Other specific characteristics help distinguish the 2 disorders (see Table 175-1). Delirium is typically caused by acute illness or drug toxicity (sometimes life threatening) and is often reversible. Dementia is typically caused by anatomic changes in the brain, has slower onset, and is generally irreversible. Delirium often develops in patients with dementia. Mistaking delirium for dementia in an elderly patient—a common clinical error—must be avoided, particularly when delirium is superimposed on chronic dementia. No laboratory test can definitively establish the cause of cognitive impairment; a thorough history and physical examination as well as knowledge of baseline function are essential.

Delirium

Delirium is an acute, transient, usually reversible, fluctuating disturbance in attention, cognition, and consciousness level. Causes include almost any disorder, intoxication, or drug. Diagnosis is clinical, with laboratory and usually imaging tests to identify the cause. Treatment is correction of the cause and supportive measures.

Delirium may occur at any age but is more common among the elderly. At least 10% of elderly patients who are admitted to the hospital have delirium; 15 to 50% experience delirium at some time during hospitalization. Delirium is also common among nursing home residents. When delirium occurs in younger

[**Table 175-1.** Differences Between Delirium and Dementia*]

people, it is usually due to drug use or a life-threatening systemic disorder. Delirium is sometimes called acute confusional state or toxic or metabolic encephalopathy.

Etiology

The most common causes are the following:

• Drugs, particularly anticholinergics, psychoactive drugs, and opioids

• Dehydration

• Infection

Many other conditions can cause delirium (see Table 175-2). In about 10 to 20% of patients, no cause is identified.

Predisposing factors include brain disorders (eg, dementia, stroke, Parkinson's disease), advanced age, sensory impairment, and multiple coexisting disorders. Precipitating factors include use of drugs (particularly ≥ 3 new drugs), infection, dehydration, immobility, undernutrition, and use of bladder catheters. Recent exposure to anesthesia also increases risk, especially if exposure is prolonged and if anticholinergics are given during surgery. Decreased sensory stimuli at night may trigger delirium in at-risk patients. For elderly patients in an ICU, risk of delirium (ICU psychosis) is particularly high.

Pathophysiology

Mechanisms are not fully understood but may involve reversible impairment of cerebral oxidative metabolism, multiple neurotransmitter abnormalities, and generation of cytokines. Stress of any kind

upregulates sympathetic tone and downregulates parasympathetic tone, impairing cholinergic function and thus contributing to delirium. The elderly are particularly vulnerable to reduced cholinergic transmission, increasing their risk of delirium. Regardless of cause, the cerebral hemispheres or arousal mechanisms of the thalamus and brain stem reticular activating system become impaired.

[**Table 175-2.** Causes of Delirium]

Symptoms and Signs

Delirium is characterized primarily by difficulty focusing, maintaining, or shifting attention (inattention). Consciousness level fluctuates; patients are disoriented to time and sometimes place or person. They may have hallucinations. Confusion regarding day-to-day events and daily routines is common, as are changes in personality and affect. Thinking becomes disorganized, and speech is often disordered, with prominent slurring, rapidity, neologisms, aphasic errors, or chaotic patterns.

Symptoms fluctuate over minutes to hours; they may lessen during the day and worsen at night.

Symptoms may include inappropriate behavior, fearfulness, and paranoia. Patients may become irritable, agitated, hyperactive, and hyperalert, or they may become quiet, withdrawn, and lethargic. Very elderly people with delirium tend to become quiet and withdrawn—changes that may be mistaken for depression. Some patients alternate between the two. Usually, patterns of sleeping and eating are grossly distorted. Because of the many cognitive disturbances, insight is poor, and judgment is impaired. Other symptoms and signs depend on the cause.

Diagnosis

• Mental status examination

• Standard diagnostic criteria to confirm delirium

• Thorough history

• Directed physical examination and selective testing to determine cause

Delirium, particularly in elderly patients, is often overlooked by clinicians. Clinicians should consider delirium in any elderly patient who presents with impairment in memory or attention.

Mental status examination: Patients with any sign of cognitive impairment require a formal mental status examination (see Sidebar 168-1 on p. 1588). Attention is assessed first. Simple tests include immediate repetition of the names of 3 objects, digit span (ability to repeat 7 digits forward and 5 backward), and naming the days of the week forward and backward. Inattention (patient does not register directions or other information) must be distinguished from poor short-term memory (patient registers information but rapidly forgets it). Further cognitive testing is futile for patients who cannot register information.

After initial assessment, standard diagnostic criteria, such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or Confusion Assessment Method (CAM) may be used. The following features are required for diagnosis: • Acute change in cognition that fluctuates during the day

• Inattention (eg, difficulty focusing or following what is said)

plus one of the following:

• Disturbance of consciousness (ie, less clarity) with DSM

or

• An altered level of consciousness (eg, hyperalert, lethargic, stuporous, comatose) or disorganized

thinking (eg, rambling, irrelevant conversation, illogical flow of ideas) with CAM

History: History is obtained by interviewing family members, caregivers, and friends. It can determine whether the change in mental status is recent and is distinct from any baseline dementia (see Table 175-1). The history helps distinguish a mental disorder from delirium. Mental disorders, unlike delirium, almost never cause inattention or fluctuating consciousness, and onset of mental disorders is nearly always subacute. Sundowning (behavioral deterioration during evening hours), which is common among institutionalized patients with dementia, may be difficult to differentiate; newly symptomatic deterioration should be presumed to be delirium until proved otherwise.

History should also include use of alcohol and illicit, OTC, and prescription drugs, focusing particularly on drugs with CNS effects and on new additions, discontinuations, or changes in dose, including overdosing.

Physical examination: Examination, particularly in patients who are not fully cooperative, should focus on the following:

• Vital signs

• Hydration status

• Potential foci for infection

• Skin, head and neck, and neurologic examination

Findings can suggest a cause. For example, fever, meningismus, or Kernig and Brudzinski signs suggest CNS infection. Tremor and myoclonus suggest uremia, liver failure, drug intoxication, or certain electrolyte disorders (eg, hypocalcemia, hypomagnesemia). Ophthalmoplegia and ataxia suggest Wernicke-Korsakoff syndrome (see p. 1523). Focal neurologic abnormalities (eg, cranial nerve palsies, motor or sensory deficits) or papilledema suggests a structural CNS disorder. Lesions, swelling, and other findings suggest head trauma.

Testing: Testing usually includes CT or MRI, tests for suspected infections (eg, CBC, blood cultures, chest x-ray, urinalysis), and measurement of electrolytes, BUN, creatinine, plasma glucose, and levels of any drugs suspected to be having toxic effects.

If the diagnosis is unclear, further testing may include pulse oximetry (or ABGs); liver function tests; measurement of serum calcium and albumin, thyroid-stimulating hormone (TSH), vitamin B_{12}, ESR, and antinuclear antibody (ANA); and a test for syphilis (eg, rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] test).

If the diagnosis is still unclear, testing may include CSF analysis (particularly to rule out meningitis, encephalitis, or subarachnoid hemorrhage), measurement of serum ammonia, and testing to check for heavy metals.

If nonconvulsive status epilepticus, a rare cause, is suspected (based on history, subtle motor twitches, automatisms, or presence of a steadier but less intense pattern of bewilderment and drowsiness), EEG should be done.

Prognosis

Morbidity and mortality rates are higher in patients who have delirium when they are hospitalized or who develop delirium during hospitalization.

Delirium due to certain conditions (eg, hypoglycemia, intoxication, infection, iatrogenic factors, drug toxicity, electrolyte imbalance) typically resolves rapidly with treatment. However, recovery may be slow (days to even weeks or months), especially in the elderly, resulting in longer hospital stays, increased risk and severity of complications, increased costs, and long-term disability. Some patients never fully recover from delirium. For up to 2 yr after delirium occurs, risk of cognitive and functional decline,

institutionalization, and death is increased.

Treatment

• Correction of the cause and removal of aggravating factors

• Supportive care

• Management of agitation

Correcting the cause (eg, treating infection, giving fluids and electrolytes for dehydration) and removing aggravating factors (eg, stopping drugs) may result in resolution of delirium. Nutritional deficiencies (eg, of thiamin or vitamin B_{12}) should be corrected, and good nutrition and hydration should be provided.

General measures: The environment should be stable, quiet, and well-lit and include visual cues to orient the patient (eg, calendar, clocks, family photographs). Frequent reorientation and reassurance by hospital staff or family members may also help. Sensory deficits should be minimized (eg, by replacing hearingaid batteries, by encouraging patients who need eyeglasses or hearing aids to use them).

Approach to treatment should be interdisciplinary (with a physician, physical and occupational therapists, nurses, and social workers); it should involve strategies to enhance mobility and range of motion, treat pain and discomfort, prevent skin breakdown, ameliorate incontinence, and minimize risk of aspiration.

Agitation may threaten the well-being of the patient, a caregiver, or a staff member. Simplifying drug regimens and avoiding use of IV lines, bladder catheters, and physical restraints (particularly in the long-term care setting) as much as possible can help prevent exacerbation of agitation and reduce risk of injury. However, in certain circumstances, physical restraints may be needed to prevent patients from harming themselves or others. Restraints should be applied by a staff member trained in their use; they should be released at least every 2 h to prevent injury and discontinued as soon as possible. Use of hospital-employed assistants (sitters) as constant observers may help avoid the need for restraints.

Explaining the nature of delirium to family members can help them cope. They should be told that delirium is usually reversible but that cognitive deficits often take weeks or months to abate after resolution of the acute illness.

Drugs: Drugs, typically low-dose haloperidol (0.5 to 1.0 mg po, IV, or IM once, then repeated q 1 to 2 h as needed), may lessen agitation or psychotic symptoms; occasionally, much higher doses are necessary. However, drugs do not correct the underlying problem and may prolong or exacerbate delirium. Second-generation (atypical) antipsychotics (eg, risperidone 0.5 to 3 mg po q 12 h, olanzapine 2.5 to 15 mg po once/day) may be used instead because they have fewer extrapyramidal adverse effects; however, long-term use in patients with dementia may increase risk of stroke and death. These drugs are not typically given IV or IM.

Benzodiazepines (eg, lorazepam 0.5 to 1.0 mg po or IV once, then repeated q 1 to 2 h as needed) have a more rapid onset of action (5 min after parenteral administration) than antipsychotics but commonly worsen confusion and sedation in patients with delirium.

Overall, antipsychotics and benzodiazepines are equally effective for managing agitation in delirium, but antipsychotics have fewer adverse effects. Benzodiazepines are preferred for delirium attributed to sedative withdrawal and for patients intolerant of antipsychotics (eg, those with Parkinson's disease or Lewy body dementia). Dose of these drugs should be reduced as quickly as possible.

Prevention

Because delirium greatly worsens prognosis for hospitalized patients, prevention should be emphasized. Hospital staff members should be trained to take measures to maintain orientation, mobility, and cognition and to ensure sleep, good nutrition and hydration, and sufficient pain relief, particularly in elderly patients. Family members can be encouraged to help with these strategies. The number and doses of drugs

should be reduced if possible.

Dementia

Dementia is chronic, global, usually irreversible deterioration of cognition. Diagnosis is clinical; laboratory and imaging tests are used to identify treatable causes. Treatment is supportive. Cholinesterase inhibitors can sometimes temporarily improve cognitive function.

Dementia may occur at any age but affects primarily the elderly (about 5% of those aged 65 to 74 and 40% of those > 85). It accounts for more than one half of nursing home admissions. At least 5 million people in the US have dementia.

Dementias can be classified in several ways:

• Alzheimer's or non-Alzheimer's type

• Cortical or subcortical

• Irreversible or potentially reversible

• Common or rare

Etiology

Dementias may result from primary diseases of the brain or other conditions (see Table 175-3).

The most common types of dementia are Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementias, and HIV-associated dementia. Dementia also occurs in patients with Parkinson's disease, Huntington's disease, progressive supranuclear palsy, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, other prion disorders, and neurosyphilis. Patients can have > 1 type (mixed dementia).

Some structural brain disorders (eg, normal-pressure hydrocephalus, subdural hematoma), metabolic disorders (eg, hypothyroidism, vitamin B_{12} deficiency), and toxins (eg, lead) cause a slow deterioration of cognition that may resolve with treatment. This impairment is sometimes called reversible dementia, but some experts restrict the term dementia to irreversible cognitive deterioration.

Depression may mimic dementia (and was formerly called pseudodementia); the 2 disorders often coexist. However, depression may be the first manifestation of dementia.

Changes in cognition, including memory, occur with aging, but they are not dementia. The elderly have a relative deficiency in recall, particularly in speed of recall, compared with recall during their youth. However, this change does not affect daily function. Mild cognitive impairment is more severe than age-associated memory impairment; memory is impaired compared with that of agematched controls, but other cognitive domains and daily function are not affected. Up to 50% of patients with mild cognitive impairment develop dementia within 3 yr.

Any disorder may exacerbate cognitive deficits in patients with dementia. Delirium often occurs in patients with dementia. Drugs, particularly benzodiazepines and anticholinergics (eg, some tricyclic antidepressants, antihistamines, antipsychotics, benztropine), may temporarily cause or worsen symptoms of dementia, as may alcohol, even in moderate amounts. New or progressive renal or liver failure may reduce drug clearance and cause drug toxicity after years of taking a stable drug dose (eg, of propranolol).

Symptoms and Signs

Dementia impairs cognition globally. Onset is gradual, although family members may suddenly notice

deficits (eg, when function becomes impaired). Often, loss of short-term memory is the first sign. Although symptoms exist in a continuum, they can be divided into early, intermediate, and late. Personality changes and behavioral disturbances may develop early or late. Motor and other focal neurologic deficits occur at different stages, depending on the type of dementia; they occur early in vascular dementia and late in Alzheimer's disease. Incidence of seizures is somewhat increased during all stages. Psychosis —hallucinations, delusions, or paranoia—occurs in about 10% of patients with dementia, although a higher percentage may experience these symptoms temporarily.

[**Table 175-3.** Classification of Some Dementias]

Early: Recent memory is impaired; learning and retaining new information become difficult. Language problems (especially with word finding), mood swings, and personality changes develop. Patients may have progressive difficulty with independent activities of daily living (eg, balancing their checkbook, finding their way around, remembering where they put things). Abstract thinking, insight, or judgment may be impaired. Patients may respond to loss of independence and memory with irritability, hostility, and agitation.

Functional ability may be further limited by the following:

• Agnosia: Impaired ability to identify objects despite intact sensory function (see p. 1638)

• Apraxia: Impaired ability to do previously learned motor activities despite intact motor function (see p. 1642)

• Aphasia: Impaired ability to comprehend or use language (see p. 1640)

Although early dementia may not compromise sociability, family members may report strange behavior accompanied by emotional lability.

Intermediate: Patients become unable to learn and recall new information. Memory of remote events is reduced but not totally lost. Patients may require help with basic activities of daily living (eg, bathing, eating, dressing, toileting). Personality changes may progress. Patients may become irritable, anxious, selfcentered, inflexible, or angry more easily, or they may become more passive, with a flat affect, depression, indecisiveness, lack of spontaneity, or general withdrawal from social situations. Behavior disorders may develop: Patients may wander or become suddenly and inappropriately agitated, hostile, uncooperative, or physically aggressive (see p. 1684).

By this stage, patients have lost all sense of time and place because they cannot effectively use normal environmental and social cues. Patients often get lost; they may be unable to find their own bedroom or bathroom. They remain ambulatory but are at risk of falls or accidents secondary to confusion. Altered sensation or perception may culminate in psychosis with hallucinations and paranoid and persecutory delusions. Sleep patterns are often disorganized.

Late (severe): Patients cannot walk, feed themselves, or do any other activities of daily living; they may become incontinent. Recent and remote memory is completely lost. Patients may be unable to swallow. They are at risk of undernutrition, pneumonia (especially due to aspiration), and pressure ulcers. Because they depend completely on others for care, placement in a long-term care facility often becomes necessary. Eventually, patients become mute.

Because such patients cannot relate any symptoms to a physician and because elderly patients often have no febrile or leukocytic response to infection, a physician must rely on experience and acumen whenever a patient appears ill. End-stage dementia results in coma and death, usually due to infection.

Diagnosis

• Differentiation of delirium from dementia, mainly by mental status examination

• Identification of treatable causes clinically and by laboratory testing and neuroimaging

• Sometimes formal neuropsychologic testing

Recommendations about diagnosis of dementia are available from the American Academy of Neurology.

Distinguishing type or cause of dementia can be difficult; definitive diagnosis often requires postmortem pathologic examination of brain tissue. Thus, clinical diagnosis focuses on distinguishing dementia from delirium and other disorders and identifying the cerebral areas affected and potentially reversible causes.

Dementia must be distinguished from the following:

• Delirium: Distinguishing between dementia and delirium is crucial (because delirium is usually reversible with prompt treatment) but can be difficult. Attention is assessed first. If a patient is inattentive, the diagnosis is likely to be delirium, although advanced dementia also severely impairs attention. Other features that suggest delirium rather than dementia (eg, duration of cognitive impairment—see Table 175-1) are determined by the history, physical examination, and tests for specific causes.

• Age-associated memory impairment: This impairment is not severe enough to affect daily function. If affected people are given enough time to learn new information, their intellectual performance is good.

• Mild cognitive impairment: Memory is impaired, but other cognitive domains and daily function are not affected.

• Dementia of depression: This cognitive disturbance resolves with treatment of depression. Depressed older patients may experience cognitive decline, but unlike patients with dementia, they tend to exaggerate their memory loss and rarely forget important current events or personal matters. Neurologic examinations are normal except for signs of psychomotor slowing. When tested, patients with depression make little effort to respond, but those with dementia often try hard but respond incorrectly. When depression and dementia coexist, treating depression does not fully restore cognition.

Clinical criteria: The best screening test for dementia is a short-term memory test (eg, registering 3 objects and recalling them after 5 min); patients with dementia forget simple information within 3 to 5 min. Another test assesses the ability to name objects within categories (eg, lists of animals, plants, or pieces of furniture). Patients with dementia struggle to name a few; those without dementia easily name many.

In addition to loss of short-term memory, diagnosis of dementia requires at least one of the following cognitive deficits:

• Aphasia

• Apraxia

• Agnosia

• Impaired ability to plan, organize, sequence, or think abstractly (executive dysfunction)

Each cognitive deficit must substantially impair function and represent a significant decline from a previous level of functioning. Also, the deficits must not occur only during delirium.

A formal mental status examination (see Sidebar 168-1 on p. 1588) should be done. The Mini-Mental Status Examination is often used. When delirium is absent, the presence of multiple deficits, particularly in patients with an average or a higher level of education, suggests dementia.

History and physical examination should then focus on signs of treatable disorders that cause cognitive impairment (eg, vitamin B_{12} deficiency, neurosyphilis, hypothyroidism, depression—see Table 175-2).

Laboratory testing: Tests should include thyroid-stimulating hormone and vitamin B_{12} levels. Routine CBC and liver function tests are sometimes recommended, but yield is very low. If clinical findings

suggest a specific disorder, other tests (eg, for HIV or syphilis) are indicated. Lumbar puncture is rarely needed but should be considered if a chronic infection or neurosyphilis is suspected. Other tests may be used to exclude causes of delirium.

Neuroimaging: CT or MRI should be done in the initial evaluation of dementia or after any sudden change in cognition or mental status. Neuroimaging can identify potentially reversible structural disorders (eg, normal-pressure hydrocephalus, brain tumors, subdural hematoma) and certain metabolic disorders (eg, Hallervorden-Spatz disease, Wilson's disease). Occasionally, EEG is useful (eg, to evaluate episodic lapses in attention or bizarre behavior). Functional MRI or single-photon emission CT can provide information about cerebral perfusion patterns and help with differential diagnosis (eg, in differentiating Alzheimer's disease from frontotemporal dementia and Lewy body dementia).

Neuropsychologic testing: If the diagnosis remains in doubt, patients should be referred for formal neuropsychologic testing, which evaluates mood as well as all mental functions and takes 1 to 3 h. It is done or supervised by a neuropsychologist. Such testing helps primarily in differentiating the following:

- Age-associated memory impairment, mild cognitive impairment, and dementia, particularly when cognition is only slightly impaired or when the patient or family members are anxious for reassurance
- Dementia and focal syndromes of cognitive impairment (eg, amnesia, aphasia, apraxia, visuospatial difficulties) when the distinction is not clinically evident

Testing may also help characterize specific deficits due to dementia.

Prognosis

Dementia is usually progressive. However, progression rate varies widely and depends on the cause. Dementia shortens life expectancy, but survival estimates vary.

Treatment

- Measures to ensure safety
- Provision of appropriate stimulation, activities, and cues for orientation
- Elimination of drugs with sedating or anticholinergic effects
- Possibly cholinesterase inhibitors
- Assistance for caregivers
- Arrangements for end-of-life care

Recommendations about treatment of dementia are available from the American Academy of Neurology. Measures to ensure patient safety and to provide an appropriate environment are essential to treatment, as is caregiver assistance. Several drugs are available.

Patient safety: Occupational and physical therapists can evaluate the home for safety; the goals are to prevent accidents (particularly falls), to manage behavior disorders, and to plan for change as dementia progresses.

How well patients function in various settings (ie, kitchen, automobile) should be evaluated using simulations. If patients have deficits and remain in the same environment, protective measures (eg, hiding knives, unplugging the stove, removing the car, confiscating car keys) may be required. Some states require physicians to notify the Department of Motor Vehicles of patients with dementia because, at some point, such patients can no longer drive safely. If patients wander, signal monitoring systems can be installed, or patients can be registered in the Safe Return program. Information is available from the Alzheimer's Association. Ultimately, assistance (eg, housekeepers, home health aides) or a change of

environment (living facilities without stairs, assisted-living facility, skilled nursing facility) may be indicated.

Environmental measures: Patients with mild to moderate dementia usually function best in familiar surroundings. Whether at home or in an institution, the environment should be designed to help preserve feelings of self-control and personal dignity by providing the following:

• Frequent reinforcement of orientation

• A bright, cheerful, familiar environment

• Minimal new stimulation

• Regular, low-stress activities

Large calendars and clocks and a routine for daily activities can help with orientation; medical staff members can wear large name tags and repeatedly introduce themselves. Changes in surroundings, routines, or people should be explained to patients precisely and simply, omitting nonessential procedures. Patients require time to adjust and become familiar with the changes. Telling patients about what is going to happen (eg, about a bath or feeding) may avert resistance or violent reactions. Frequent visits by staff members and familiar people encourage patients to remain social.

The room should be reasonably bright and contain sensory stimuli (eg, radio, television, night-light) to help patients remain oriented and focus their attention. Quiet, dark, private rooms should be avoided.

Activities can help patients function better; those related to interests before dementia began are good choices. Activities should be enjoyable, provide some stimulation, but not involve too many choices or challenges. Exercise to reduce restlessness, improve balance, and maintain cardiovascular tone should be done daily. Exercise can also help improve sleep and manage behavior disorders. Occupational therapy and music therapy help maintain fine motor control and provides nonverbal stimulation. Group therapy (eg, reminiscence therapy, socialization activities) may help maintain conversational and interpersonal skills.

Drugs: Eliminating or limiting drugs with CNS activity often improves function. Sedating and anticholinergic drugs, which tend to worsen dementia, should be avoided.

The cholinesterase inhibitors donepezil, rivastigmine, and galantamine (see p. 1679) are somewhat effective in improving cognitive function in patients with Alzheimer's disease or Lewy body dementia and may be useful in other forms of dementia. These drugs inhibit acetylcholinesterase, increasing the acetylcholine level in the brain.

Memantine, an NMDA (*N*-methyl-D-aspartate) antagonist, may help slow progression of moderate to severe dementia and can be used with a cholinesterase inhibitor.

Other drugs (eg, antipsychotics) have been used to control behavior disorders (see p. 1686). Patients with dementia and signs of depression should be treated with nonanticholinergic antidepressants, preferably SSRIs.

Caregiver assistance: Immediate family members are largely responsible for care of a patient with dementia. Nurses and social workers can teach them and other caregivers how to best meet the patient's needs (eg, how to deal with daily care and handle financial issues); teaching should be ongoing. Other resources (eg, support groups, educational materials, Internet web sites) are available.

Caregivers may experience substantial stress. Stress may be caused by worry about protecting the patient and by frustration, exhaustion, anger, and resentment from having to do so much to care for someone. Health care practitioners should watch for early symptoms of caregiver stress and burnout and, when needed, suggest support services (eg, social worker, nutritionist, nurse, home health aide). If a patient with dementia has an unusual injury, the possibility of elder abuse should be investigated.

End-of-life issues: Because insight and judgment deteriorate in patients with dementia, appointment of a family member, guardian, or lawyer to oversee finances may be necessary. Early in dementia, before the patient is incapacitated, the patient's wishes about care should be clarified, and financial and legal arrangements (eg, durable power of attorney, durable power of attorney for health care) should be made. When these documents are signed, the patient's capacity should be evaluated, and evaluation results recorded (see also p. 3468). Decisions about artificial feeding and treatment of acute disorders are best made before the need develops. In advanced dementia, palliative measures may be more appropriate than highly aggressive interventions or hospital care.

Alzheimer's Disease

Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, β-amyloid deposits, and neurofibrillary tangles in the cerebral cortex and subcortical gray matter.

Alzheimer's disease is the most common cause of dementia; it accounts for > 65% of dementias in the elderly. The disease is twice as common among women as among men, partly because women have a longer life expectancy. Alzheimer's disease affects about 4% of people aged 65 to 74 and 30% of those > 85. Prevalence in industrialized countries is expected to increase as the proportion of the elderly increases.

Etiology

Most cases are sporadic, with late onset (≥ 60 yr) and unclear etiology. However, about 5 to 15% are familial; one half of these cases have an early (presenile) onset (< 60 yr) and are typically related to specific genetic mutations.

At least 5 distinct genetic loci, located on chromosomes 1, 12, 14, 19, and 21, influence initiation and progression of Alzheimer's disease. Mutations in genes for the amyloid precursor protein, presenilin I, and presenilin II may lead to autosomal dominant forms of Alzheimer's disease, typically with presenile onset. In affected patients, the processing of amyloid precursor protein is altered, leading to deposition and fibrillar aggregation of β-amyloid. β-Amyloid may lead to neuronal death and formation of neurofibrillary tangles and senile plaques, which consist of degenerated axonal or dendritic processes, astrocytes, and glial cells around an amyloid core.

Other genetic determinants include the apolipoprotein (apo) E alleles (ε). Apo E proteins influence β-amyloid deposition, cytoskeletal integrity, and efficiency of neuronal repair. Risk of Alzheimer's disease is substantially increased in people with 2 ε4 alleles and may be decreased in those who have the ε2 allele. Variants in *SORL1* may also be involved; they are more common among people with lateonset Alzheimer's disease. These variants may cause the gene to malfunction, possibly resulting in increased production of β-amyloid.

The relationship of other factors (eg, low hormone levels, metal exposure) and Alzheimer's disease is under study, but no definite causal links have been established.

Pathophysiology

Typically, extracellular β-amyloid deposits, intracellular neurofibrillary tangles (paired helical filaments), and senile plaques develop, and neurons are lost. Cerebrocortical atrophy is common, and use of cerebral glucose is reduced, as is perfusion in the parietal lobe, temporal cortices, and prefrontal cortex.

Other common abnormalities include increased brain and CSF concentrations of the tau protein (a component of neurofibrillary tangles and β-amyloid) and reduced levels of choline acetyltransferase and various neurotransmitters (eg, somatostatin).

Symptoms and Signs

Symptoms and signs of Alzheimer's disease are similar to those of other dementias, with early,

intermediate, and late stages (see p. 1673). Loss of short-term memory is often the first sign. Cognitive deficits tend to involve multiple functions. The disease progresses gradually but may plateau for periods of time. Behavior disorders (eg, wandering, agitation, yelling, persecutory ideation) are common (see p. 1684).

Diagnosis

• Similar to that of other dementias

• Formal mental status examination

• History and physical examination

• Laboratory testing

• Neuroimaging

Generally, diagnosis is similar to that of other dementias (see p. 1675). Clinical criteria (including a thorough history and standard neurologic examination) are 85% accurate in establishing the diagnosis and differentiating Alzheimer's disease from other forms of dementia, such as vascular dementia and Lewy body dementia.

Traditional diagnostic criteria for Alzheimer's disease include all of the following:

• Dementia established clinically and documented by a formal mental status examination Deficits in ≥ 2 areas of cognition

• Gradual onset and progressive worsening of memory and other cognitive functions

• No disturbance of consciousness

• Onset after age 40, most often after age 65

• No systemic or brain disorders that could account for the progressive deficits in memory and cognition

However, deviations from these criteria do not exclude a diagnosis of Alzheimer's disease, particularly because patients may have mixed dementia.

Differential diagnosis: Distinguishing Alzheimer's disease from other dementias is difficult. Assessment tools (eg, Hachinski Ischemic Score—see Table 175-4) can help distinguish vascular dementia from Alzheimer's disease. Fluctuations in cognition, parkinsonian symptoms, well-formed visual hallucinations, and relative preservation of short-term memory suggest Lewy body dementia rather than Alzheimer's disease (see Table 175-5). Patients with Alzheimer's disease are often better-groomed and neater than patients with other dementias.

Prognosis

Although progression rate varies, cognitive decline is inevitable. Average survival from time of diagnosis is 7 yr, although this figure

[**Table 175-4.** Modified Hachinski Ischemic Score]

[**Table 175-5.** Differences Between Alzheimer's Disease and Lewy Body Dementia]

is debated. Average survival from the time patients can no longer walk is about 6 mo.

Treatment

• Generally, similar to that of other dementias

• Possibly cholinesterase inhibitors and memantine

General treatment is the same as that of all dementias (see p. 1676).

Cholinesterase inhibitors modestly improve cognitive function and memory in some patients. Four are available; generally, donepezil, rivastigmine, and galantamine are equally effective, but tacrine is rarely used because of its hepatotoxicity. Donepezil is a first-line drug because it has once/day dosing and is well-tolerated. The recommended dose is 5 mg once/day for 4 to 6 wk, then increased to 10 mg once/day. Treatment should be continued if functional improvement is apparent after several months, but otherwise it should be stopped. The most common adverse effects are GI (eg, nausea, diarrhea). Rarely, dizziness and cardiac arrhythmias occur. Adverse effects can be minimized by increasing the dose gradually (see Table 175-6).

Memantine, an *N*-methyl-D-aspartate receptor antagonist, appears to slow the progression of Alzheimer's disease. The dose is 5 mg po once/day, which is increased to 10 mg po bid over about 4 wk. For patients with renal insufficiency, the dose should be reduced or the drug should be avoided. Memantine can be used with a cholinesterase inhibitor.

Efficacy of high-dose vitamin E (1000 IU po once/day or bid), selegiline, NSAIDs, *Ginkgo biloba* extracts, and statins is unclear. Estrogen therapy does not appear useful in prevention or treatment and may be harmful.

Prevention

Preliminary, observational evidence suggests that risk of Alzheimer's disease may be decreased by the following:

• Continuing to do challenging mental activities (eg, learning new skills, doing crossword puzzles) well into old age

• Exercising

• Controlling hypertension

• Lowering cholesterol levels

• Consuming a diet rich in ω-3 fatty acids and low in saturated fats

• Drinking alcohol in modest amounts

[**Table 175-6.** Drugs for Alzheimer's Disease]

However, there is no convincing evidence that people who do not drink alcohol should start drinking to prevent Alzheimer's disease.

Vascular Dementia

Vascular dementia is acute or chronic cognitive deterioration due to diffuse or focal cerebral infarction that is most often related to cerebrovascular disease.

Vascular dementia is the 2nd most common cause of dementia among the elderly. It is more common among men and usually begins after age 70. It occurs more often in people who have vascular risk factors (eg, hypertension, diabetes mellitus, hyperlipidemia, smoking) and in those who have had several strokes. Many people have both vascular dementia and Alzheimer's disease.

Vascular dementia occurs when multiple small cerebral infarcts (or sometimes hemorrhages) cause

enough neuronal or axonal loss to impair brain function. Vascular dementias include the following:

- **Lacunar disease:** Small blood vessels are affected.
- **Multi-infarct dementia:** Medium-sized blood vessels are affected.
- **Strategic single-infarct dementia:** A single infarct occurs in a crucial area of the brain (eg, angular gyrus, thalamus).
- **Binswanger's dementia (subcortical arteriosclerotic encephalopathy):** This uncommon variant of small-vessel dementia is associated with severe, poorly controlled hypertension and systemic vascular disease. It involves multiple lacunar infarcts in deep hemispheric white and gray matter.

Symptoms and Signs

Symptoms and signs are similar to those of other dementias (see p. 1673). However, because infarction is the cause, vascular dementia tends to progress in discrete steps; each episode is accompanied by intellectual decline, sometimes followed by modest recovery.

As the disease progresses, focal neurologic deficits often develop:

- Exaggeration of deep tendon reflexes
- Extensor plantar response
- Gait abnormalities
- Weakness of an extremity
- Hemiplegias
- Pseudobulbar palsy with pathologic laughing and crying
- Other signs of extrapyramidal dysfunction

However, because small-vessel ischemic damage tends to cause small, incremental deficits, the decline appears to be gradual.

Cognitive loss may be focal. For example, short-term memory may be less affected than in other dementias. Patients with partial aphasia may be more aware of their deficits; thus, depression may be more common than in other dementias.

Diagnosis

- Generally similar to diagnosis of other dementias

Diagnosis is similar to that of other dementias (see p. 1675). If focal signs or evidence of cerebrovascular disease is present, a thorough evaluation for stroke should be done (see p. 1645).

CT and MRI may show bilateral multiple infarcts in the dominant hemisphere and limbic structures, multiple lacunar strokes, or periventricular white-matter lesions extending into the deep white matter. In Binswanger's dementia, imaging shows leukoencephalopathy in the cerebrum semiovale adjacent to the cortex, often with multiple lacunae affecting structures deep in the gray matter (eg, basal ganglia, thalamic nuclei).

The Hachinski Ischemic Score is sometimes used to help differentiate vascular dementia from Alzheimer's disease (see Table 175-4).

Prognosis

The 5-yr mortality rate is 61%, which is higher than that for most forms of dementia, presumably because other atherosclerotic disorders coexist.

Treatment

• Generally similar to treatment of other dementias

Generally, treatment is the same as that of other dementias (see p. 1676). However, vascular dementia may be preventable, and its progression may be slowed by BP control, cholesterol-lowering therapy, regulation of plasma glucose (90 to 150 mg/dL), and smoking cessation.

The efficacy of cholinesterase inhibitors and memantine is uncertain. However, because many patients also have Alzheimer's disease, these drugs may have some benefit. Adjunctive drugs for depression, psychosis, and sleep disorders are useful.

Lewy Body Dementia

Lewy body dementia is chronic cognitive deterioration characterized by cellular inclusions called Lewy bodies in the cytoplasm of cortical neurons.

Lewy body dementia is the 3rd most common dementia. Age of onset is typically > 60.

Lewy bodies are spherical, eosinophilic, neuronal cytoplasmic inclusions composed of aggregates of α-synuclein, a synaptic protein. They occur in the cortex of some patients with primary Lewy body dementia. Neurotransmitter levels and neuronal pathways between the striatum and the neocortex are abnormal.

Lewy bodies also occur in the substantia nigra of patients with Parkinson's disease, and patients with Parkinson's disease may develop Lewy body dementia. Thus, some experts think that Parkinson's disease and Lewy body dementia may be part of a more generalized synucleopathy affecting the central and peripheral nervous systems (see p. 1765). Lewy bodies sometimes occur in patients with Alzheimer's disease, and patients with Lewy body dementia may have neuritic plaques and neurofibrillary tangles. Lewy body dementia, Parkinson's disease, and Alzheimer's disease overlap considerably. Further research is needed to clarify the relationships among them.

Symptoms and Signs

Initial cognitive deterioration resembles that of other dementias (see p. 1673). Extrapyramidal symptoms occur. However, unlike in Parkinson's disease, in Lewy body dementia, cognitive and extrapyramidal symptoms usually begin within 1 yr of each other. Also the extrapyramidal symptoms differ from those of Parkinson's disease: In Lewy body dementia, tremor does not occur early, rigidity of axial muscles with gait instability occurs early, and deficits tend to be symmetric. Repeated falls are common.

Fluctuating cognitive function is a relatively specific feature of Lewy body dementia. Periods of being alert, coherent, and oriented may alternate with periods of being confused and unresponsive to questions, usually over a period of days to weeks but sometimes during the same interview. Memory is impaired, but the impairment appears to result more from deficits in alertness and attention than in memory acquisition; thus, short-term recall is affected less than digit span memory (ability to repeat 7 digits forward and 5 backward). Patients may stare into space for long periods. Excessive daytime drowsiness is common. Visuospatial and visuoconstructional abilities (tested by block design, clock drawing, or figure copying) are affected more than other cognitive deficits. Thus, Lewy body dementia may be difficult to distinguish from delirium, and all patients presenting with these symptoms and signs should be evaluated for delirium.

Visual hallucinations are common and often threatening, unlike the benign hallucinations of Parkinson's

disease. Auditory, olfactory, and tactile hallucinations are less common. Delusions occur in 50 to 65% of patients and are often complex and bizarre, compared with the simple persecutory ideation common in Alzheimer's disease.

Autonomic dysfunction is common, and unexplained syncope may result. Autonomic dysfunction may occur simultaneously with or after onset of cognitive deficits. Extreme sensitivity to antipsychotics is typical. Many patients have rapid eye movement (REM) sleep behavior disorder, a parasomnia characterized by vivid dreams without the usual physiologic paralysis of skeletal muscles during REM sleep. As a result, dreams may be acted out, sometimes injuring the bed partner.

Lewy body dementia progresses; prognosis is poor.

Diagnosis

• Clinical criteria

• Neuroimaging to rule out other disorders

Diagnosis is clinical, but sensitivity and specificity are poor.

Diagnosis is considered probable if 2 of 3 features—fluctuations in cognition, visual hallucinations, and parkinsonism—are present and possible if only one is present. Supportive evidence consists of repeated falls, syncope, and sensitivity to antipsychotics. Overlap of symptoms in Lewy body dementia and Parkinson's disease may complicate diagnosis. When motor deficits (eg, tremor, bradykinesia, rigidity) precede and are more severe than cognitive impairment, Parkinson's disease is usually diagnosed. When early cognitive impairment and behavioral disturbances predominate, Lewy body dementia is usually diagnosed.

CT and MRI show no characteristic changes but are helpful initially in ruling out other causes of dementia. Positron emission tomography with fluorine-18-labeled deoxyglucose and single-photon emission CT (SPECT) with ^{123}I-FP-CIT (*N*-3-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl]tropane), a fluoroalkyl analog of cocaine, may help identify Lewy body dementia but are not routinely done. Definitive diagnosis requires autopsy samples of brain tissue.

Treatment

• Supportive care

Treatment is generally supportive (see p. 1676). Rivastigmine 1.5 mg po bid, titrated upward as needed to 6 mg bid, may improve cognition. Other cholinesterase inhibitors may also be useful. In about one half of patients, extrapyramidal symptoms respond to antiparkinsonian drugs (see p. 1767), but psychiatric symptoms may worsen. If such drugs are needed, levodopa is preferred.

Traditional antipsychotics, even at very low doses, tend to acutely worsen extrapyramidal symptoms and are best avoided.

HIV-Associated Dementia

HIV-associated dementia is chronic cognitive deterioration due to brain infection by HIV.

HIV-associated dementia (AIDS dementia complex) may occur in the late stages of HIV infection. Unlike almost all other forms of dementia, it tends to occur in younger people. Purely HIV-associated dementia is caused by neuronal damage by the HIV virus. However, in patients with HIV infection, dementia may result from other infections, such as secondary infection with JC virus causing progressive multifocal leukoencephalopathy. Other opportunistic infections (eg, fungal, bacterial, viral, protozoan) may also contribute.

In purely HIV-associated dementia, subcortical pathologic changes result when infected macrophages or

microglial cells infiltrate into the deep gray matter (ie, basal ganglia, thalamus) and white matter.

Prevalence of dementia in late-stage HIV infection ranges from 7 to 27%, but 30 to 40% may have milder forms. Incidence is inversely proportional to CD4+ count.

Symptoms and Signs

Symptoms and signs may be similar to those of other dementias (see p. 1673). Early manifestations include slowed thinking and expression, difficulty concentrating, and apathy; insight is preserved, and manifestations of depression are few. Motor movements are slowed; ataxia and weakness may be evident. Abnormal neurologic signs may include paraparesis, lower-extremity spasticity, ataxia, and extensor-plantar responses. Mania or psychosis is sometimes present.

Diagnosis

• Generally similar to initial diagnosis of other dementias

• Prompt evaluation, including MRI, when deterioration is acute

Generally, diagnosis of dementia in patients with HIV infection is similar to that of other dementias (see p. 1675). However, when patients present with an acute change in cognitive function, the cause must be identified as soon as possible.

CT or MRI should be done to check for signs of CNS infection (eg, toxoplasmosis). MRI is more useful than CT because it can exclude other CNS causes of dementia (eg, progressive multifocal leukoencephalopathy, cerebral lymphoma). Late-stage findings of HIV dementia may include diffuse nonenhancing white matter hyperintensities, cerebral atrophy, and ventricular enlargement. If no contraindication is identified by neuroimaging, lumbar puncture is done to rule out infection.

Prognosis

Patients with HIV infection and untreated dementia have a worse prognosis (average life expectancy of 6 mo) than those without dementia.

Treatment

• Highly active antiretroviral therapy

The primary treatment is highly active antiretroviral therapy, which increases CD4+ counts and improves cognitive function (see p. 1450). Supportive measures are similar to those for other dementias (see p. 1676).

Frontotemporal Dementia

Frontotemporal dementia (FTD) refers to sporadic and hereditary disorders that affect the frontal and temporal lobes, including Pick's disease.

FTD accounts for up to 10% of dementias. Age at onset is typically younger (age 55 to 65) than in Alzheimer's disease. FTDs affect men and women about equally. Pick's disease is a variant of FTD, which may be pathologically characterized by severe atrophy, neuronal loss, gliosis, and presence of abnormal neurons (Pick cells) containing inclusions (Pick bodies).

About one half of FTDs are inherited; most mutations involve chromosome 17q21-22 and result in abnormalities of the microtubule-binding tau protein; thus, FTDs are considered tauopathies. Some experts classify supranuclear palsy and corticobasal degeneration with FTDs because they share similar pathology and gene mutations affecting the tau protein. Symptoms, gene mutations, and pathologic changes may not correspond to each other. For example, the same mutation causes FTD symptoms in one family member but symptoms of corticobasal degeneration in another, and Pick's cells may be absent

in patients with typical symptoms of Pick's disease.

Symptoms and Signs

Generally, FTD affects personality, behavior, and usually language function (syntax and fluency) more and memory less than does Alzheimer's disease. Abstract thinking and attention (maintaining and shifting) are impaired; responses are disorganized. Orientation is preserved, but retrieval of information may be impaired. Motor skills are generally preserved. Patients have difficulty sequencing tasks, although visual-spatial and constructional tasks are affected less.

Frontal release signs (grasp, root, suck, snout, and palmomental reflexes and glabellar sign—see p. 1593) appear late in the disease but also occur in other dementias. Some patients develop motor neuron disease with generalized muscle atrophy, weakness, fasciculations, bulbar symptoms (eg, dysphagia, dysphonia, difficulty chewing), and increased risk of aspiration pneumonia and early death.

Frontal variant FTD: Social behavior and personality change because the orbitobasal frontal lobe is affected. Patients become impulsive and lose their social inhibitions (eg, they may shoplift); they neglect personal hygiene. Some have Kluver-Bucy syndrome, which involves emotional blunting, hypersexual activity, hyperorality (eg, bulimia, sucking and smacking of lips), and visual agnosias. Impersistence (impaired concentration), inertia, and mental rigidity appear.

Behavior becomes repetitive and stereotyped (eg, patients may walk to the same location every day). Patients may pick up and manipulate random objects for no reason (called utilization behavior). Verbal output is reduced; echolalia, perseveration (inappropriate repetition of a response), and eventually mutism occur.

Primary progressive aphasia: Language function deteriorates because of asymmetric (worse on left) anterolateral temporal lobe atrophy; the hippocampus and memory are relatively spared. Most patients present with difficulty finding words. Attention (eg, digit span) may be severely impaired. Many patients have aphasia, with decreased fluency and difficulty comprehending language; hesitancy in speech production and dysarthria are also common. In some patients, aphasia is the only symptom for ≥ 10 yr; in others, global deficits develop within a few years.

Semantic dementia is a type of primary progressive aphasia. When the left side of the brain is affected most, the ability to comprehend words is progressively lost. Speech is fluent but lacks meaning; a generic or related term may be used instead of the specific name of an object. When the right side is affected most, patients have progressive anomia (inability to name objects) and prosopagnosia (inability to recognize familiar faces). They cannot remember topographic relationships. Some patients with semantic dementia also have Alzheimer's disease.

Diagnosis

• Generally similar to diagnosis of other dementias

• Additional clinical evaluation to differentiate from some other dementias

Diagnosis is suggested by typical clinical findings. As for other dementias, cognitive deficits are evaluated (see p. 1675). CT and MRI are done to determine location and extent of brain atrophy and to exclude other possible causes (eg, brain tumors, abscesses, stroke). FTDs are characterized by severely atrophic, sometimes paper-thin gyri in the temporal and frontal lobes. However, MRI or CT may not show these changes until late in FTD. Thus, FTDs and Alzheimer's disease can usually be differentiated more easily by clinical criteria. For example, primary progressive aphasia differs from Alzheimer's disease in that memory and visuospatial function are preserved and syntax and fluency are impaired.

Prognosis

FTDs usually progress gradually, but progression rate varies; if symptoms are limited to speech and language, progression to general dementia may be slower.

Treatment

There is no specific treatment. Treatment is generally supportive (see p. 1676).

Normal-Pressure Hydrocephalus

Normal-pressure hydrocephalus is characterized by gait disturbance, urinary incontinence, dementia, enlarged brain ventricles, and normal or slightly elevated CSF pressure.

Normal-pressure hydrocephalus is thought to result from a defect in CSF resorption in arachnoid granulations. This disorder accounts for up to 6% of dementias.

Symptoms and Signs

Most commonly, the gait disturbance is nonspecific unsteadiness and impaired balance, although a magnetic gait (the feet appear to stick to the floor) is considered the characteristic gait disturbance. Dementia may not occur until late in the disorder. The most common early symptoms of dementia are disturbances of executive function and attention; memory tends to become impaired later.

Diagnosis

• Clinical evaluation

• Neuroimaging

• Sometimes removal of CSF

The classic symptoms (gait disturbance, urinary incontinence, and dementia), even combined, are nonspecific for normal-pressure hydrocephalus, particularly in the elderly. For example, some forms of vascular dementia can cause dementia, gait disturbance, and, less commonly, urinary incontinence. Brain imaging may show ventricular enlargement disproportionate to cortical atrophy; this finding is nonspecific but may support the diagnosis of normal-pressure hydrocephalus.

Lumbar puncture with removal of 20 to 30 mL of CSF can be done as a diagnostic trial. Improvement in gait, continence, and cognition after removal helps confirm the diagnosis, but improvement may not be evident until several hours after removal.

Treatment

• Sometimes ventriculoperitoneal shunting

Ventriculoperitoneal shunting is useful for patients with acceptable surgical risks. Improvements after lumbar puncture to remove CSF, done during diagnosis, may predict the response to shunting. In several case series (but in no randomized trials), patients improved substantially, typically in gait, continence, and daily functioning, after shunting; improvement in cognition was less common.

Behavioral and Psychologic Symptoms of Dementia

Disruptive actions are common among patients with dementia and are the primary reason for up to 50% of nursing home admissions. Disruptive actions include wandering, restlessness, yelling, throwing, hitting, refusing treatment, incessantly questioning, disrupting work of staff members, insomnia, and crying. Behavioral and psychologic symptoms of dementia have not been well characterized, and their treatment is poorly understood.

Deciding what actions constitute a behavioral symptom is highly subjective. Tolerability (what actions caregivers can tolerate) depends partly on the patient's living arrangements, particularly safety. For example, wandering may be tolerable if a patient lives in a safe environment (with locks and alarms on all

doors and gates); however, if the patient lives in a nursing home or hospital, wandering may be intolerable because it disturbs other patients or interferes with the operation of the institution. Many behaviors (eg, wandering, repeatedly questioning, being uncooperative) are better tolerated during the day. Whether sundowning (exacerbation of disruptive behaviors at sundown or early evening) represents decreased tolerance by caregivers or true diurnal variation is unknown. In nursing homes, 12 to 14% of patients with dementia act disruptively more often during the evening than during the day.

Etiology

Behavioral and psychologic symptoms may result from functional changes related to dementia:

- Reduced inhibition of inappropriate behaviors (eg, patients may undress in public places)
- Misinterpretation of visual and auditory cues (eg, they may resist treatment, which they perceive as an assault)
- Impaired short-term memory (eg, they repeatedly ask for things already received)
- Reduced ability or inability to express needs (eg, they wander because they are lonely, frightened, or looking for something or someone)

Patients with dementia often adapt poorly to the regimentation of institutional living. Mealtimes, bedtimes, and toileting times are not individualized. For many elderly patients with dementia, behavioral and psychologic symptoms develop or worsen after they are moved to a more restrictive environment.

Physical problems (eg, pain, shortness of breath, urinary retention, constipation, physical abuse) can exacerbate behavioral and psychologic symptoms partly because patients may be unable to adequately communicate. Physical problems can lead to delirium, and delirium superimposed on chronic dementia may worsen the behavioral symptom.

Evaluation

- Characterization of behaviors (eg, by Cohen-Mansfield Agitation Inventory)
- Recording of specific behaviors
- Evaluation for coexisting depression and psychosis

The best approach is to characterize and classify the behavior, rather than to label all such behaviors agitation, a term with too many meanings to be useful. The Cohen-Mansfield Agitation Inventory is commonly used; it classifies behaviors as follows:

- Physically aggressive: For example, hitting, pushing, kicking, biting, scratching, or grabbing people or things
- Physically nonaggressive: For example, handling things inappropriately, hiding things, dressing or undressing inappropriately, pacing, repeating mannerisms or sentences, acting restless, or trying to go elsewhere
- Verbally aggressive: For example, cursing, making strange noises, screaming, or having temper outbursts
- Verbally nonaggressive: For example, complaining, whining, constantly requesting attention, not liking anything, interrupting with relevant or irrelevant remarks, or being negative or bossy

Specific behaviors, precipitating events (eg, feeding, toileting, drug administration, visits), and time the behavior started and resolved should be recorded; this information helps identify changes in pattern or intensity of a behavior and makes planning a management strategy easier. If behavior changes, a

physical examination should be done to exclude physical disorders and physical abuse, but environmental changes (eg, a different caregiver) should also be noted because they, rather than a patient-related factor, may be the reason.

Depression, common among patients with dementia, may affect behavior and must be identified. It may first manifest as an abrupt change in cognition, decreased appetite, deterioration in mood, a change in sleep pattern (often hypersomnolence), withdrawal, decreased activity level, crying spells, talk of death and dying, sudden development of irritability or psychosis, or other sudden changes in behavior. Often, depression is suspected first by family members.

Psychotic behavior must also be identified because management differs. Presence of delusions or hallucinations indicates psychosis. Delusions and hallucinations must be distinguished from disorientation, fearfulness, and misunderstanding, which are common among patients with dementia. Delusions without paranoia may be confused with disorientation, but delusions are usually fixed (eg, a nursing home is repeatedly called a prison), and disorientation varies (eg, a nursing home is called a prison, a restaurant, and a home). Hallucinations occur without external sensory stimuli; hallucinations should be distinguished from illusions, which involve misinterpreting external sensory stimuli (eg, cellular phones, pagers).

Treatment

• Environmental measures and caregiver support

• Drugs only when necessary

Management of behavioral and psychologic symptoms of dementia is controversial and has been inadequately studied. Supportive measures are preferred; however, drugs are commonly used.

Environmental measures: The environment should be safe and flexible enough to accommodate behaviors that are not dangerous. Signs to help patients find their way and doors equipped with locks or alarms can help ensure the safety of patients who wander. Flexible sleeping hours and organization of beds can help patients with sleeping problems. Measures used to treat dementia generally also help minimize behavioral symptoms:

• Providing cues about time and place

• Explaining care before giving it

• Encouraging physical activity (see p. 1676)

If an institution cannot provide an appropriate environment for a particular patient, transferring the patient to one that can may be preferable to drug treatment.

Caregiver support: Learning how dementia leads to behavioral and psychologic symptoms and how to respond to disruptive behavior can help family members and other caregivers provide care for and cope with the patient better.

Learning how to manage stress, which may be considerable, is essential. Stressed caregivers should be referred to support services (eg, social workers, caregiver support groups, home health aides) and should be told how to obtain respite care if such care is available.

Family members who are caregivers should be monitored for depression, which occurs in nearly half of them. Depression in caregivers should be treated promptly.

Drugs: Drugs that improve cognition may also help manage behavioral and psychologic symptoms in patients with dementia. However, drugs directed primarily at behavior are used only when other approaches are ineffective and when drugs are essential for safety. The need for continued treatment should be reassessed at least every month. Drugs should be selected to target the most intolerable

behaviors. Antidepressants, preferably SSRIs, should be prescribed only for patients with signs of depression.

Antipsychotics are often used even though their efficacy has been shown only in psychotic patients (see p. 1562). Other patients are unlikely to benefit and likely to experience adverse effects, particularly extrapyramidal symptoms. Tardive dyskinesia or tardive dystonia may develop; these conditions often do not resolve when the dose is reduced or the drug is stopped.

Choice of antipsychotic depends on relative toxicity. Of conventional antipsychotics, haloperidol is relatively nonsedating and has less potent anticholinergic effects but is most likely to cause extrapyramidal symptoms; thioridazine and thiothixene are less likely to cause extrapyramidal symptoms but are more sedating and have more anticholinergic effects than haloperidol. Second-generation (atypical) antipsychotics (eg, aripiprazole, olanzapine, quetiapine, risperidone) are minimally anticholinergic and cause fewer extrapyramidal symptoms than conventional antipsychotics; however, these drugs, used for an extended period, may be associated with an increased risk of hyperglycemia and all-cause mortality. Also, they may increase risk of stroke in elderly patients who have dementia-related psychosis.

If antipsychotics are used, they should be given in a low dose (eg, olanzapine 2.5 to 15 mg po once/day; risperidone 0.5 to 3 mg po q 12 h; haloperidol 0.5 to 1.0 mg po, IV, or IM) and for a short time.

Anticonvulsants, particularly valproate, may be useful in controlling impulsive behavioral outbursts.

Sedatives (eg, a short-acting benzodiazepine such as lorazepam 0.5 mg po q 12 h as needed) are sometimes used in the short term to alleviate event-related anxiety, but such treatment is not recommended for the long term.

Chapter 176. Seizure Disorders

Introduction

(See also Febrile Seizures on p. 2898, Infantile Spasms on p. 2899, and Neonatal Seizure Disorders on p. 2900.)

A seizure is an abnormal, unregulated electrical discharge that occurs within the brain's cortical gray matter and transiently interrupts normal brain function. A seizure typically causes altered awareness, abnormal sensations, focal involuntary movements, or convulsions (widespread violent involuntary contraction of voluntary muscles).

About 2% of adults have a seizure at some time during their life. Two thirds of these people never have another one.

Definitions: Terminology can be confusing.

Epilepsy (also called epileptic seizure disorder) is a chronic brain disorder characterized by recurrent (≥ 2), unprovoked seizures (ie, not related to reversible stressors). Epilepsy is often idiopathic, but various brain disorders, such as malformations, strokes, and tumors, can cause symptomatic epilepsy.

Nonepileptic seizures are provoked by a temporary disorder or stressor (eg, metabolic disorders, CNS infections, cardiovascular disorders, drug toxicity or withdrawal).

[
Table 176-1. Causes of Seizures]

In children, fever can provoke a seizure (see p. 2898).

Symptomatic seizures are due to a known cause (eg, brain tumor, stroke). Symptomatic seizures are most common among neonates (see p. 2900) and the elderly.

Psychogenic seizures (pseudoseizures) are symptoms that simulate seizures in patients with psychiatric disorders but that do not involve an abnormal electrical discharge in the brain.

Etiology

Common causes of seizures (see Table 176-1) vary by age of onset:

- **Before age 2:** Developmental defects, birth injuries, and metabolic disorders
- **Ages 2 to 14:** Idiopathic seizure disorders
- **Adults:** Cerebral trauma, alcohol withdrawal, tumors, strokes, and unknown cause (in 50%)
- **The elderly:** Tumors and strokes

In reflex epilepsy, a rare disorder, seizures are triggered predictably by an external stimulus, such as repetitive sounds, flashing lights, video games, or even touching certain parts of the body.

Classification

Seizures are classified as generalized or partial.

Generalized: In generalized seizures, the aberrant electrical discharge diffusely involves the entire cortex of both hemispheres from the onset, and consciousness is usually lost. Generalized seizures result most often from metabolic disorders and sometimes from genetic disorders. Generalized seizures include the following:

• Infantile spasms

• Absence seizures

• Tonic-clonic seizures

• Atonic seizures

• Myoclonic seizures

Partial seizures: In partial seizures, the excess neuronal discharge occurs in one cerebral cortex, and most often results from structural abnormalities. Partial seizures may be

• Simple (no impairment of consciousness)

• Complex (reduced but not complete loss of consciousness)

Partial seizures may be followed by a generalized seizure (called secondary generalization), which causes loss of consciousness. Secondary generalization occurs when a partial seizure spreads and activates the entire cerebrum bilaterally. Activation may occur so rapidly that the initial partial seizure is not clinically apparent or is very brief.

Symptoms and Signs

Seizures may be preceded by an aura. Auras may consist of sensory, autonomic, or psychic sensations (eg, paresthesias, a rising epigastric sensation, abnormal smells, a sensation of fear, a deja vu sensation).

Most seizures end spontaneously in 1 to 2 min. Generalized seizures are often followed by a postictal state, characterized by deep sleep, headache, confusion, and muscle soreness; this state lasts from minutes to hours. Sometimes the postictal state includes Todd's paralysis (a transient neurologic deficit, usually weakness, of the limb contralateral to the seizure focus).

Most patients appear neurologically normal between seizures, although high doses of the drugs used to treat seizure disorders, particularly anticonvulsants, can reduce alertness. Any progressive mental deterioration is usually related to the neurologic disorder that caused the seizures rather than to the seizures themselves. Rarely, seizures are unremitting.

Partial seizures: There are several types of partial seizures.

Simple partial seizures cause motor, sensory, or psychomotor symptoms without loss of consciousness. Specific symptoms reflect the affected area of the brain (see Table 176-2). In jacksonian seizures, focal motor symptoms begin in one hand, then march up the arm. Other focal seizures affect the face first, then spread to an arm and sometimes a leg. Some partial motor seizures begin with an arm raising and the head turning toward the moving arm.

[**Table 176-2.** Manifestations of Partial Seizures by Site]

Epilepsia partialis continua, a rare disorder, causes focal motor seizures that usually involve the arm, hand, or one side of the face; seizures recur every few seconds or minutes for days to years at a time. In adults, the cause is usually a structural lesion (eg, stroke). In children, it is usually a focal cerebral cortical inflammatory process (eg, Rasmussen encephalitis), possibly caused by a chronic viral infection or autoimmune processes.

Complex partial seizures are often preceded by an aura. During the seizure, patients may stare. Consciousness is impaired, but patients have some awareness of the environment (eg, they purposefully withdraw from noxious stimuli). The following may also occur:

- Oral automatisms (involuntary chewing or lip smacking)
- Limb automatisms (eg, automatic purposeless movements of the hands)
- Utterance of unintelligible sounds without understanding what they say
- Resistance to assistance
- Tonic or dystonic posturing of the extremity contralateral to the seizure focus
- Head and eye deviation, usually in a direction contralateral to the seizure focus
- Bicycling or pedaling movements of the legs if the seizure emanates from the medial frontal or orbitofrontal head regions

Motor symptoms subside after 1 to 2 min, but confusion and disorientation may continue for another 1 or 2 min. Postictal amnesia is common. Patients may lash out if restrained during the seizure or while recovering consciousness if the seizure generalizes. However, unprovoked aggressive behavior is unusual.

Left temporal lobe seizures may cause verbal memory abnormalities; right temporal lobe seizures may cause visual spatial memory abnormalities.

Generalized seizures: Consciousness is usually lost, and motor function is abnormal from the onset.

Infantile spasms (see p. 2899) are characterized by sudden flexion and adduction of the arms and forward flexion of the trunk. Seizures last a few seconds and recur many times a day. They occur only in the first 5 yr of life, then are replaced by other types of seizures. Developmental defects are usually present.

Typical absence seizures (formerly called petit mal seizures) consist of 10- to 30-sec loss of consciousness with eyelid fluttering; axial muscle tone may or may not be lost. Patients do not fall or convulse; they abruptly stop activity, then just as abruptly resume it, with no postictal symptoms or knowledge that a seizure has occurred. Absence seizures are genetic and occur predominantly in children. Without treatment, such seizures are likely to occur many times a day. Seizures often occur when patients are sitting quietly, can be precipitated by hyperventilation, and rarely occur during exercise. Neurologic and cognitive examination results are usually normal.

Atypical absence seizures usually occur as part of the Lennox-Gastaut syndrome, a severe form of epilepsy that begins before age 4 yr. They differ from typical absence seizures as follows:

- They last longer.
- Jerking or automatic movements are more pronounced.
- Loss of awareness is less complete.

Many patients have a history of damage to the nervous system, developmental delay, abnormal neurologic examination results, and other types of seizures. Atypical absence seizures usually continue into adulthood.

Atonic seizures occur most often in children, usually as part of Lennox-Gastaut syndrome. Atonic seizures are characterized by brief, complete loss of muscle tone and consciousness. Children fall or pitch to the ground, risking trauma, particularly head injury.

Tonic seizures occur most often during sleep, usually in children. The cause is usually the Lennox-Gastaut syndrome. Tonic (sustained) contraction of axial muscles may begin abruptly or gradually, then

spread to the proximal muscles of the limbs. Tonic seizures usually last 10 to 15 sec. In longer tonic seizures, a few, rapid clonic jerks may occur as the tonic phase ends.

Tonic-clonic seizures may be primarily or secondarily generalized. Primarily generalized seizures typically begin with an outcry; they continue with loss of consciousness and falling, followed by tonic contraction, then clonic (rapidly alternating contraction and relaxation) motion of muscles of the extremities, trunk, and head. Urinary and fecal incontinence, tongue biting, and frothing at the mouth sometimes occur. Seizures usually last 1 to 2 min. There is no aura. Secondarily generalized tonic-clonic seizures begin with a simple partial or complex partial seizure.

Myoclonic seizures are brief, lightning-like jerks of a limb, several limbs, or the trunk. They may be repetitive, leading to a tonic-clonic seizure. The jerks may be bilateral or unilateral. Unlike other seizures with bilateral motor movements, consciousness is not lost unless the myoclonic seizure progresses into a generalized tonic-clonic seizure.

Juvenile myoclonic epilepsy is an epilepsy syndrome characterized by myoclonic, tonic-clonic, and absence seizures. It typically appears during adolescence. Seizures begin with a few bilateral, synchronous myoclonic jerks, followed in 90% by generalized tonic-clonic seizures. They often occur when patients awaken in the morning, especially after sleep deprivation or alcohol use. Absence seizures may occur in one third of patients.

Febrile seizures occur, by definition, with fever and in the absence of intracranial infection; they are considered a type of provoked seizure. They affect about 4% of children aged 3 mo to 5 yr (see p. 2898). Benign febrile seizures are brief, solitary, and generalized tonic-clonic in appearance. Complicated febrile seizures are focal, last > 15 min, or recur ≥ 2 times in < 24 h. Overall, 2% of patients with febrile seizures develop a subsequent seizure disorder. However, incidence of seizure disorders and risk of recurrent febrile seizures are much greater among children with complicated febrile seizures, preexisting neurologic abnormalities, onset before age 1 yr, or a family history of seizure disorders.

Status epilepticus: Generalized convulsive status epilepticus involves at least one of the following:

• Tonic-clonic seizure activity lasting > 5 to 10 min

• ≥ 2 seizures between which patients do not fully regain consciousness

The previous definition of > 30-min duration was revised to encourage more prompt identification and treatment. Untreated generalized seizures lasting > 60 min may result in permanent brain damage; longer-lasting seizures may be fatal. Heart rate and temperature increase. Generalized convulsive status epilepticus has many causes, including rapid withdrawal of anticonvulsants and head trauma.

Complex partial status epilepticus and absence status epilepticus often manifest as prolonged episodes of mental status changes. EEG may be required for diagnosis.

Diagnosis

• Clinical evaluation

• For new-onset seizures, neuroimaging, laboratory testing, and usually EEG

• For known seizure disorder, usually anticonvulsant levels

• For new-onset or known seizure disorders, other testing as clinically indicated

Evaluation must determine whether the event was a seizure vs another cause of obtundation, a pseudoseizure, or syncope), then identify possible causes or precipitants. Patients with new-onset seizures are evaluated in an emergency department; they can sometimes be discharged after thorough evaluation. Those with a known seizure disorder may be evaluated in a physician's office.

History: Patients should be asked about unusual sensations, suggesting an aura and thus a seizure, and about typical seizure manifestations. However, other conditions, such as suddenly decreased brain circulation (eg, due to ventricular arrhythmia) can have similar manifestations, including loss of consciousness and some myoclonic jerks.

History should include information about the first and any subsequent seizures (eg, duration, frequency, sequential evolution, longest and shortest interval between seizures, aura, postictal state, precipitating factors). All patients should be asked about risk factors for seizures:

• Prior head trauma or CNS infection

• Known neurologic disorders

• Drug use or withdrawal, particularly of recreational drugs

• Alcohol withdrawal

• Nonadherence to anticonvulsants

• Family history of seizures or neurologic disorders

Patients should also be asked about rare triggers (eg, repetitive sounds, flashing lights, video games, touching certain parts of the body) and about sleep deprivation, which can lower the seizure threshold.

Physical examination: A bitten tongue, incontinence (eg, urine or feces in clothing), or, in patients who have lost consciousness, prolonged confusion suggest seizure.

In pseudoseizures, generalized muscular activity and lack of response to verbal stimuli may at first glance suggest generalized tonic-clonic seizures. However, pseudoseizures can usually be distinguished from true seizures by clinical characteristics:

• Pseudoseizures often last longer (several minutes or more).

• Postictal confusion tends to be absent.

• Typical tonic phase activity, followed by clonic phase, usually does not occur.

• The progression of muscular activity does not correspond to true seizure patterns (eg, jerks moving from one side to the other and back [nonphysiologic progression], exaggerated pelvic thrusting).

• Intensity may wax and wane.

• Vital signs, including temperature, usually remain normal.

• Patients often actively resist passive eye opening.

Physical examination rarely indicates the cause when seizures are idiopathic but may provide clues when seizures are symptomatic (see
Table 176-3).

Testing: Testing is done routinely, but normal results do not necessarily exclude a seizure disorder. Thus, the diagnosis may ultimately be clinical. Testing depends on the status of seizures and results of the neurologic examination.

If patients have a known seizure disorder and examination results are normal or unchanged, little testing is required except for blood anticonvulsant levels, unless patients have symptoms or signs of a treatable disorder such as trauma, infection, or a metabolic

[Table 176-3. Clinical Clues to the Causes of Symptomatic Seizures]

disorder. If seizures are new-onset or if examination results are abnormal for the first time, neuroimaging is required.

Head CT is usually done immediately to exclude a mass or hemorrhage. Some experts say that CT can be deferred and possibly avoided in children with typical febrile seizures whose neurologic status rapidly returns to normal.

Follow-up MRI is recommended when CT is negative. It provides better resolution of brain tumors and abscesses and can detect cortical dysplasias, cerebral venous thrombosis, and herpes encephalitis. An epilepsy-protocol MRI of the head uses high-resolution coronal T1 and T2 sequences, which can detect hippocampal atrophy or sclerosis. MRI can detect some common causes of seizures, such as malformations of cortical development in young children and mesial temporal sclerosis, traumatic gliosis, and small tumors in adults.

EEG is critical in the diagnosis of epileptic seizures, particularly of complex partial or absence status epilepticus, when EEG may be the most definitive indication of a seizure. EEG may detect epileptiform abnormalities (spikes, sharp waves, spike and slow-wave complexes, polyspike and slow-wave complexes). Epileptiform abnormalities may be bilateral and generalized in patients with generalized seizures and may be localized in patients with partial seizures. EEG findings may include the following:

- Epileptiform abnormalities in temporal lobe foci between seizures (interictal) in complex partial seizures originating in the temporal lobe
- Interictal symmetric bursts of 4- to 7-Hz epileptiform activity in primarily generalized tonic-clonic seizures
- Focal epileptiform discharges in secondarily generalized seizures
- Spikes and slow-wave discharges at a rate of 3/sec in typical absence seizures
- Slow spike and wave discharges usually at a rate of < 2.5/sec in atypical absence seizures
- Bilateral polyspike and wave abnormality at a rate of 4- to 6-Hz in juvenile myoclonic epilepsy

However, normal EEG cannot exclude the diagnosis of epileptic seizures, which must be made clinically. EEG is less likely to detect abnormalities if seizures are infrequent. The initial EEG may detect an epileptiform abnormality in only 30 to 55% of patients with a known epileptic seizure disorder. Serial EEG may detect epileptiform abnormalities in up to 80 to 90% of such patients. In general, serial EEG with extended recording times and with tests done during sleep deprivation greatly increases the chance of detecting epileptiform abnormalities in patients with epileptic seizures. Inpatient combined video-EEG monitoring, usually for 2 to 7 days, records EEG activity and clinical behavior simultaneously. It is the most sensitive EEG testing available and is thus useful in differentiating epileptic from nonepileptic seizures.

Testing is also done to check for other disorders:

- Laboratory tests (eg, plasma glucose, BUN, creatinine, Na, Ca, Mg, and P, liver function tests) are done if a metabolic disorder is suspected.
- Head CT is done if meningitis or CNS infection is suspected; if results are normal, a lumbar puncture is required.
- Drug screens may be done to check for unreported use of recreational drugs, although this practice is controversial because positive results do not indicate causality and test results can be inaccurate.

If seizures are refractory and surgical resection is being considered, advanced imaging tests may be done in epilepsy centers. Functional MRI can identify functioning cortex and guide surgical resection. If EEG

and MRI do not clearly identify the epileptic focus, magnetoencephalography (MEG) with EEG (called magnetic source imaging, or MSI) may localize the lesion, avoiding the need for invasive intraoperative mapping procedures. Single-photon emission CT (SPECT) during the peri-ictal period may detect increased perfusion in the seizure focus and help localize the area to be surgically removed. Because injection of contrast is required at the time of seizure, patients must be admitted for continuous EEG-video monitoring when SPECT is done during the peri-ictal period.

Neuropsychologic testing may help identify functional deficits before and after surgery and help predict social and psychologic prognosis and capacity for rehabilitation.

Prognosis

With treatment, seizures are eliminated in one third of patients with epileptic seizures, and frequency of seizures is reduced by > 50% in another third. About 60% of patients whose seizures are well-controlled by drugs can eventually stop the drugs and remain seizure-free.

Sudden unexplained death in epilepsy (SUDEP) is a rare complication of unknown cause.

Treatment

• Elimination of the cause if possible

• Avoidance of or precautions during situations when loss of consciousness could be life threatening

• Drugs to control seizures

• Surgery if ≥ 2 drugs do not control seizures

Optimal treatment is to eliminate the causes whenever possible. If the cause cannot be corrected or identified, anticonvulsants are often required, particularly after a 2nd seizure; usefulness of anticonvulsants after a single seizure is controversial, and risks and benefits should be discussed with the patient. Because the risk of a subsequent seizure is low, drugs may be withheld until a 2nd seizure occurs, particularly in children. In children, certain anticonvulsants cause important behavior and learning problems.

During a generalized tonic-clonic seizure, injury should be prevented by loosening clothing around the neck and placing a pillow under the head. Attempting to protect the tongue is futile and likely to damage the patient's teeth or the rescuer's fingers. Patients should be rolled onto their left side to prevent aspiration. These measures should be taught to the patient's family members and coworkers.

Because partial seizures can become generalized, patients are at risk of losing consciousness and thus should be advised to take certain precautions. Until seizures are controlled, patients should refrain from activities in which loss of consciousness could be life threatening (eg, driving, swimming, climbing, operating power tools, bathing in a bathtub). After seizures are completely controlled (typically for > 6 mo), many such activities can be resumed if appropriate safeguards (eg, lifeguards) are used, and patients should be encouraged to lead a normal life, including exercise and social activities. In a few states, physicians must report patients with seizures to the Department of Motor Vehicles. However, most states allow automobile driving after patients have been seizure-free for 6 mo to 1 yr.

Patients should be advised to avoid cocaine and some other illicit drugs (eg, phencyclidine, amphetamines), which can trigger seizures, and to avoid alcohol. Some drugs (eg, haloperidol, phenothiazines) may lower seizure threshold and should be avoided if possible.

Family members must be taught a commonsense approach toward the patient. Overprotection should be replaced with sympathetic support that lessens negative feelings (eg, of inferiority or self-consciousness); invalidism should be prevented. Institutional care is rarely advisable and should be reserved for severely cognitively impaired patients and for patients with seizures so frequent and violent despite drug treatment that they cannot be cared for elsewhere.

Acute seizures and status epilepticus: Most seizures remit spontaneously in several minutes or less and do not require emergency drug treatment. Status epilepticus and most seizures lasting > 5 min require drugs to terminate the seizures, with monitoring of respiratory status. Endotracheal intubation is necessary if there is any indication of airway compromise. IV access should be quickly obtained, and lorazepam 0.05 to 0.1 mg/kg IV is given at a rate of 2 mg/min. Larger doses are sometimes required. However, if seizures continue after about 8 mg is given, fosphenytoin 15 to 20 PE (phenytoin equivalents)/kg IV is given at a rate of 100 to 150 PE/min; phenytoin 15 to 20 mg/kg IV at a rate of 50 mg/min is a 2nd choice. Additional seizures require an additional 5 to 10 PE/kg of fosphenytoin or 5 to 10 mg/kg of phenytoin. If IV access cannot be obtained, options include IM fosphenytoin and sublingual or rectal benzodiazepines.

Seizures that persist after use of lorazepam and phenytoin define refractory status epilepticus. Recommendations for a 3rd anticonvulsant vary and include phenobarbital, propofol, midazolam, and valproate. Phenobarbital 15 to 20 mg/kg IV at 100 mg/min (3 mg/kg/min in children) is given; continued seizures require another 5 to 10 mg/kg. A loading dose of valproate 10 to 15 mg/kg IV is an alternative. At this point, if status epilepticus has not abated, intubation and general anesthesia are necessary. The optimal anesthetic to use is controversial, but many physicians use propofol 15 to 20 mg/kg at 100 mg/min or pentobarbital 5 to 8 mg/kg (loading dose) followed by infusion of 2 to 4 mg/kg/h until EEG manifestations of seizure activity have been suppressed. Inhalational anesthetics are rarely used. After initial treatment, the cause of status epilepticus must be identified and treated.

Posttraumatic seizures: Drugs are given to prevent seizures if head injury causes significant structural injury (eg, large contusions or hematomas, brain laceration, depressed skull fracture) or a Glasgow Coma Scale (GCS) score of < 10. These drugs reduce risk of seizures during the first week after injury but do not prevent permanent posttraumatic epilepsy months or years later. They should be stopped after 1 wk unless seizures occur. If seizures begin > 1 wk after head injury, long-term treatment with drugs is required.

Principles of long-term treatment: No single drug controls all types of seizures, and different patients require different drugs. Some patients require multiple drugs. Some general principles apply:

- A single drug, usually the 1st or 2nd one tried, controls epileptic seizures in about 60% of patients.

- If seizures are difficult to control from the outset (in 30 to 40% of patients), ≥ 2 drugs may eventually be required.

- If seizures are intractable (refractory to an adequate trial of ≥ 2 drugs), patients should be referred to an epilepsy center to determine whether they are candidates for surgery.

Some drugs (eg, phenytoin, valproate), given IV or orally, reach the targeted therapeutic range very rapidly. Others (eg, lamotrigine, topiramate) must be started at a relatively low dose and gradually increased over several weeks to the standard therapeutic dose, based on the patient's lean body mass. Dose should be tailored to the patient's tolerance of the drug. Some patients have symptoms of drug toxicity when blood drug levels are low; others tolerate high levels without symptoms. If seizures continue, the daily dose is increased by small increments. The appropriate dose of any drug is the lowest dose that stops all seizures and has the fewest adverse effects, regardless of blood drug level. Blood drug levels are only guidelines. Once drug response is known, following the clinical course is more useful than measuring blood levels.

If toxicity develops before seizures are controlled, the dose is reduced to the pretoxicity dose. Then, another drug is added at a low dose, which is gradually increased until seizures are controlled. Patients should be closely monitored because the 2 drugs can interact, interfering with either drug's rate of metabolic degradation. The initial, ineffective drug is then slowly tapered and eventually withdrawn completely. Use of multiple drugs should be avoided if possible because incidence of adverse effects, poor adherence, and drug interactions increases significantly. Adding a 2nd drug helps about 10% of patients, but incidence of adverse effects more than doubles. The blood level of anticonvulsants is altered by many other drugs, and vice versa. Physicians should be aware of all potential drug-drug

interactions before prescribing a new drug.

Once seizures are controlled, the drug should be continued without interruption until patients have been seizure-free for at least 2 yr. At that time, stopping the drug may be considered. Most of these drugs can be tapered by 10% every 2 wk. Relapse is more likely in patients who have had any of the following:

• A seizure disorder since childhood

• Need for > 1 drug to be seizure-free

• Previous seizures while taking an anticonvulsant

• Partial or myoclonic seizures

• Underlying static encephalopathy

• Abnormal EEG results within the last year

Of patients who relapse, about 60% do so within 1 yr, and 80% within 2 yr. Patients who have a relapse when they are not taking anticonvulsants should be treated indefinitely.

Drug choice for long-term treatment: The drugs preferred vary according to type of seizure (see Table 176-4). For more detailed drug-specific information, see Table 176-5.

For partial seizures and generalized tonic-clonic seizures, the newer anticonvulsants

[**Table 176-4.** Choice of Drugs for Seizures]

[**Table 176-5.** Drugs Used in Seizure Disorders[a]]

(eg, clonazepam, felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zosinamide) are no more effective than the established drugs. However, the newer drugs tend to have fewer adverse effects and to be better tolerated.

Infantile spasms, atonic seizures, and myoclonic seizures are difficult to treat. Valproate is preferred, followed by clonazepam. For infantile spasms, corticosteroids for 8 to 10 wk are often effective. The optimal regimen is controversial. ACTH 20 to 60 units IM once/day may be used. A ketogenic diet (a very high fat diet that induces ketosis) may help but is difficult to maintain.

For juvenile myoclonic epilepsy, life-long treatment is usually recommended. Carbamazepine, oxcarbazepine, or gabapentin can exacerbate the seizures.

For febrile seizures, drugs are not recommended unless children have a subsequent seizure in the absence of febrile illness. Previously, many physicians gave phenobarbital or other anticonvulsants to children with complicated febrile seizures to prevent nonfebrile seizures from developing, but this treatment does not appear effective, and long-term use of phenobarbital reduces learning capacity.

For seizures due to alcohol withdrawal, drugs are not recommended. Instead, treating the withdrawal syndrome tends to prevent seizures. Treatment usually includes a benzodiazepine.

Adverse drug effects: All anticonvulsants may cause an allergic scarlatiniform or morbilliform rash, and none is completely safe during pregnancy (see p. 2648).

For patients taking carbamazepine, CBC should be monitored routinely for the first year of therapy. Decreases in WBC count and dose-dependent neutropenia (neutrophil count < 1000/μL) are common. Sometimes, if no other drug can be readily substituted, decreasing the dose can manage these effects. However, if the WBC count decreases rapidly, the drug should be stopped.

Patients taking valproate should have liver function tests every 3 mo for 1 yr; if serum transaminases or ammonia levels increase significantly (> 2 times the upper limit of normal), the drug should be stopped. An increase in ammonia up to 1.5 times the upper limit of normal can be tolerated safely.

Carbamazepine, phenytoin, and valproate are pregnancy category D drugs (ie, teratogenicity occurs in animal and human pregnancies). Risk of neural tube defects is somewhat greater with valproate than other commonly used anticonvulsants. The newer drugs are category C (ie, teratogenicity occurs in animals, but human risk is unknown).

Fetal antiepileptic drug syndrome (cleft lip, cleft palate, cardiac defects, microcephaly, growth retardation, developmental delay, abnormal facies, limb or digit hypoplasia) occurs in 4% of children of women who take anticonvulsants during pregnancy. Yet, because uncontrolled generalized seizures during pregnancy can lead to fetal injury and death, continued treatment with drugs is generally advisable (see p. 2648). The risk should be put in perspective: Alcohol is more toxic to the developing fetus than any anticonvulsant. Taking folate supplements before conception helps reduce risk of neural tube defects and should be recommended to all women who are of childbearing age and who take anticonvulsants.

Surgery: About 10 to 20% of patients have intractable seizures refractory to medical treatment and are potential surgical candidates. If seizures originate from a focal, resectable area in the brain, resection of the epileptic focus usually improves seizure control markedly. If the focus is in the anteromesial temporal lobe, resection eliminates seizures in about 60% of patients. After surgical resection, some patients remain seizure-free without taking anticonvulsants, but many still require the drugs, but in reduced doses and possibly as monotherapy. Because surgery requires extensive testing and monitoring, these patients are best treated in specialized epilepsy centers.

Vagus nerve stimulation: Intermittent electrical stimulation of the left vagus nerve with an implanted pacemaker-like device (vagus nerve stimulator) is used as an adjunct to drug therapy in patients who have intractable seizures and are not candidates for epilepsy surgery. This procedure reduces the number of partial seizures by ≥ 50% in about 40%. After the device is programmed, patients can activate it with a magnet to abort an imminent seizure. Adverse effects include deepening of the voice during stimulation, cough, and hoarseness. Complications are minimal. Duration of effectiveness is unclear.

Chapter 177. Sleep and Wakefulness Disorders

Introduction

(See also Sleep Apnea on p. 1903; for sleep problems in children, see p. 2750.)

Almost half of all people in the US report sleep-related problems. Disordered sleep can cause emotional disturbance, memory difficulty, poor motor skills, decreased work efficiency, and increased risk of traffic accidents. It can even contribute to cardiovascular disorders and mortality.

Approach to the Patient With a Sleep or Wakefulness Disorder

The most commonly reported sleep-related symptoms are insomnia and excessive daytime sleepiness (EDS).

• **Insomnia** is difficulty falling or staying asleep or a sensation of unrefreshing sleep.

• **EDS** is the tendency to fall asleep during normal waking hours.

Insomnia and EDS are not disorders themselves but are symptoms of various sleep-related disorders. Parasomnias are abnormal sleep-related events.

Pathophysiology

There are 2 states of sleep, each marked by characteristic physiologic changes:

• **Nonrapid eye movement (NREM):** NREM sleep constitutes about 75 to 80% of total sleep time in adults. It consists of 4 stages in increasing depth of sleep. Slow, rolling eye movements, which characterize quiet wakefulness and early stage 1 sleep, disappear in deeper sleep stages. Muscle activity decreases as well. Stages 3 and 4 are referred to as deep sleep because arousal threshold is high; people may perceive these stages as high-quality sleep.

• **Rapid eye movement (REM):** REM sleep follows each cycle of NREM sleep. It is characterized by low-voltage fast activity on the EEG and postural muscle atonia. Respiration rate and depth fluctuate dramatically. Most dreams occur during REM sleep.

Progression through the stages, typically followed by a brief interval of REM sleep, occurs cyclically 5 to 6 times a night (see Fig. 177-1).

Individual sleep requirements vary widely, ranging from 6 to 10 h/24 h. Infants sleep a large part of the day; with aging, total sleep time and deep sleep tend to decrease, and sleep becomes more interrupted. In the elderly, stages 3 and 4 may disappear. These changes may account for increasing EDS and fatigue with aging, but their clinical significance is unclear.

Etiology

Some disorders can cause either insomnia or EDS (sometimes both), and some cause one or the other (see Table 177-1).

Insomnia is most often caused by

• Inadequate sleep hygiene

• Psychiatric disorders, particularly mood, anxiety, and substance use disorders

• Miscellaneous medical disorders such as cardiopulmonary disorders, musculoskeletal conditions, and

chronoic pain

• Adjustment sleep disorder and psychophysiologic insomnia

EDS is most often caused by

• Insufficient sleep syndrome

• Obstructive sleep apnea syndrome

• Miscellaneous medical, neurologic, and psychiatric conditions

• Circadian rhythm disorders such as jet lag and shift work sleep disorders

Inadequate sleep hygiene refers to behaviors that are not conducive to sleep. They include consumption of caffeine or sympathomimetic or other stimulant drugs (typically near bedtime, but even in the afternoon for people who are particularly sensitive), exercise or excitement (eg, a thrilling TV show) late in the evening, and an irregular sleep-wake schedule. Patients who compensate for lost sleep by sleeping late or by napping further fragment their nocturnal sleep.

Adjustment insomnia results from acute emotional stressors (eg, job loss, hospitalization) that disrupt sleep.

Psychophysiologic insomnia is insomnia (regardless of cause) that persists well beyond resolution of precipitating factors, usually because patients feel anticipatory anxiety about the prospect of another sleepless night followed by another day of fatigue. Typically, patients spend hours in bed focusing on and brooding about their sleeplessness, and they have greater difficulty falling asleep in their own bedroom than falling asleep away from home.

[**Fig. 177-1.** Typical sleep pattern in young adults.]

Physical disorders that cause pain or discomfort (eg, arthritis, cancer, herniated disks), particularly those that worsen with movement, can cause transient awakenings and poor sleep quality. Nocturnal seizures can also interfere with sleep.

Most **major mental disorders** are associated with EDS and insomnia. About 80% of patients with major depression report EDS and insomnia; conversely, 40% of chronic insomniacs have a major mental disorder, most commonly a mood disorder.

Insufficient sleep syndrome involves not sleeping enough at night despite adequate opportunity to do so, typically because of various social or employment commitments.

Drug-related sleep disorders result from chronic use of or withdrawal from various drugs (see Table 177-2).

Circadian rhythm disorders result in misalignment between endogenous sleep-wake rhythms and environmental light-darkness cycle. The cause may be external (eg, jet lag, shift work) or internal (eg, delayed or advanced sleep phase syndrome).

Central sleep apnea consists of repeated episodes of breathing cessation or shallow breathing during sleep, lasting at least 10 sec, caused by diminished respiratory effort. The disorder typically manifests as insomnia or as disturbed and unrefreshing sleep.

Obstructive sleep apnea consists of episodes of partial or complete closure of the upper airway during sleep, leading to cessation of breathing for > 10 sec. Sometimes patients awaken, gasping. These episodes disrupt sleep and result in a feeling of unrefreshing sleep and EDS.

Narcolepsy is characterized by chronic EDS, often with cataplexy, sleep paralysis, and hypnagogic or

hypnopompic hallucinations. Cataplexy is momentary muscular weakness or paralysis without loss of consciousness that is evoked by sudden emotional reactions (eg, mirth, anger, fear, joy, surprise). Weakness may be confined to the limbs (eg, patients may drop the rod when a fish strikes their line) or may cause a limp fall during hearty laughter (as in "weak with laughter") or sudden anger. Sleep paralysis is momentary inability to move when just falling asleep or immediately after awakening. Hypnagogic and hypnopompic phenomena are vivid auditory or visual illusions or hallucinations that occur when just falling asleep (hypnagogic) or, less often, immediately after awakening (hypnopompic).

Periodic limb movement disorder (PLMD) is characterized by repetitive (usually every 20 to 40 sec) twitching or kicking of the lower extremities during sleep. Patients usually complain of interrupted nocturnal sleep or EDS. They are typically unaware of the movements

[**Table 177-1.** Some Causes of Insomnia and Excessive Daytime Sleepiness]

and brief arousals that follow and have no abnormal sensations in the extremities.

Restless legs syndrome is characterized by an irresistible urge to move the legs and, less frequently, the arms, usually accompanied by paresthesias (eg, creeping or crawling sensations) in the limbs when reclining. To relieve symptoms, patients move the affected extremity by stretching, kicking, or walking. As a result, they have difficulty falling asleep, repeated nocturnal awakenings, or both.

Evaluation

History: History of present illness should include duration and age at onset of symptoms and any events (eg, a life or work change, new drug, new medical disorder) that coincided with onset. Symptoms during sleeping and waking hours should be noted. The quality and quantity of sleep are identified by determining bedtime, latency of sleep (time from bedtime to falling asleep), number and time of awakenings, final morning awakening and arising times, and frequency and duration of naps. Having patients keep a sleep log for several weeks is more accurate than questioning them. Bedtime events (eg, food or alcohol consumption, physical or mental activity) should be evaluated. Intake of and withdrawal from drugs, alcohol, caffeine, and nicotine as well as level and timing of physical activity should also be included.

If EDS is the problem, severity should be quantified based on the propensity for falling asleep in different situations (eg, resting comfortably vs when driving a car). The Epworth Sleepiness Scale (see Table 177-3) may be used; a cumulative score ≥ 10 represents abnormal daytime sleepiness.

Review of systems should check for symptoms of specific sleep disorders, including snoring, interrupted breathing patterns, other nocturnal respiratory disturbances (sleep apnea syndromes); depression, anxiety, mania, and hypomania (mental sleep disorders); restlessness in the legs, an irresistible desire to move them, and jerking leg movements (restless

[**Table 177-2.** Some Drugs that Interfere with Sleep]

[**Table 177-3.** Epworth Sleepiness Scale]

legs syndrome); and cataplexy, sleep paralysis, and hypnagogic phenomena (narcolepsy). Bed partners or other family members can best identify some of these symptoms.

Past medical history should check for known disorders that can interfere with sleep, including COPD, asthma, heart failure, hyperthyroidism, gastroesophageal reflux, neurologic disorders (particularly movement and degenerative disorders), and painful disorders (eg, RA). Risk factors for obstructive sleep apnea include obesity, heart disorders, hypertension, stroke, smoking, snoring, and nasal trauma. Drug history should include questions about use of any drugs associated with sleep disturbance (see Table 177-2).

Physical examination: The physical examination is useful mainly for identifying signs associated with obstructive sleep apnea syndrome. Signs include obesity with fat distributed around the neck or midriff;

large neck circumference (≥ 43.2 cm in males, ≥ 40.6 cm in females); mandibular hypoplasia and retrognathia; nasal obstruction; enlarged tonsils, tongue, uvula, or soft palate; decreased pharyngeal patency; increased obstruction of uvula and soft palate by the tongue; and redundant pharyngeal mucosa. The chest should be examined for expiratory wheezes and kyphoscoliosis. Signs of right ventricular failure should be noted. A thorough neurologic examination should be done.

Red flags: The following findings are of particular concern:

• Falling asleep while driving or other potentially dangerous situations

• Repeated sleep attacks (falling asleep without warning)

• Breathing interruptions or awakening with gasping reported by bed partner

• Unstable cardiac or pulmonary status

• Recent stroke

• Status cataplecticus (continuous cataplexy attacks)

• History of violent behaviors or injury to self or others during asleep

• Frequent sleepwalking or other out-of-bed behavior

Interpretation of findings: Inadequate sleep hygiene and situational stressors are usually apparent in the history. EDS that disappears when sleep time is increased (eg, on weekends or vacations) suggests inadequate sleep syndrome. EDS that occurs without insomnia and is accompanied by cataplexy, hypnagogic/hypnopompic hallucinations, or sleep paralysis suggests narcolepsy.

Difficulty falling asleep (initial insomnia) should be distinguished from difficulty maintaining sleep (sleep maintenance insomnia). Initial insomnia suggests delayed sleep phase syndrome, chronic psychophysiologic insomnia, or childhood phobias. Sleep maintenance insomnia suggests advanced sleep phase syndrome, major depression, central or obstructive sleep apnea, periodic limb movement disorder, or aging. In patients with significant snoring, frequent awakenings, and other risk factors, obstructive sleep apnea is quite likely.

Testing: Tests are usually done when the clinical diagnosis is in doubt or when response to initial presumptive treatment is inadequate. Patients with obvious problems (eg, poor sleep habits, transient stress, shift work) do not require testing.

Polysomnography is particularly useful when obstructive sleep apnea syndrome, narcolepsy, nocturnal seizures, or periodic limb movement disorder is suspected. It also helps clinicians evaluate violent and potentially injurious sleep-related behaviors. It monitors brain activity (via EEG), eye movements, heart rate, respirations, O_2 saturation, and muscle tone and activity during sleep. Video recording may be used to identify abnormal movements during sleep. Polysomnography is typically done in a sleep laboratory; equipment for home use has been devised but is not widely used.

The **multiple sleep latency test** assesses speed of sleep onset in 5 daytime nap opportunities 2 h apart during the patient's typical daytime. Patients lie in a darkened room and are asked to sleep. Onset and stage of sleep (including REM) are monitored by polysomnography. This test's main use is in the diagnosis of narcolepsy.

For the **maintenance of wakefulness test**, patients are asked to stay awake in a quiet room. This test is probably a more accurate measure of ability to remain awake in everyday situations.

Patients with EDS may require laboratory tests of renal, liver, and thyroid function.

Treatment

Specific conditions are treated. Good sleep hygiene (see Table 177-4) is important whatever the cause and is often the only treatment patients with mild problems need.

Hypnotics: General guidelines for use of hypnotics (see Table 177-5) aim at minimizing abuse, misuse, and addiction.

For commonly used hypnotics, see Table 177-6. All hypnotics except ramelteon act at the benzodiazepine recognition site on the γ-aminobutyric (GABA) receptor and augment the inhibitory effects of GABA. The drugs differ primarily in elimination half-life and onset of action. Drugs with a short half-life are used for sleep-onset insomnia. Drugs with a longer half-life are useful for both sleep-onset and sleep-maintenance insomnia; they have greater potential for daytime carryover effects, especially after prolonged use or in the elderly. Patients who experience daytime sedation, incoordination, or other daytime

[**Table 177-4.** Sleep Hygiene]

[**Table 177-5.** Guidelines for the Use of Hypnotics]

effects should avoid activities requiring alertness (eg, driving), and the dose should be reduced, the drug stopped, or, if needed, another drug used. Other adverse effects include amnesia, hallucinations, incoordination, and falls.

Hypnotics should be used cautiously in patients with pulmonary insufficiency. In the elderly, any hypnotic, even in small doses, can cause restlessness, excitement, or exacerbation of delirium and dementia. Rarely, hypnotics can cause complex sleep-related behaviors, such as sleepwalking and even sleep driving; use of higher-than-recommended doses and concurrent consumption of alcoholic beverages may increase risk of such behaviors. Rarely, severe allergic reactions occur.

Prolonged use is discouraged because tolerance can develop (see p. 1524) and because abrupt discontinuation can cause rebound insomnia or even anxiety, tremor, and seizures. These effects are more common with benzodiazepines (particularly triazolam) and less common with the nonbenzodiazepines. Difficulties can be minimized by using the lowest effective dose for brief periods and by tapering the dose before stopping the drug (see also p. 1525).

Other sedatives: Many drugs not specifically indicated for insomnia are used to induce and maintain sleep.

Many patients use alcohol to help them sleep, but alcohol is a poor choice because after prolonged use and at higher doses, it produces unrefreshing, disturbed sleep with frequent nocturnal awakenings, often increasing daytime sleepiness. Alcohol can further impair respiration during sleep in patients with obstructive sleep apnea syndrome.

OTC antihistamines (eg, doxylamine, diphenhydramine) can induce sleep. However, efficacy is unpredictable, and these drugs have adverse effects such as daytime sedation, confusion, and systemic anticholinergic effects, which are particularly worrisome in the elderly.

Low doses of some antidepressants at bedtime may improve sleep, eg, doxepin 25 to 50 mg, paroxetine 5 to 20 mg, trazodone 50 mg, trimipramine 75 to 200 mg. However, antidepressants should be used in these low doses mainly when standard hypnotics are not tolerated (rare) or in higher (antidepressant) doses when depression is present.

Melatonin is a hormone that is secreted by the pineal gland (and that occurs naturally in some foods). Darkness stimulates secretion, and light inhibits it. By binding with melatonin receptors in the suprachiasmatic nucleus, melatonin mediates circadian rhythm, especially during physiologic sleep onset. Oral melatonin (typically 0.5 to 5 mg at bedtime) may be effective for sleep problems due to delayed sleep phase syndrome. It must be taken at the appropriate time (when endogenous melatonin is normally

secreted, in early evening for most people); taken at the wrong time, it can aggravate sleep problems. Its efficacy is largely unproved, and its safety is in question because it appears to stimulate coronary artery changes in animals. Available preparations of melatonin are unregulated, so content and purity cannot be ensured, and the effects of long-term use are unknown. Its use should be supervised by a physician.

Key Points

- Poor sleep hygiene and situational disruptors (eg, shift work, emotional stressors) cause many cases of insomnia.
- Medical conditions (eg, sleep apnea syndromes, pain disorders) and psychiatric conditions (eg, mood disorders) must be considered.
- Sleep studies (eg, polysomnography) are usually done when sleep apnea syndrome, periodic limb movements, or other sleep disorders are suspected; the clinical diagnosis

[Table 177-6. Oral Hypnotics in Common Use]

is in doubt; or when response to initial presumptive treatment is inadequate.

- Hypnotics and sedatives should be used with caution in the elderly.
- Good sleep hygiene may be the only treatment needed by patients with mild insomnia problems.

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders are caused by desynchronization between internal sleep-wake rhythms and the light-darkness cycle. Patients typically have insomnia, excessive daytime sleepiness, or both, which typically resolve as the body clock realigns itself. Diagnosis is clinical. Treatment depends on the cause.

In circadian rhythm disorders, endogenous sleep-wake rhythms (body clock) and the external light-darkness cycle become misaligned (desynchronized). The cause may be internal (eg, delayed or advanced sleep phase syndrome) or external (eg, jet lag, shift work).

If the cause is external, the timing of other circadian body rhythms, including temperature and hormone secretion, is altered; in addition to insomnia and sleepiness, these alterations may cause nausea, malaise, irritability, and depression. Risk of cardiovascular disorders may also be increased.

Repetitive circadian shifts (eg, due to frequent long-distance travel or rotating shift work) are particularly difficult to adapt to, especially when the shifts change in a counterclockwise direction. Counterclockwise shifts are those that shift awakening and sleeping times earlier (eg, when flying eastward or when rotating shifts from days to nights to evenings). Symptoms resolve over several days or, in some patients (eg, the elderly), over a few weeks or months, as rhythms readjust. Because light is the strongest synchronizer of circadian rhythms, exposure to bright light (sunlight or artificial light of 5,000 to 10,000 lux intensity) after desired awakening time speeds readjustment. Melatonin given in the evening may be tried (see p. 1708).

Patients with circadian rhythm disorders often misuse alcohol, hypnotics, and stimulants.

Circadian rhythm disorders include the following.

Circadian rhythm sleep disorder, jet lag type (jeg lag disorder): This syndrome is caused by rapid travel across > 2 time zones. Eastward travel (advancing the sleep cycle) causes more severe symptoms than westward travel (delaying sleep).

If possible, travelers should gradually shift their sleep-wake schedule before travel to approximate that of their destination and maximize exposure to daylight (particularly in the morning) in the new locale. Short-acting hypnotics or wake-promoting drugs (eg, modafinil) may be used for brief periods after arrival.

Circadian rhythm sleep disorder, shift work type (shift work disorder): Severity of symptoms is proportional to the frequency of shift changes, the magnitude of each change, and the frequency of counterclockwise (sleep advancing) changes. Fixed-shift work (ie, fulltime night or evening) is preferable; rotating shifts should go clockwise (ie, day to evening to night). However, even fixed-shift workers have difficulties because daytime noise and light interfere with sleep quality, and workers often shorten sleep times to participate in social or family events.

Shift workers should maximize their exposure to bright light (sunlight or, for night workers, especially constructed bright artificial lightboxes) at times when they should be awake and ensure that the bedroom is as dark and quiet as possible during sleep. Sleep masks and white-noise devices are helpful. When symptoms persist and interfere with functioning, judicious use of hypnotics with a short half-life and wake-promoting drugs is appropriate.

Circadian rhythm sleep disorder, altered sleep phase types: In these syndromes, patients have normal sleep quality and duration with a 24-h circadian rhythm cycle, but the cycle is out of synch with desired or necessary wake times. Less commonly, the cycle is not 24 h, and patients awaken and sleep earlier or later each day. If able to follow their natural cycle, patients have no symptoms.

- Delayed sleep phase syndrome: Patients consistently go to sleep and awaken late (eg, 3 AM and 10 AM). This pattern is more common during adolescence. If required to awaken earlier for work or school, excessive daytime sleepiness results; patients often present because school performance is poor or they miss morning classes. They can be distinguished from people who stay up late by choice because they cannot fall asleep earlier even if they try. Mild phase delay (< 3 h) is treated by progressive earlier arising plus morning bright light therapy, perhaps with melatonin 1 h before the desired bedtime. An alternative method is to progressively delay bedtime and awakening time by 3 h/day until the correct sleep and awake times are reached.

- Advanced sleep phase syndrome: This syndrome (early to bed and early to rise) is more common among the elderly and responds to treatment with bright light in the evening and light-preventing goggles in the morning.

- Non-24-h sleep-wake syndrome: Much less common, this syndrome is characterized by a free-running sleep-wake rhythm. The sleep-wake cycle commonly remains constant in length but is > 24 h, resulting in a delay of sleep and wake times by 1 to 2 h each day. This disorder is more common among blind people.

Insomnia and Excessive Daytime Sleepiness

Many sleep disorders manifest with insomnia and usually excessive daytime sleepiness (EDS). Sleep disorders may be caused by factors inside the body (intrinsic) or outside the body (extrinsic).

Inadequate sleep hygiene: Sleep is impaired by certain behaviors. They include consumption of caffeine or sympathomimetic or other stimulant drugs (typically near bedtime, but even in the afternoon for people who are particularly sensitive), exercise or excitement (eg, a thrilling TV show) late in the evening, and an irregular sleep-wake schedule. Patients who compensate for lost sleep by sleeping late or by napping further fragment nocturnal sleep.

Insomniacs should adhere to a regular awakening time and avoid naps regardless of the amount of nocturnal sleep.

Adequate sleep hygiene can improve sleep (see Table 177-4).

Adjustment insomnia: Acute emotional stressors (eg, job loss, hospitalization) can cause insomnia. Symptoms typically remit shortly after the stressors abate; insomnia is usually transient and brief. Nevertheless, if daytime sleepiness and fatigue develop, especially if they interfere with daytime functioning, short-term treatment with hypnotics is warranted. Persistent anxiety may require specific treatment.

Psychophysiologic insomnia: Insomnia, regardless of cause, may persist well beyond resolution of precipitating factors, usually because patients feel anticipatory anxiety about the prospect of another sleepless night followed by another day of fatigue. Typically, patients spend hours in bed focusing on and brooding about their sleeplessness, and they have greater difficulty falling asleep in their own bedroom than falling asleep away from home.

Optimal treatment combines cognitive-behavioral strategies and hypnotics. Although cognitive-behavioral strategies are more difficult to implement and take longer, effects are longer lasting, up to 2 yr after treatment is ended. These strategies include sleep hygiene (particularly restriction of time in bed), education, relaxation training, stimulus control, and cognitive therapy.

Hypnotics are suitable for patients who need rapid relief and whose insomnia has had daytime effects, such as EDS and fatigue. These drugs must not be used indefinitely in most cases.

Physical sleep disorders: Physical disorders may interfere with sleep and cause insomnia and EDS. Disorders that cause pain or discomfort (eg, arthritis, cancer, herniated disks), particularly those that worsen with movement, cause transient awakenings and poor sleep quality. Nocturnal seizures can also interfere with sleep.

Treatment is directed at the underlying disorder and symptom relief (eg, with bedtime analgesics).

Mental sleep disorders: Most major mental disorders can cause insomnia and EDS. About 80% of patients with major depression report these symptoms. Conversely, 40% of chronic insomniacs have a major mental disorder, most commonly a mood disorder.

Patients with depression may have initial sleeplessness or sleep maintenance insomnia. Sometimes in the depressed phase of bipolar disorder and in seasonal affective disorder, sleep is uninterrupted, but patients complain of unrelenting daytime fatigue.

If depression is accompanied by sleeplessness, antidepressants that provide more sedation (eg, amitriptyline, doxepin, mirtazapine, paroxetine, trazodone) may be chosen. These drugs are used at regular, not low, doses to ensure correction of the depression. These drugs may cause EDS and other adverse effects, such as weight gain. Alternatively, any antidepressant may be used with a hypnotic.

If depression is accompanied by EDS, antidepressants with activating qualities (eg, bupropion, venlafaxine, certain SSRIs such as fluoxetine and sertraline) may be chosen.

Insufficient sleep syndrome (sleep deprivation): Patients with this syndrome do not sleep enough at night, despite adequate opportunity to do so, to stay alert when awake. The cause is usually various social or employment commitments. This syndrome is probably the most common cause of EDS, which disappears when sleep time is increased (eg, on weekends or vacations).

Drug-related sleep disorders: Drug-related sleep disorders: Insomnia and EDS can result from chronic use of CNS stimulants (eg, amphetamines, caffeine), hypnotics (eg, benzodiazepines), other sedatives, antimetabolite chemotherapy, anticonvulsants (eg, phenytoin), oral contraceptives, methyldopa, propranolol, alcohol, and thyroid hormone preparations (see Table 177-2). Commonly prescribed hypnotics can cause irritability and apathy and reduce mental alertness. Many psychoactive drugs can induce abnormal movements during sleep.

Insomnia can develop during withdrawal of CNS depressants (eg, barbiturates, opioids, sedatives), tricyclic antidepressants, monoamine oxidase inhibitors, or illicit drugs (eg, cocaine, heroin, marijuana, phencyclidine). Abrupt withdrawal of hypnotics or sedatives can cause nervousness, tremors, and seizures.

Narcolepsy

Narcolepsy is characterized by chronic excessive daytime sleepiness, often with sudden loss

of muscle tone (cataplexy). Other symptoms include sleep paralysis and hypnagogic and hypnopompic hallucinations. Diagnosis is by polysomnography and multiple sleep latency testing. Treatment is with modafinil, various stimulants, or Na oxybate for excessive daytime sleepiness and certain antidepressants for associated symptoms.

The cause is unknown. In Europe, Japan, and the US, incidence is 0.2 to 1.6/1000. Narcolepsy is equally common in both sexes.

Narcolepsy is strongly associated with specific HLA haplotypes, and children of patients with narcolepsy have a 40-fold increased risk, suggesting a genetic cause. However, concordance in twins is low (25%), suggesting a prominent role for environmental factors, which often trigger the disorder. The neuropeptide hypocretin-1 is deficient in CSF of narcoleptic animals and most human patients, suggesting that the cause may be HLA-associated autoimmune destruction of hypocretin-containing neurons in the lateral hypothalamus.

Narcolepsy features dysregulation of the timing and control of REM sleep. Therefore, REM sleep intrudes into wakefulness and into the transition from wakefulness to sleep. Many symptoms of narcolepsy result from postural muscle paralysis and vivid dreaming, which characterize REM.

Symptoms and Signs

The main symptoms are excessive daytime sleepiness (EDS), cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis; about 10% of patients have all 4. Nocturnal sleep is often also disturbed and some patients develop hypersomnia (prolonged sleep times). Symptoms usually begin in adolescents or young adults without prior illness, although onset can be precipitated by an illness, a stressor, or a period of sleep deprivation. Once established, narcolepsy persists throughout life; life span is unaffected.

EDS: EDS can occur anytime. Sleep episodes vary from few to many per day, and each may last minutes or hours. Patients can resist the desire to sleep only temporarily but can be roused as readily as from normal sleep. Sleep tends to occur during monotonous conditions (eg, reading, watching television, attending meetings) but may also occur during complex tasks (eg, driving, speaking, writing, eating). Patients may also experience sleep attacks—episodes of sleep that strike without warning. Patients may feel refreshed when they awaken yet fall asleep again in a few minutes. Nighttime sleep may be unsatisfying and interrupted by vivid, frightening dreams. Consequences include low productivity, breaches in interpersonal relationships, poor concentration, low motivation, depression, a dramatic reduction in quality of life, and potential for physical injury (particularly due to motor vehicle collisions).

Cataplexy: Momentary muscular weakness or paralysis occurs without loss of consciousness; it is evoked by sudden emotional reactions, such as mirth, anger, fear, joy, or, often, surprise. Weakness may be confined to the limbs (eg, patients may drop the rod when a fish strikes their line) or may cause a limp fall during hearty laughter (as in "weak with laughter") or sudden anger. These attacks resemble the loss of muscle tone that occurs during REM sleep. Cataplexy occurs in about three fourth of patients.

Sleep paralysis: Patients are momentarily unable to move as they are just falling asleep or immediately after they awaken. These occasional episodes may be very frightening. They resemble the motor inhibition that accompanies REM sleep. Sleep paralysis occurs in about one fourth of patients but also in some healthy children and, less commonly, in healthy adults.

Hypnagogic or hypnopompic hallucinations: Particularly vivid auditory or visual illusions or hallucinations may occur when just falling asleep (hypnagogic) or, less often, immediately after awakening (hypnopompic). They are difficult to distinguish from intense reverie and are somewhat similar to vivid dreams, which are normal in REM sleep. Hypnagogic hallucinations occur in about one third of patients, are common among healthy young children, and occasionally occur in healthy adults.

Diagnosis

• Polysomnography

• Multiple sleep latency testing

A delay of 10 yr from onset to diagnosis is common. A history of cataplexy strongly suggests narcolepsy in patients with EDS. Nocturnal polysomnography, followed by multiple sleep latency testing, is diagnostic. Findings include the following:

• REM episodes during at least 2 of 5 daytime nap opportunities

• Average sleep latency (time to fall asleep) of ≤ 8 min, observed after a minimum of 6 h of nocturnal sleep

• No other diagnostic abnormalities on nocturnal polysomnography

The maintenance of wakefulness test does not help with diagnosis but does help monitor treatment efficacy.

Other disorders that can cause chronic EDS are usually suggested by the history and physical examination; brain imaging and blood and urine tests can confirm the diagnosis. These disorders include space-occupying lesions affecting the hypothalamus or upper brain stem, increased intracranial pressure, and certain forms of encephalitis. Hypothyroidism, hyperglycemia, hypoglycemia, anemia, uremia, hypercapnia, hypercalcemia, hepatic failure, and seizure disorders can also cause EDS with or without hypersomnia. Acute, relatively brief EDS and hypersomnia commonly accompany acute systemic disorders such as influenza.

The Kleine-Levin syndrome, a very rare disorder in adolescent boys, causes episodic hypersomnia and hyperphagia. Etiology is unclear but may be an autoimmune response to an infection.

Treatment

• Modafinil

• Sometimes amphetamine derivatives or Na oxybate

• Certain REM-suppressant antidepressants

Some patients who have occasional episodes of sleep paralysis or hypnagogic and hypnopompic hallucinations, infrequent and partial cataplexy, and mild EDS need no treatment. For others, stimulant drugs and anticataplectic drugs are used. Patients should also get enough sleep at night and take brief naps (< 30 min) at the same time every day (typically afternoon).

Patients with mild to moderate EDS benefit from modafinil, a long-acting wake-promoting drug. Its mechanism of action is unclear. Typically, modafinil 100 to 200 mg po is given in the morning. Dose is increased to 400 mg as needed, but some patients require considerably more. If effects do not last into the evening, a small 2nd dose (eg, 100 mg) at noon or 1 PM may be used, although this dose sometimes interferes with nocturnal sleep. Adverse effects include nausea and headache, which are mitigated by lower initial doses and slower titration. Modafinil can lower the effectiveness of oral contraceptives. It has abuse potential, although this is low.

Patients who do not respond to modafinil are usually given amphetamine derivatives instead of or with modafinil. Methylphenidate 5 mg po bid to 20 mg po tid is especially useful for immediate management because modafinil's onset is delayed. Methamphetamine 5 to 20 mg po bid or dextroamphetamine 5 mg po bid to 20 mg po tid may be used; all are available in long-acting preparations and therefore can be dosed once/day in many patients. They can also be used on an as needed basis for patients already taking modafinil because onset is rapid and duration is relatively short. Adverse effects include agitation, hypertension, tachycardia, and mood changes (eg, manic reactions); abuse potential is high.

Pemoline, although less addictive than amphetamines, is not recommended because it may be

hepatotoxic and liver enzymes must be monitored every 2 wk.

Na oxybate can also be used to treat EDS and cataplexy. A dose of 2.25 g po is taken at bedtime while in bed, followed by the same dose 2.5 to 4 h later. The maximum dose is 9 g/night. Adverse effects include headache, nausea, dizziness, nasopharyngitis, somnolence, vomiting, urinary incontinence, and sometimes sleepwalking. Na oxybate is a schedule III drug and has potential for abuse and dependence. It is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency and should not be used in patients with respiratory disorders.

Tricyclic antidepressants (particularly clomipramine, imipramine, and protriptyline) and monoamine oxidase inhibitors are useful in treating cataplexy, sleep paralysis, and hypnagogic and hypnopompic hallucinations. Clomipramine 25 to 150 mg po once/day in the morning seems to be the most potent anticataplectic but should be taken only during the day to reduce nocturnal arousal. SSRIs can also be used.

Idiopathic Hypersomnia

Idiopathic hypersomnia is EDS with or without long sleep time; it is differentiated from narcolepsy by lack of cataplexy, hypnagogic hallucinations, and sleep paralysis.

Idiopathic hypersomnia is not well characterized. Cause is presumed to be CNS dysfunction.

In idiopathic hypersomnia with long sleep time, the history or sleep logs reveal noctural sleep > 10 h; in idiopathic hypersomnia without long sleep time it is > 6 h but < 10 h. In both cases, polysomnography shows no evidence of other sleep abnormalities. Multiple sleep latency testing shows short sleep latencies (< 8 min) with fewer than 2 REM periods.

Treatment is similar to that of narcolepsy, except that anticataplectic drugs are unnecessary.

Parasomnias

Parasomnias are undesirable behaviors that occur during entry into sleep, during sleep, or during arousal from sleep. Diagnosis is clinical. Treatment may include drugs and psychotherapy.

For many of these disorders, history and physical examination can confirm the diagnosis.

Somnambulism: Sitting, walking, or other complex behavior occurs during sleep, usually with the eyes open but without evidence of recognition. Somnambulism is most common during late childhood and adolescence and occurs after and during arousal from nonrapid eye movement (NREM) stage 3 or 4 sleep. Prior sleep deprivation and poor sleep hygiene increase the likelihood of these episodes, and risk is higher for 1st-degree relatives of patients with the disorder. Patients may mumble repetitiously, and some injure themselves on obstacles or stairs. There is no accompanying dream. Usually, patients do not remember the episode.

Treatment is directed at protecting patients from injury. It includes using electronic alarms to awaken patients when they leave the bed, using a low bed, and removing obstacles from the bedroom. Benzodiazepines, particularly clonazepam 0.5 to 2 mg po, at bedtime may help.

Sleep (night) terrors: During the night, patients have episodes of fear, screaming, and flailing, often with sleepwalking. Patients are difficult to awaken. Sleep terrors are more common among children and occur after arousal from NREM stages 3 or 4 sleep; thus, they do not represent nightmares. In adults, sleep terrors can be associated with mental difficulties or alcoholism. If daily activities are affected (eg, if school work deteriorates), intermediate- or long-acting oral benzodiazepines (eg, clonazepam 1 to 2 mg, diazepam 2 to 5 mg) at bedtime may help.

Nightmares: Children are more likely to have nightmares than adults. Nightmares occur during REM sleep, more commonly when fever is present or after alcohol has been ingested. Treatment is directed at

any underlying mental distress.

REM sleep behavior disorder: Verbalization (sometimes profane) and often violent movements (eg, waving the arms, punching, kicking) occur during REM sleep. These behaviors may represent acting out dreams by patients who, for unknown reasons, do not have the atonia normally present during REM sleep.

This disorder is more common among the elderly, particularly those with CNS degenerative disorders (eg, Parkinson's or Alzheimer's disease, vascular dementia, olivopontocerebellar degeneration, multiple system atrophy, progressive supranuclear palsy). It can also occur in patients who have narcolepsy and with use of norepinephrine reuptake inhibitors (eg, atomoxetine, reboxetine, venlafaxine). Cause is usually unknown.

Diagnosis may be suspected based on symptoms reported by patients or the bed partner. Polysomnography can usually confirm the diagnosis. It may detect excessive motor activity during REM; audiovisual monitoring may document abnormal body movements and vocalizations. A neurologic examination is done to rule out neurodegenerative disorders. If an abnormality is detected, CT or MRI may be done.

Treatment is with clonazepam 0.5 to 2 mg po at bedtime. Most patients need to take the drug indefinitely to prevent recurrences; potential for tolerance or abuse is low. Bed partners should be warned about the possibility of harm and may wish to sleep in another bed until symptoms resolve. Sharp objects should be removed from the bedside.

Sleep-related leg cramps:

Muscles of the calf or foot muscles often cramp during sleep in otherwise healthy middle-aged and elderly patients. Diagnosis is based on the history and lack of physical signs or disability.

Prevention includes stretching the affected muscles for several minutes before sleep. Stretching as soon as cramps occur relieves symptoms promptly and is preferable to drug treatment. Numerous drugs (eg, quinine, Ca and Mg supplements, diphenhydramine, benzodiazepines, mexiletine) have been used; none is likely to be effective, and adverse effects may be significant (particularly with quinine and mexiletine). Avoiding caffeine and other sympathetic stimulants may help.

Periodic Limb Movement Disorder and Restless Legs Syndrome

Periodic limb movement disorder (PLMD) and restless legs syndrome (RLS) are characterized by abnormal motions of and sometimes sensations in the lower or upper extremities, which may interfere with sleep.

PLMD and RLS are more common during middle and older age; > 80% of patients with RLS also have PLMD.

The mechanism is unclear but may involve abnormalities in dopamine neurotransmission in the CNS. The disorders can occur in isolation or during drug withdrawal, with use of stimulants or certain antidepressants, during pregnancy, or in patients with chronic renal or hepatic failure, iron deficiency, anemia, and other disorders. In primary RLS, heredity may be involved; more than one third of patients with primary RLS have a family history of it. Risk factors may include a sedentary lifestyle, smoking, and obesity.

Symptoms and Signs

PLMD is characterized by repetitive (usually every 20 to 40 sec) twitching or kicking of the lower or upper extremities during sleep. Patients usually complain of interrupted nocturnal sleep or excessive daytime sleepiness. They are typically unaware of the movements and brief arousals that follow and have no abnormal sensations in the extremities.

RLS is a sensorimotor disorder characterized by an irresistible urge to move the legs, usually accompanied by paresthesias (eg, creeping or crawling sensations) and sometimes pain in the upper or lower extremities, which are more prominent when patients are inactive or recline, and peak in severity around bedtime. To relieve symptoms, patients move the affected extremity by stretching, kicking, or walking. As a result, they have difficulty falling asleep, repeated nocturnal awakenings, or both.

Diagnosis

• For RLS, history alone

• For PLMD, history and polysomnography

Diagnosis may be suggested by the patient's or bed partner's history. Polysomnography is necessary to confirm the diagnosis of PLMD, which is usually apparent as repetitive bursts of electromyographic activity. Polysomnography may be also done after RLS is diagnosed to determine whether patients also have PLMD, but polysomnography is not necessary for diagnosis of RLS itself.

Patients with either disorder should be evaluated medically for disorders that can contribute (eg, with blood tests for anemia and iron deficiency and with hepatic and renal function tests).

Treatment

• Pramipexole or ropinirole

Numerous drugs (eg, dopaminergic drugs, benzodiazepines, anticonvulsants, vitamins and minerals) are used; only dopaminergic drugs are specific for RLS.

Dopaminergic drugs, although often effective, may have adverse effects such as augmentation (symptoms are felt earlier in the day), rebound (symptoms worsen after stopping the drug or after effects of the drug dissipate), nausea, orthostatic hypotension, and insomnia. Two D_2 and D_3 dopamine agonists, pramipexole and ropinirole, are effective and have few serious adverse effects. Pramipexole 0.125 mg po is given 2 h before onset of severe symptoms and increased, as needed, by 0.125 mg po q 2 nights until symptoms are relieved (maximum dose 0.5 mg). Ropinirole 0.25 mg po is given 1 to 3 h before symptoms occur and is increased, as needed, by 0.25 mg nightly (maximum dose 4 mg).

Benzodiazepines may improve sleep continuity but do not reduce limb movements; they should be used cautiously to avoid tolerance and daytime sleepiness. Gabapentin beginning with 300 mg at bedtime can help when RLS is accompanied by pain. Dose is increased by 300 mg weekly (maximum dose 2700 mg). Opioids may also work but are used as a last resort because of tolerance, adverse effects, and abuse potential. Ferritin levels should be obtained and, if low (< 50 µg/L), supplementation with ferrous sulfate 325 mg with 100 to 200 mg of vitamin C at bedtime is warranted. Patients should exercise good sleep hygiene.

Chapter 178. Headache

Approach to the Patient With Headache

Headache is pain in any part of the head, including the scalp, face (including the orbitotemporal area), and interior of the head. Headache is one of the most common reasons patients seek medical attention.

Pathophysiology

Headache is due to activation of pain-sensitive structures in or around the brain, skull, face, sinuses, or teeth.

Etiology

Headache may occur as a primary disorder or be secondary to another disorder. Primary headache disorders include migraine, cluster headache (including chronic paroxysmal hemicrania and hemicrania continua), and tension-type headache. Secondary headache has numerous causes (see Table 178-1).

Overall, the most common causes of headache are

• Tension-type headache

• Migraine

Some causes of headache are common; others are important to recognize because they are

[**Table 178-1.** Disorders Causing Secondary Headache]

dangerous, require specific treatment, or both (see Table 178-2).

Evaluation

Evaluation focuses on determining whether a secondary cause is present. If no cause is identified, it focuses on diagnosing primary headache disorders.

History: History of present illness includes questions about headache location, duration, severity, onset (eg, sudden, gradual), and quality (eg, throbbing, constant, intermittent, pressure-like). Exacerbating and remitting factors (eg, head position, time of day, sleep, light, sounds, physical activity, odors, chewing) are noted. If the patient has had previous or recurrent headaches, the previous diagnosis (if any) needs to be identified, and whether the current headache is similar or different needs to be determined. For recurrent headaches, age at onset, frequency of episodes, temporal pattern (including any relationship to phase of menstrual cycle), and response to treatments (including OTC treatments) are noted.

[**Table 178-2.** Some Characteristics of Headache Disorders by Cause]

Review of systems should seek symptoms suggesting a cause, including

• Vomiting: Migraine, increased intracranial pressure

• Fever: Infection (eg, encephalitis, meningitis, sinusitis)

• Red eye and/or visual symptoms (halos, blurring): Acute angle-closure glaucoma

• Visual field deficits, diplopia, or blurring vision: Ocular migraine, brain mass lesion, idiopathic intracranial hypertension

- Lacrimation and facial flushing: Cluster headache
- Rhinorrhea: Sinusitis
- Pulsatile tinnitus: Idiopathic intracranial hypertension
- Preceding aura: Migraine
- Focal neurologic deficit: Encephalitis, meningitis, intracerebral hemorrhage, subdural hematoma, tumor or other mass lesion
- Seizures: Encephalitis, tumor or other mass lesion
- Syncope at headache onset: Subarachnoid hemorrhage
- Myalgias and/or vision changes (in people > 55 yr): Giant cell arteritis

Past medical history should identify risk factors for headache, including exposure to drugs, substances (particularly caffeine), and toxins (see Table 178-1), recent lumbar puncture, immunosuppressive disorders or IV drug use (risk of infection); hypertension (risk of brain hemorrhage); cancer (risk of brain metastases); and dementia, trauma, coagulopathy, or use of anticoagulants or ethanol (risk of subdural hematoma).

Family and social history should include any family history of headaches, particularly because migraine headache may be undiagnosed in family members.

Physical examination: Vital signs, including temperature, are measured. General appearance (eg, whether restless or calm in a dark room) is noted. A general examination, with a focus on the head and neck, and a full neurologic examination are done.

The scalp is examined for areas of swelling and tenderness. The ipsilateral temporal artery is palpated, and both temporomandibular joints are palpated for tenderness and crepitance while the patient opens and closes the jaw.

The eyes and periorbital area are inspected for lacrimation, flushing, and conjunctival injection. Pupillary size and light responses, extraocular movements, and visual fields are assessed. The fundi are checked for spontaneous venous pulsations and papilledema. If patients have vision-related symptoms or eye abnormalities, visual acuity is measured. If the conjunctiva is red, the anterior chamber and cornea are examined with a slit lamp if possible, and intraocular pressure is measured.

The nares are inspected for purulence. The oropharynx is inspected for swellings, and the teeth are percussed for tenderness.

Neck is flexed to detect discomfort, stiffness, or both, indicating meningismus. The cervical spine is palpated for tenderness.

Red flags: The following findings are of particular concern:

- Neurologic symptoms or signs (eg, altered mental status, weakness, diplopia, papilledema, focal neurologic deficits)
- Immunosuppression or cancer
- Meningismus
- Onset of headache after age 50

- Thunderclap headache (severe headache that peaks within a few seconds)
- Symptoms of giant cell arteritis (eg, visual disturbances, jaw claudication, fever, weight loss, temporal artery tenderness, proximal myalgias)
- Systemic symptoms (eg, fever, weight loss)
- Progressively worsening headache
- Red eye and halos around lights

Interpretation of findings: If similar headaches recur in patients who appear well and have a normal examination, the cause is rarely ominous. Headaches that have recurred since childhood or young adulthood suggest a primary headache disorder. If headache type or pattern clearly changes in patients with a known primary headache disorder, secondary headache should be considered.

Most single symptoms of primary headache disorders other than aura are nonspecific. A combination of symptoms and signs is more characteristic (see Table 178-2).

Red flag findings suggest a cause (see Table 178-3).

Testing: Most patients can be diagnosed without testing. However, some serious disorders may require urgent or immediate testing. Some patients require tests as soon as possible. CT (or MRI) should be done in patients with any of the following findings:

- Thunderclap headache
- Altered mental status
- Meningismus
- Papilledema
- Signs of sepsis (eg, rash, shock)
- Acute focal neurologic deficit
- Severe hypertension (eg, systolic > 220 mm Hg or diastolic > 120 mm Hg on consecutive readings)

In addition, if meningitis, subarachnoid hemorrhage, or encephalitis is being considered,

[**Table 178-3.** Matching Red Flag Findings with a Cause for Headache]

lumbar puncture and CSF analysis should be done, if not contraindicated by imaging results.

Tonometry should be done if findings suggest acute narrow-angle glaucoma (eg, visual halos, nausea, corneal edema, shallow anterior chamber).

Other testing should be done within hours or days, depending on the acuity and seriousness of findings and suspected causes.

Neuroimaging, usually MRI, should be done if patients have any of the following:

- Focal neurologic deficit of subacute or uncertain onset
- Age > 50 yr

- Weight loss
- Cancer
- HIV infection or AIDS
- Change in an established headache pattern
- Diplopia

ESR should be done if patients have visual symptoms, jaw or tongue claudication, temporal artery signs, or other findings suggesting giant cell arteritis.

CT of the paranasal sinuses is done to rule out complicated sinusitis if patients have a moderately severe systemic illness (eg, high fever, dehydration, prostration, tachycardia) and findings suggesting sinusitis (eg, frontal, positional headache, epistaxis, purulent rhinorrhea).

Lumbar puncture and CSF analysis are done if headache is progressive and findings suggest idiopathic intracranial hypertension (eg, transient obscuration of vision, diplopia, pulsatile intracranial tinnitus) or chronic meningitis (eg, lethargy, vomiting, focal neurologic deficits).

Treatment

Treatment of headache is directed at the cause.

Geriatrics Essentials

New-onset headache after age 50 should be considered a secondary disorder until proven otherwise.

Key Points

- Recurrent headaches that began at a young age in patients with a normal examination are usually benign.
- Immediate neuroimaging is recommended for patients with altered mental status, seizures, papilledema, focal neurologic deficits, or thunderclap headache.
- CSF analysis is required for patients with meningismus and usually, after neuroimaging, for immunosuppressed patients.
- Patients with thunderclap headache require CSF analysis even if CT and examination findings are normal.

Cluster Headache

Cluster headaches cause excruciating, unilateral periorbital or temporal pain, with ipsilateral autonomic symptoms (ptosis, lacrimation, rhinorrhea, nasal congestion). Diagnosis is clinical. Acute treatment is with parenteral triptans, dihydroergotamine, or O_2. Prevention is with verapamil, lithium, topiramate, divalproex, or a combination.

Cluster headache affects primarily men, typically beginning at age 20 to 40; prevalence in the US is 0.4%. Usually, cluster headache is episodic; for 1 to 3 mo, patients experience ≥ 1 attack/day, followed by remission for months to years. Some patients have cluster headaches without remission.

Pathophysiology is unknown, but the periodicity suggests hypothalamic dysfunction. Alcohol intake triggers cluster headache during the attack period but not during remission.

Symptoms and Signs

Symptoms are distinctive. Attacks usually occur at the same time each day, often awakening patients from sleep. Pain is always unilateral in an orbitotemporal distribution. It is excruciating, peaking within minutes; it usually subsides spontaneously within 30 min to 1 h. Patients are agitated, restlessly pacing the floor, unlike migraine patients who prefer to lie quietly in a darkened room.

Autonomic features, including nasal congestion, rhinorrhea, lacrimation, facial flushing, and Horner's syndrome, are prominent and usually occur on the same side as the headache.

Diagnosis

• Clinical evaluation

Diagnosis is based on the distinctive symptom pattern and exclusion of intracranial abnormalities.

Other unilateral primary headache syndromes with autonomic symptoms should be excluded:

• Chronic paroxysmal hemicrania: Attacks are more frequent (> 5/day) and much briefer (usually just minutes) than in cluster headache.

• Hemicrania continua: Moderately severe continuous unilateral head pain occurs with superimposed brief episodes of more intense pain.

These 2 painful disorders, unlike cluster headache (and migraine), respond dramatically to indomethacin, but not to other NSAIDs.

Treatment

• For aborting attacks, parenteral triptans, dihydroergotamine, or 100% O_2

• For long-term prophylaxis, verapamil, lithium, topiramate, divalproex, or a combination

Acute attacks of cluster headache can be aborted with either parenteral triptans or dihydroergotamine alone (see
Table 178-4) and/or 100% O_2 inhalation given by nonrebreathing face mask.

All patients require preventive drugs because cluster headache is frequent, severe, and incapacitating. Prednisone (eg, 60 mg po once/day) or a greater occipital nerve block (with a local anesthetic and a corticosteroid) can provide prompt temporary prevention while preventive drugs with slower onset of action (eg, verapamil, lithium, topiramate, divalproex) are initiated.

Idiopathic Intracranial Hypertension

(Benign Intracranial Hypertension; Pseudotumor Cerebri)

Idiopathic intracranial hypertension causes increased intracranial pressure without a mass lesion or hydrocephalus, probably by obstructing venous drainage; CSF composition is normal.

Idiopathic intracranial hypertension typically occurs in women of childbearing age. Incidence is 1/100,000 in normal-weight women but 20/100,000 in obese women. Intracranial pressure is elevated (> 250 mm H_2O); the cause is unknown but probably involves obstruction of cerebral venous outflow.

Symptoms and Signs

Almost all patients have a daily or near daily generalized headache of fluctuating intensity, at times with nausea. They may also have transient obscuration of vision, diplopia (due to 6th cranial nerve dysfunction), and pulsatile intracranial tinnitus. Vision loss begins peripherally and may not be noticed by

patients until late in the course. Permanent vision loss is the most serious consequence.

Bilateral papilledema is common; a few patients have unilateral or no papilledema. In some asymptomatic patients, papilledema is discovered during routine ophthalmoscopic examination. Neurologic examination may detect partial 6th cranial nerve palsy but is otherwise unremarkable.

[**Table 178-4.** Drugs for Migraine and Cluster Headaches*]

Diagnosis

• MRI with magnetic resonance venography

• Lumbar puncture

Diagnosis is suspected clinically and established by brain imaging (preferably MRI with magnetic resonance venography) that shows normal results, followed by lumbar puncture showing elevated opening pressure and normal CSF composition. Use of certain drugs and certain disorders can produce a clinical picture resembling idiopathic intracranial hypertension (see Table 178-5).

Treatment

• Acetazolamide

• Often weight loss

• NSAIDs or drugs used for migraines

Treatment is aimed at reducing pressure and relieving symptoms. Acetazolamide 250 mg po qid is used as a diuretic. Obese patients are encouraged to lose weight, which may help reduce intracranial pressure. Serial lumbar punctures are controversial but are sometimes used. Any potential causes (disorders or drugs) are corrected or eliminated if possible. NSAIDs or drugs used for migraine may relieve headache.

[**Table 178-5.** Conditions Associated with Papilledema and Idiopathic Intracranial Hypertension]

If vision deteriorates despite treatment, optic nerve sheath fenestration, shunting (lumboperitoneal or ventriculoperitoneal), or endovascular venous stenting may be indicated. Bariatric surgery with sustained weight loss may cure the disorder in obese patients who were otherwise unable to lose weight.

Frequent ophthalmologic assessment (including quantitative visual fields) is required to monitor response to treatment; testing visual acuity is not sensitive enough to warn of impending vision loss.

Migraine

Migraine is an episodic primary headache disorder. Symptoms typically last 4 to 72 h and may be severe. Pain is often unilateral, throbbing, worse with exertion, and accompanied by symptoms such as nausea and sensitivity to light, sound, or odors. Auras occur in about 25% of patients, usually just before but sometimes after the headache. Diagnosis is clinical. Treatment is with triptans, dihydroergotamine, antiemetics, and analgesics. Preventive regimens include lifestyle modifications (eg, of sleeping habits or diet) and drugs (eg, β-blockers, amitriptyline, topiramate, divalproex).

Epidemiology

Migraine is the most common cause of recurrent moderate to severe headache; 1-year prevalence is 18% for women and 6% for men in the US. Migraine most commonly begins during puberty or young adulthood, waxing and waning in frequency and severity over the ensuing years; it often diminishes after

age 50. Studies show familial aggregation of migraine.

Pathophysiology

Migraine is thought to be a neurovascular pain syndrome with altered central neuronal processing (activation of brain stem nuclei, cortical hyperexcitability, and spreading cortical depression) and involvement of the trigeminovascular system (triggering neuropeptide release, which causes painful inflammation in cranial vessels and the dura mater).

Many potential migraine triggers have been identified; they include the following:

• Drinking red wine

• Skipping meals

• Excessive afferent stimuli (eg, flashing lights, strong odors)

• Weather changes

• Sleep deprivation

• Stress

• Hormonal factors

Head trauma, neck pain, or temporomandibular joint dysfunction sometimes triggers or exacerbates migraine.

Fluctuating estrogen levels are a potent migraine trigger. Many women have onset of migraine at menarche, severe attacks during menstruation (menstrual migraine), and worsening during menopause. For most women, migraines remit during pregnancy (but sometimes they worsen during the 1st or 2nd trimester). Oral contraceptives and other hormone therapy occasionally trigger or worsen migraine and have been associated with stroke in women who have migraine with aura.

A rare subtype of migraine called familial hemiplegic migraine is associated with genetic defects on chromosomes 1, 2, and 19. The role of genes in the more common forms of migraine is under study.

Symptoms and Signs

Often, attacks are heralded by a prodrome (a sensation that a migraine is beginning), which may include mood changes, loss of appetite, nausea, or a combination.

An aura precedes attacks in about 25% of patients. Auras are temporary neurologic disturbances that can affect sensation, balance, muscle coordination, speech, or vision; they last minutes to an hour. The aura may persist after headache onset. Most commonly, auras involve visual symptoms (fortification spectra —eg, binocular flashes, arcs of scintillating lights, bright zigzags, scotomata). Paresthesias and numbness (typically starting in one hand and marching to the ipsilateral arm and face), speech disturbances, and transient brain stem dysfunction (causing, eg, ataxia, confusion or even obtundation) are less common than visual auras. Some patients have an aura with little or no headache.

Headache varies from moderate to severe, and attacks last from 4 hours to several days, typically resolving with sleep. The pain is often unilateral but may be bilateral, most often in a frontotemporal distribution, and is typically described as pulsating or throbbing.

Migraine is more than a headache. Associated symptoms such as nausea (and occasionally vomiting), photophobia, sonophobia, and osmophobia are prominent. Patients report difficulty concentrating during attacks. Routine physical activity usually aggravates migraine headache; this effect, plus the photophobia and sonophobia, encourages most patients to lie in a dark, quiet room during attacks. Severe attacks can

be incapacitating, disrupting family and work life.

Attacks vary significantly in frequency and severity. Many patients have several types of headache, including milder attacks without nausea or photophobia; they may resemble tension-type headache but are a forme fruste of migraine.

Chronic migraines: Patients with episodic migraine can develop chronic migraine. These patients have headaches ≥ 15 days/mo. This headache disorder used to be called combination or mixed headache because it had features of migraine and tension-type headache. These headaches often develop in patients who overuse drugs for acute treatment of headaches.

Other symptoms: Other, rare forms of migraine can cause other symptoms. Basilar artery migraine causes combinations of vertigo, ataxia, visual field loss, sensory disturbances, focal weakness, and altered level of consciousness. Hemiplegic migraine, which may be sporadic or familial, causes unilateral weakness.

Diagnosis

• Clinical evaluation

Diagnosis is based on characteristic symptoms and a normal physical examination, which includes a thorough neurologic examination.

Red flag findings include the following:

• Pain that reaches peak intensity within a few seconds or less (thunderclap headache)

• Onset after age 50

• Headaches that increase in intensity or frequency for weeks or longer

• History of cancer (brain metastases) or an immunosuppressive disorder (eg, HIV infection, AIDS)

• Fever, meningismus, altered mental status, or a combination

• Persistent focal neurologic deficits

• Papilledema

• A clear change in an established headache pattern

Patients with characteristic symptoms and no red flag findings do not require testing. Patients with red flag findings often require brain imaging and sometimes lumbar puncture.

Common diagnostic errors include the following:

• Not realizing that migraine often causes bilateral pain and is not always described as throbbing

• Misdiagnosing migraine as sinus headache or eyestrain because of autonomic and visual symptoms of migraine

• Assuming that any headache in patients known to have migraine represents another migraine attack—a thunderclap headache or a change in the previous headache pattern may indicate a new, potentially serious disorder

• Mistaking migraine with aura for a transient ischemic attack, especially when the aura occurs without headache, in older people

Several unusual disorders can mimic migraine with aura: dissection of the carotid or vertebral artery, cerebral vasculitis, moyamoya disease, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), and MELAS (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes) syndrome.

Prognosis

For some patients, migraine is an infrequent, tolerable inconvenience. For others, it is a devastating disorder resulting in frequent periods of incapacity, loss of productivity, and severely impaired quality of life.

Treatment

• Elimination of triggers

• For stress, behavioral interventions

• For mild headaches, acetaminophen or NSAIDs

• For severe attacks, triptans

A thorough explanation of the disorder helps patients understand that, although migraine cannot be cured, it can be controlled, enabling them to better participate in treatment.

Patients are urged to keep a written headache diary to document the number and timing of attacks, possible triggers, and response to treatment. Identified triggers are eliminated when possible. Behavioral interventions (biofeedback, stress management, psychotherapy) are used when stress is a major trigger or when analgesics are being overused. Treatment of acute migraine headache is based on frequency, duration, and severity of attacks.

Mild to moderate attacks: NSAIDs or acetaminophen is used. Analgesics containing opioids, caffeine, or butalbital are helpful for infrequent, mild attacks but are prone to being overused, sometimes leading to a type of daily headache syndrome called medication overuse headache. Opioids should be used as a last resort (rescue drug) for severe headache when other measures are ineffective.

An antiemetic alone may be used to relieve mild or moderate attacks.

Severe attacks: If mild attacks evolve into incapacitating migraine or if attacks are severe from the onset, triptans are used. Triptans are selective serotonin 1B,1D receptor agonists. They are not analgesic per se but specifically block the release of vasoactive neuropeptides that trigger migraine pain. Triptans are most effective when taken at the onset of attacks. They are available in oral, intranasal, and sc forms (see Table 178-4); sc forms are more effective but have more adverse effects. Overuse of triptans can also lead to medication overuse headache. When nausea is prominent, combining a triptan with an antiemetic at the onset of attacks is effective.

IV dihydroergotamine with a dopamine antagonist antiemetic (eg, metoclopramide 10 mg IV, prochlorperazine 5 to 10 mg IV) helps abort very severe, persistent attacks. Dihydroergotamine is also available in an sc form and as a nasal spray.

Triptans and dihydroergotamine can cause coronary artery constriction and are thus contraindicated in patients with coronary artery disease or uncontrolled hypertension; these drugs must be used with caution in elderly patients and in patients with vascular risk factors.

A good response to dihydroergotamine or a triptan should not be interpreted as diagnostic for migraine because these drugs may relieve headache due to subarachnoid hemorrhage and other structural abnormalities.

Prochlorperazine suppositories (25 mg) or tablets (10 mg) are an option for patients who cannot tolerate

triptans and other vasoconstrictors.

Chronic migraines: The same drugs used to prevent episodic migraine are used to treat chronic migraine.

Prevention

Daily preventive therapy is warranted when frequent migraines interfere with activity despite acute treatment.

For patients who use analgesics frequently, particularly those with medication overuse headache, preventive drugs (see Table 178-4) should be combined with a program for stopping overused analgesics. Choice of drug can be guided by coexisting disorders, as for the following:

- A small bedtime dose of amitriptyline for patients with insomnia
- A β-blocker for patients with anxiety or coronary artery disease
- Topiramate, which can induce weight loss, for obese patients or for patients who wish to avoid weight gain
- Divalproex for patients with mania

Post-Lumbar Puncture and Other Low-Pressure Headaches

Low-pressure headaches result from reduction in CSF volume and pressure due to lumbar puncture or spontaneous or traumatic CSF leaks.

Removal of CSF by lumbar puncture (LP) reduces CSF volume and pressure, as do spontaneous or traumatic CSF leaks.

Headache after LP is common, usually occurring hours to a day or two afterward, and can be severe. Younger patients with a small body mass are at greatest risk. Using small, noncutting needles reduces risk. The amount of CSF removed and duration of recumbency after LP do not affect incidence.

Spontaneous CSF leaks may result when an arachnoid cyst along the spinal canal ruptures. Coughing or sneezing may cause the rupture. CSF may leak after certain head or facial injuries (eg, basilar skull fractures).

Headache results when head elevation while sitting or standing stretches the pain-sensitive basal meninges. Headaches are intense, postural, and often accompanied by neck pain, meningismus, and vomiting. Headache is alleviated only by lying completely flat.

Diagnosis

- Clinical evaluation

Post-LP headache is clinically obvious, and testing is rarely needed; other low-pressure headaches may require brain imaging. MRI with gadolinium often shows diffuse enhancement of the pachymeninges and, in severe cases, downward sagging of the brain. CSF pressure is typically low or unobtainable if patients have been upright for any length of time (gravity accelerates CSF loss).

Treatment

- Hydration and analgesics
- Sometimes an epidural blood patch

The first line of treatment is recumbency, hydration, an elastic abdominal binder, mild analgesics, and caffeine. If post-LP headache persists after a day of such treatment, an epidural blood patch (injection of a few mL of the patient's clotted venous blood into the lumbar epidural space) is usually effective. A blood patch may also be effective for spontaneous or traumatic CSF leaks, which rarely require surgical closure.

Tension-Type Headache

Tension-type headache causes mild generalized pain without the incapacity, nausea, or photophobia associated with migraine.

Tension-type headaches may be episodic or chronic. Episodic tension-type headaches occur < 15 days/mo. Episodic tension-type headache is very common; most patients obtain relief with OTC analgesics and do not seek medical attention. Tension-type headaches that occur ≥ 15 days/mo are considered chronic.

Symptoms and Signs

The pain is usually mild to moderate and often described as viselike. These headaches originate in the occipital or frontal region bilaterally and spread over the entire head. Unlike migraine headaches, tension-type headaches are not accompanied by nausea and vomiting and are not made worse by physical activity, light, sounds, or smells. Potential triggers for chronic tension-type headache include sleep disturbances, stress, temporomandibular joint dysfunction, neck pain, and eyestrain.

Many patients with frequent tension-type headache often have mild headaches with some but not all features of migraine; these headaches resemble tension-type headaches but are a forme fruste of migraine and respond to migraine specific drugs.

Episodic headaches may last 30 min to several days. They typically start several hours after waking and worsen as the day progresses. They rarely awaken patients from sleep.

Chronic headaches may vary in intensity throughout the day but are almost always present.

Diagnosis

• Clinical evaluation

Diagnosis is based on characteristic symptoms and a normal physical examination, which includes a neurologic examination. Potential triggers for chronic tension-type headache should be identified and treated.

Treatment

• Analgesics

• Sometimes behavioral and psychologic intervention

Some drugs used to prevent migraine, particularly amitriptyline, can help prevent chronic tension-type headache.

For most mild to moderate tension-type headaches, OTC analgesics (eg, aspirin, acetaminophen) can provide relief. Massaging the affected area may help.

For severe headaches, prescription analgesics (eg, those that contain opioids) may be used.

Behavioral and psychologic interventions (eg, relaxation and stress management techniques) are often used and are effective, especially when combined with drug treatment.

Chapter 179. Brain Infections

Introduction

Inflammation of the brain (encephalitis) is usually secondary to viral infection. Other brain infections include brain abscesses, helminthic infections, prion diseases, and subdural empyema. Meningitis (inflammation of the brain and spinal cord—see p. 1734), cytomegalovirus infection (see p. 1416), and HIV infection (see p. 1438) can also affect the brain. Slow virus infections, such as progressive multifocal leukoencephalopathy (see p. 1731), caused by JC virus, or subacute sclerosing panencephalitis, caused by the measles virus, are characterized by a long incubation and a prolonged course. Slow virus infection involving the rubella virus is now very rare in the US.

Brain Abscess

A brain abscess is an intracerebral collection of pus. Symptoms may include headache, lethargy, fever, and focal neurologic deficits. Diagnosis is by contrast-enhanced MRI or CT and sometimes culture. Treatment is with antibiotics and usually surgical drainage.

An abscess forms when an area of cerebral inflammation becomes necrotic and encapsulated by glial cells and fibroblasts. Edema around the abscess may increase intracranial pressure.

Etiology

A brain abscess can result from

• Direct extension of cranial infections (eg, osteomyelitis, mastoiditis, sinusitis, subdural empyema)

• Penetrating head wounds (including neurosurgical procedures)

• Hematogenous spread (eg, in bacterial endocarditis, congenital heart disease with right-to-left shunt, or IV drug abuse)

• Unknown causes

The bacteria involved are usually anaerobic and sometimes mixed, often including anaerobic streptococci or *Bacteroides*. Staphylococci are common after cranial trauma, neurosurgery, or endocarditis. Enterobacteriaceae are common with ear infections. Fungi (eg, *Aspergillus*) and protozoa (eg, *Toxoplasma gondii*, particularly in HIV-infected patients) can cause abscesses.

Symptoms and Signs

Symptoms result from increased intracranial pressure and mass effect. Headache, nausea, vomiting, lethargy, seizures, personality changes, papilledema, and focal neurologic deficits develop over days to weeks. Fever, chills, and leukocytosis may develop before the infection is encapsulated, but they may be absent or subside over time.

Diagnosis

• MRI

• Sometimes CT-guided aspiration

When symptoms suggest an abscess, contrast-enhanced MRI or CT is done. An abscess appears as an edematous mass with ring enhancement, which may be difficult to distinguish from a tumor or occasionally infarction; CT-guided aspiration, culture, surgical excision, or a combination may be necessary. Lumbar puncture is not done because it may precipitate transtentorial herniation and because CSF findings are nonspecific (see

Table 168-1 on p. 1594).

Treatment

• Antibiotics (initially cefotaxime or ceftriaxone, then as guided by culture and susceptibility testing)

• Usually surgical drainage

• Sometimes corticosteroids, anticonvulsants, or both

All patients receive antibiotics for ≥ 4 to 8 wk. Initial empiric antibiotics include cefotaxime 2 g IV q 4 h or ceftriaxone 2 g IV q 12 h; both are effective against streptococci, Enterobacteriaceae, and most anaerobes but not against *Bacteroides fragilis*, which requires metronidazole 15 mg/kg (loading dose), then 7.5 mg/kg IV q 6 h. If *Staphylococcus aureus* is suspected, vancomycin 1 g q 12 h is used until sensitivity to nafcillin (2 g q 4 h) is determined. Response to antibiotics is best monitored by serial CT or MRI.

Drainage, stereotactic or open, provides optimal therapy and is necessary for most abscesses that are solitary and surgically accessible, particularly those > 2 cm in diameter.

Patients with increased intracranial pressure may benefit from a short course of high-dose corticosteroids (dexamethasone 10 mg IV once, then 4 mg IV q 6 h for 3 or 4 days). Anticonvulsants are sometimes recommended to prevent seizures.

Encephalitis

Encephalitis is inflammation of the parenchyma of the brain, resulting from direct viral invasion. Acute disseminated encephalomyelitis is brain and spinal cord inflammation caused by a hypersensitivity reaction to a virus or another foreign protein. Both disorders can be caused by many viruses. Symptoms include fever, headache, and altered mental status, often accompanied by seizures or focal neurologic deficits. Diagnosis requires CSF analysis and neuroimaging. Treatment is supportive and, for certain causes, includes antiviral drugs.

Etiology

Encephalitis may be a primary manifestation or a secondary (postinfectious) immunologic complication of viral infection.

Primary viral infection: Viruses causing primary encephalitis directly invade the brain. These infections may be

• Epidemic (eg, due to arbovirus, poliovirus, echovirus, or coxsackievirus)

• Sporadic (eg, due to herpes simplex, rabies, varicella-zoster, or mumps virus)

Mosquito-borne arboviral encephalitides infect people during the spring, summer, and early fall when the weather is warm. Incidence in the US varies from 150 to > 4000 cases yearly, mostly in children. Most cases occur during epidemics. Among arboviruses, La Crosse virus (California virus) is identified as a cause primarily in the north central US. However, the virus is geographically widespread, and La Crosse encephalitis is probably underrecognized and accounts for most cases of arbovirus encephalitis in children. Mortality rate is probably < 1%. Until 1975, St. Louis encephalitis occurred every 10 yr, mostly in the central and eastern US; it is now rare. As of 2009, West Nile encephalitis has spread from the East Coast, where it first appeared in 1999, to all of the western states. Mortality rate is about 9%. Small epidemics of eastern equine encephalitis occur every 10 to 20 yr in the eastern US, mainly among young children and people > 55. Mortality rate is about 50 to 70%. For unknown reasons, western equine encephalitis has largely disappeared from the US since 1988.

In the US, the most common sporadic encephalitis is caused by herpes simplex virus (HSV); hundreds to

several thousand cases occur yearly. Most are due to HSV-1, but HSV-2 may be more common among immunocompromised patients. HSV encephalitis occurs at any time of the year, tends to affect patients < 20 or > 40 yr, and is often fatal if untreated.

Primary encephalitis can occur as a late consequence of a viral infection. The best known types are HIV encephalopathy (which causes dementia—see p. 1682), subacute sclerosing panencephalitis (which occurs years after a measles infection and is thought to represent reactivation of the original infection—see p. 1466), and progressive multifocal leukoencephalopathy (which is caused by reactivation of JC virus—see p. 1731).

Immunologic reaction: Encephalitis can occur as a secondary immunologic complication of certain viral infections or vaccinations. Inflammatory demyelination of the brain and spinal cord can occur 1 to 3 wk later (as acute disseminated encephalomyelitis); the immune system attacks one or more CNS antigens that resemble proteins of the infectious agent. The most common causes used to be measles, rubella, chickenpox, and mumps (all now uncommon because childhood vaccination is widespread); smallpox vaccine; and live-virus vaccines (eg, the older rabies vaccines prepared from sheep or goat brain). In the US, most cases now result from influenza A or B virus, enteroviruses, Epstein-Barr virus, hepatitis A or B virus, or HIV.

Pathophysiology

In acute encephalitis, cerebral edema and petechial hemorrhages occur throughout the hemispheres, brain stem, cerebellum, and, occasionally, spinal cord. Direct viral invasion of the brain usually damages neurons, sometimes producing visible inclusion bodies. Severe infection, particularly untreated HSV encephalitis, can cause brain hemorrhagic necrosis.

Acute disseminated encephalomyelitis is characterized by perivenous demyelination and absence of virus in the brain.

Symptoms and Signs

Symptoms include fever, headache, and altered mental status, often accompanied by seizures and focal neurologic deficits. A GI or respiratory prodrome may precede these symptoms. Meningeal signs are typically mild and less prominent than other manifestations. Status epilepticus, particularly convulsive status epilepticus, or coma suggests severe brain inflammation and a poor prognosis. Olfactory seizures, manifested as an aura of foul smells (rotten eggs, burnt meat), indicate temporal lobe involvement and suggest HSV encephalitis.

Diagnosis

• MRI

• CSF testing

Encephalitis is suspected in patients with unexplained alterations in mental status. Clinical presentation and differential diagnoses may suggest certain diagnostic tests, but MRI and CSF analysis (including PCR for HSV) are usually done, sometimes with other tests to identify the causative virus. Despite extensive testing, the cause of most cases of encephalitis remains unknown.

MRI: MRI is sensitive for early HSV encephalitis, showing edema in the orbitofrontal and temporal areas, which HSV typically infects. MRI shows demyelination in progressive multifocal leukoencephalopathy and may show basal ganglia and thalamic abnormalities in West Nile and eastern equine encephalitis. MRI can also exclude lesions that mimic viral encephalitis (eg, brain abscess, sagittal sinus thrombosis). CT is much less sensitive than MRI for HSV encephalitis but can help because it is rapidly available and can exclude disorders that make lumbar puncture risky (eg, mass lesions, hydrocephalus, cerebral edema).

CSF testing: If encephalitis is present, CSF is characterized by lymphocytic pleocytosis, normal glucose, mildly elevated protein, and an absence of pathogens using Gram stain and culture (similar to CSF in

aseptic meningitis). CSF abnormalities may not develop until 8 to 24 h after onset of symptoms. Hemorrhagic necrosis can introduce many RBCs and some neutrophils into CSF, elevate protein, and modestly lower glucose.

PCR testing of CSF for many viruses (eg, HSV-1, HSV-2, varicella-zoster virus, cytomegalovirus, West Nile virus, enteroviruses, JC virus) is becoming increasingly available. PCR for HSV in CSF is sensitive and specific. However, results may not be available rapidly and, despite advances in technology, false-negative and false-positive results may still occur due to a variety of causes, not all being technical failures (eg, the blood in a mildly traumatic CSF tap may inhibit the PCR amplification step).

CSF viral cultures grow enteroviruses but not most other viruses.

CSF viral IgM titers are often useful for diagnosing acute infection, especially West Nile encephalitis, for which they are more reliable than PCR. Paired acute and convalescent serologic tests of CSF and blood must be drawn several weeks apart; they can detect an increase in viral titers specific for certain viral infections.

Brain biopsy: Brain biopsy may be indicated for patients who are worsening, who are responding poorly to treatment with acyclovir or another antimicrobial, or who have a lesion that is still undiagnosed.

Prognosis

Mortality rate varies with cause, but severity of epidemics due to the same virus varies during different years. Permanent neurologic deficits are more likely to occur in infants.

Treatment

• Supportive care

• Acyclovir for HSV encephalitis

Supportive therapy includes treatment of fever, dehydration, electrolyte disorders, and seizures. Euvolemia should be maintained.

If HSV encephalitis is suspected, acyclovir 10 mg/kg IV q 8 h is started promptly and continued usually for 14 days. Acyclovir is relatively nontoxic but can cause liver function abnormalities, bone marrow suppression, and transient renal failure. Giving acyclovir IV slowly over 1 h helps prevent nephrotoxicity.

Helminthic Brain Infections

Parasitic helminthic worms infect the CNS of millions of people in developing countries. Infected people who visit or immigrate to nonendemic areas, including the US, may present there. Worms may cause meningitis, encephalitis, cerebral masses, hydrocephalus, stroke, and myelopathy.

Neurocysticercosis: (See also p. 1365.) Among about 20 helminths that can cause neurologic disorders, the pork tapeworm *Taenia solium* causes by far the most cases in the Western Hemisphere. The resulting disorder is neurocysticercosis. After a person eats food contaminated with the worm's eggs, larvae migrate to tissues, including the brain, spinal cord, and CSF pathways, and form cysts. Cyst diameter rarely exceeds 1 cm in neural parenchyma but may exceed 5 cm in CSF spaces. Brain parenchymal cysts cause few symptoms until death of the worms triggers local inflammation, gliosis, and edema, causing seizures (most commonly), cognitive or focal neurologic deficits, or personality changes. Larger cysts in CSF pathways may cause obstructive hydrocephalus. Cysts may rupture into CSF, inducing subacute eosinophilic meningitis. Mortality rate for symptomatic neurocysticercosis is up to 50%.

Neurocysticercosis is suspected in patients who come from developing countries and who have eosinophilic meningitis or unexplained seizures, cognitive or focal deficits, or personality changes. It is suggested by multiple calcified cystic lesions seen on CT or MRI; a contrast agent may enhance the lesions. Diagnosis requires serum and CSF serologic tests and occasionally cyst biopsy.

Albendazole (7.5 mg/kg po q 12 h for 8 to 30 days; maximum daily dose, 800 mg) is the antihelminthic drug of choice. Alternatively, praziquantel 20 to 33 mg/kg po tid may be given for 30 days. Dexamethasone 8 mg once/day IV or po for the first 2 to 4 days may lessen the acute inflammatory response as the worms die. Antihelminthic therapy can cause serious morbidity in patients with a large number of cysts and may not help patients with a single cyst. Treatment must be carefully individualized. Short- or long-term anticonvulsant treatment may be required. Surgical excision of cysts and ventricular shunts may also be required.

Other infections: In schistosomiasis (see p. 1358), necrotizing eosinophilic granulomas develop in the brain, causing seizures, increased intracranial pressure, and diffuse and focal neurologic deficits.

Large, solitary echinococcal cysts (see Echinococcosis on p. 1362) can cause focal deficits and, occasionally, seizures.

Coenurosis, caused by tapeworm larvae, usually produces grapelike cysts that may obstruct CSF outflow in the 4th ventricle.

Gnathostomiasis, a rare infection, results in necrotic tracts surrounded by inflammation along the nerve roots, spinal cord, and brain or in subarachnoid hemorrhage, causing low-grade fever, stiff neck, photophobia, headache, migratory neurologic deficits (occasionally affecting the 6th or 7th cranial nerve), and paralysis.

Prion Diseases

(Transmissible Spongiform Encephalopathies)

Prion diseases are progressive, fatal, and untreatable degenerative brain disorders. They include

• Creutzfeldt-Jakob disease (CJD), the prototypic example

• Gerstmann-Straussler-Scheinker disease (GSS)

• Fatal insomnia (FI)

• Variant CJD (vCJD)

• Kuru

Prion diseases usually occur sporadically, with a worldwide annual incidence of about 1/1 million.

Prion diseases result from misfolding of a normal cell-surface brain protein called prion protein (PrP), whose exact function is unknown. Misfolded prion proteins (or prions) induce previously normal PrP to misfold; they are markedly resistant to degradation (similar to β-amyloid, which they resemble), resulting in slow but inexorable intracellular accumulation and neuronal cell death. Accompanying pathologic changes include gliosis and characteristic histologic vacuolar (spongiform) changes, resulting in dementia and other neurologic deficits. Symptoms and signs develop months to years after exposure.

Prion diseases can be caused by spontaneous or hereditary defects of the *PrP* gene, contained in the short arm of chromosome 20. Some defects cause familial CJD, some cause GSS, and others cause FI. Small abnormalities in particular codons may determine the predominant symptoms and rate of disease progression.

Prion diseases can also be transmitted by infected tissue. Cannibalism caused the spread of kuru in New Guinea, and prions can be transmitted via organ transplants and rarely by blood transfusion. Prion diseases can be transmitted between species via the food chain (eg, in vCJD). Prion diseases occur in mink, elk, deer, domestic sheep and cattle, and other mammals. In several western US states and Canada, chronic wasting disease of elk and deer, a prion disease, is a concern; whether this disease can

be transmitted to people who hunt, butcher, or eat affected animals is unknown.

Prion diseases should be considered in all patients with dementia, especially if it progresses rapidly.

Treatment is symptomatic. Prions resist standard disinfection techniques and pose risks to surgeons, pathologists, and technicians who handle contaminated tissues and instruments.

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease is a sporadic or familial prion disease. Bovine spongiform encephalopathy (mad cow disease) is a variant form. Symptoms include dementia, myoclonus, and other CNS deficits; death occurs in 1 to 2 yr. Transmission can be prevented by taking precautions when handling infected tissues and using bleach to clean contaminated instruments. Treatment is supportive.

CJD typically affects people > 40 yr (median, about 60 yr). It occurs worldwide; incidence is higher among North African Jews. Most cases are sporadic, but 5 to 15% are familial, with autosomal dominant transmission. In the familial form, age at onset is earlier and duration of disease is longer. CJD can be transmitted iatrogenically (eg, after cadaveric corneal or dural transplants, use of stereotactic intracerebral electrodes, or use of growth hormone prepared from human pituitary glands).

vCJD is most common in the United Kingdom (UK); it develops at a younger average age (< 30 yr) than does sporadic CJD. In the early 1980s, because of relaxed regulations for processing animal by-products, tissue from sheep infected with scrapie, a prion disease, was introduced into cattle feed. Thousands of cattle developed bovine spongiform encephalopathy (BSE), called mad cow disease. Some people who ate meat from affected cattle developed vCJD.

Because the incubation period in BSE is long, a connection between BSE and contaminated feed was not recognized in the UK until BSE had become an epidemic, which was controlled by massive slaughter of cattle. In the UK, the annual number of cases of vCJD starting in 1995 peaked at 28 in 2000 and then steadily declined, with only 5 cases/yr reported between 2005 and 2007 and only 1 in 2008; as of December 2008, the total number of cases was 167. However, 2 of 3 cases linked to blood transfusion occurred in 2006. Whether there exists a latent pool of people who have received blood transfusions who are thus at risk for development of vCJD is unclear. Although vCJD has been restricted to the UK and Europe thus far, BSE has been reported in a small number of North American cattle.

Symptoms and Signs

About 70% of patients present with memory loss and confusion, which eventually occur in all patients; 15 to 20% present with incoordination and ataxia, which often develop early in the disease. Myoclonus provoked by noise or other sensory stimuli (startle myoclonus) often develops in the middle to late stages of disease. Although dementia, ataxia, and myoclonus are most characteristic, other neurologic abnormalities (eg, hallucinations, seizures, neuropathy, various movement disorders) can occur. Ocular disturbances (eg, visual field defects, diplopia, dimness or blurring of vision, visual agnosia) are common.

Prognosis

Death typically occurs after 6 to 12 mo, commonly due to pneumonia. Life expectancy in vCJD is longer (averaging 1.5 yr).

Diagnosis

• MRI

• Exclusion of other disorders

CJD should be considered in elderly patients with rapidly progressive dementia, especially if accompanied by myoclonus or ataxia; however, CNS vasculitis, hyperthyroidism, and bismuth intoxication

must be excluded.

vCJD is considered in younger patients who have ingested processed beef in the UK; Wilson's disease should be excluded.

Diagnosis may be difficult, and diagnostic findings may develop only over time. MRI may show cerebral atrophy. Diffusion-weighted MRI frequently shows basal ganglia and cortical abnormalities. CSF is typically normal, but characteristic 14-3-3 protein is often detected. EEG may show characteristic periodic sharp waves. Brain biopsy is usually unnecessary.

Prevention

Because there is no effective treatment, prevention is essential. Workers handling fluids and tissues from patients suspected of having CJD must wear gloves and avoid mucous membrane exposure. Contaminated skin can be disinfected by 5 to 10 min of exposure to 4% Na hydroxide, followed by extensive washing with water. Steam autoclaving of materials at 132°C for 1 h or immersion in 4% Na hydroxide or 10% Na hypochlorite solution for 1 h is recommended. Standard methods of sterilization (eg, exposure to formalin) are ineffective. The US Department of Agriculture (USDA) currently carries out BSE surveillance for 2000 to 5000 cattle/mo. In 2004, a positive BSE case in the US caused testing to be expanded to an average 1000 cattle/day, but testing was subsequently reduced when ensuing years yielded only 2 positive cases.

Gerstmann-Straussler-Scheinker Disease

Gerstmann-Straussler-Scheinker disease is an autosomal dominant prion brain disease that begins during middle age.

GSS occurs worldwide and is similar to but about 100-fold less common than CJD. It develops at an earlier age (40 vs 60 yr), and average life expectancy is longer (5 yr vs 6 mo).

Patients have cerebellar dysfunction with unsteady gait, dysarthria, and nystagmus. Gaze palsies, deafness, dementia, parkinsonism, hyporeflexia, and extensor plantar responses are also common. Myoclonus is much less common than in CJD.

GSS should be considered in patients with characteristic symptoms and signs and a family history, particularly if they are ≤ 45 yr. Genetic testing can confirm the diagnosis.

Fatal Insomnia

Fatal insomnia is a typically hereditary prion disorder causing difficulty sleeping, motor dysfunction, and death.

FI, a very rare disease, usually results from an autosomal dominant mutation, but several sporadic cases have been identified. Average age at onset is 40 yr (ranging from the late 30s to the early 60s).

Common early symptoms include difficulty falling asleep and intermittent motor dysfunction (eg, myoclonus, spastic paresis). This stage can last for months but eventually progresses to severe insomnia, myoclonus, sympathetic hyperactivity (eg, hypertension, tachycardia, hyperthermia, sweating), and dementia. Death occurs in an average of 13 mo.

FI should be considered in patients with motor dysfunction, sleep disturbances, and a family history. Genetic testing can confirm the diagnosis.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is caused by reactivation of the JC virus. The disease usually occurs in patients with impaired cell-mediated immunity. It causes subacute and progressive CNS demyelination, multifocal neurologic deficits, and death, usually

within a year. Diagnosis is with contrast-enhanced CT or MRI plus CSF PCR. In AIDS patients, highly active antiretroviral therapy may slow down the progression, and patients taking immunosuppressants may improve when those drugs are withdrawn. Treatment is otherwise supportive.

Etiology

PML is caused by reactivation of the JC virus, a ubiquitous human papovavirus that is typically acquired during childhood and remains latent in the kidneys and possibly other sites (eg, mononuclear cells, CNS). The reactivated virus has a tropism for oligodendrocytes. Most patients have depressed cell-mediated immunity due to AIDS (the most common risk factor), reticuloendothelial system disorders (eg, leukemia, lymphoma), or other conditions (eg, Wiskott-Aldrich syndrome, organ transplantation). The risk in AIDS increases with increasing HIV viral load; prevalence of PML has decreased because of widespread use of more effective antiretrovirals. Rarely, PML occurs as a complication of immunomodulatory therapy (eg, natalizumab, rituximab).

Symptoms and Signs

Clumsiness may be the first symptom. Hemiparesis is the most common finding. Aphasia, dysarthria, and hemianopia are also common. Multifocal cortical damage produces cognitive impairment in two thirds of patients. Sensory, cerebellar, and brain stem deficits may be present. Headaches and convulsive seizures are rare and occur most often in patients with AIDS. Gradual, relentless progression culminates in death, usually 1 to 9 mo after symptoms begin.

Diagnosis

• MRI

• CSF testing for JC viral antigen

PML is suspected in patients with unexplained progressive brain dysfunction, particularly in those with depressed cell-mediated immunity. Provisional diagnosis is made by contrast-enhanced MRI, which shows single or multiple white matter lesions on T2-weighted images. A contrast agent enhances, usually faintly and peripherally, 5 to 15% of lesions. CT usually shows low-density, nonenhancing lesions but is significantly less sensitive than MRI.

CSF is analyzed for JC viral antigen using PCR; a positive result with compatible neuroimaging findings is nearly pathognomonic. Routine CSF analysis is usually normal.

Serologic tests are not helpful. Stereotaxic biopsy can provide a definitive diagnosis but is rarely warranted.

Treatment

• Supportive care

Treatment is supportive. Experimental use of drugs such as cidofovir and other antivirals has failed to provide benefit. However, highly active antiretroviral therapy (HAART) in AIDS patients has improved outcome in PML, increasing the 1-yr survival rate from 10% to 50%. Withdrawal of immunosuppressants may also result in clinical improvement.

However, using aggressive antiretroviral therapy (or stopping immunosuppressants) has been associated with immune reconstitution inflammatory syndrome (IRIS—see p. 1450), in which the recovering immune system produces an intense inflammatory response against the JC virus, thus worsening symptoms. If IRIS develops, imaging shows new contrast enhancement of the lesions and may show significant cerebral edema. Corticosteroids may be helpful.

Rabies

Rabies is a viral encephalitis transmitted by the saliva of infected bats and certain other infected mammals. Symptoms include depression and fever, followed by agitation, excessive salivation, and hydrophobia. Diagnosis is by serologic tests or biopsy. Vaccination is indicated for people at high risk of exposure. Postexposure prophylaxis involves wound care and passive and active immunoprophylaxis. The disorder is almost universally fatal. Treatment is supportive.

Rabies causes > 50,000 human deaths worldwide annually, mostly in Latin America, Africa, and Asia, where canine rabies is endemic. In the US, vaccination of domestic animals has reduced rabies cases in people to < 6/yr, mostly transmitted by infected bats. Infected raccoons, skunks, and foxes can also transmit rabies.

Rabid animals transmit the infection through their saliva, usually by biting. Rarely, the virus can enter through a skin abrasion or across mucous membranes of the eyes, nose, or mouth. The virus travels from the site of entry via peripheral nerves to the spinal cord (or to the brain stem when the face is bitten), then to the brain. It spreads from the CNS via peripheral nerves to other parts of the body. Involvement of the salivary glands and oral mucosa is responsible for transmissibility.

Symptoms and Signs

Pain or paresthesias may develop at the site of the bite. Rapidity of progression depends on the viral inoculum and proximity of the wound to the brain. The incubation period averages 1 to 2 mo but may be > 1 yr. Initial symptoms are nonspecific: fever, headache, and malaise. Within days, encephalitis (furious rabies; in 80%) or paralysis (dumb rabies; in 20%) develops. Encephalitis causes restlessness, confusion, agitation, bizarre behavior, hallucinations, and insomnia. Salivation is excessive, and attempts to drink cause painful spasms of the laryngeal and pharyngeal muscles (hydrophobia). In the paralytic form, ascending paralysis and quadriplegia develop without delirium and hydrophobia.

Diagnosis

• Skin biopsy

• Sometimes PCR testing of fluid or tissue samples

Rabies is suspected in patients with encephalitis or ascending paralysis and a history of an animal bite or exposure to bats; bat bites may be superficial and overlooked.

Direct fluorescence antibody testing of a biopsy specimen of skin from the nape of the neck is the diagnostic test of choice. Diagnosis can also be made by PCR of CSF, saliva, or tissue. Specimens tested for rabies antibodies include serum and CSF. CT, MRI, and EEG are normal or show nonspecific changes.

Treatment

• Supportive care

Treatment is only supportive and includes heavy sedation (eg, with ketamine and midazolam) and comfort measures. Death usually occurs 3 to 10 days after symptoms begin. Only a handful of patients have survived; all but one of them received immunoprophylaxis before onset of symptoms. There is evidence that giving rabies vaccine and immune globulin *after* clinical rabies develops may cause more rapid deterioration.

Experimental therapies with ribavirin, amantadine, interferon-alfa, and other drugs are sometimes tried in desperation.

Prevention

Preexposure: Rabid animals can often be recognized by their strange behavior; they may be agitated and vicious, weak, or paralyzed and may show no fear of people. Nocturnal animals (eg, bats, skunks, raccoons) may be out during the day. Bats may make unusual noises and have difficulty flying. An animal suspected of having rabies should not be approached. Local health authorities should be contacted to remove the animal.

Human diploid cell rabies vaccine (HDCV) is safe and recommended for preexposure prophylaxis for people at risk, including veterinarians, animal handlers, spelunkers, workers who handle the virus, and travelers to endemic areas. A total of three 1-mL doses are given IM, one each on days 0, 7, and between day 21 and 28.

Postexposure: Exposure is considered to be a bite that breaks the skin or any contact between mucous membrane or broken skin and animal saliva. If exposure occurs, prompt, meticulously executed prophylaxis almost always prevents human rabies. The wound is cleansed immediately and thoroughly with soap and water or benzalkonium chloride. Deep puncture wounds are flushed with soapy water using moderate pressure. Wounds are usually left open.

Postexposure prophylaxis (PEP) with rabies vaccine and rabies immune globulin (RIG) is given depending on the biting animal and circumstances (see Table 179-1). PEP is begun, and the animal's brain is tested for virus. Local or state health departments or the Centers for Disease Control and Prevention usually conduct testing and can advise on other treatment issues.

For PEP, RIG 20 IU/kg is infiltrated around the wound for passive immunization; if injection volume is too much for distal areas (eg, fingers, nose), some RIG may be given IM. This treatment is accompanied by HDCV for active immunization. HDCV is given in a series of five 1-mL IM injections (deltoid area is preferred), beginning on the day of exposure (day 0), in a limb other than the one used for RIG. Subsequent injections occur on days 3, 7, 14, and 28. The WHO also recommends a 6th injection on day 90. Rarely, a serious systemic or neuroparalytic reaction occurs; then, completion of vaccination is weighed against the patient's risk of developing rabies. Rabies antibody titer is measured to help assess risk of stopping vaccination.

PEP for a person previously vaccinated against rabies includes 1-mL IM injections of HDCV on days 0 and 3 but no RIG.

Subdural Empyema

Subdural empyema is a collection of pus between the dura mater and arachnoid. Symptoms include

[**Table 179-1.** Rabies Postexposure Prophylaxis]

fever, lethargy, focal neurologic deficits, and seizures. Diagnosis is by contrast-enhanced CT or MRI. Treatment is with surgical drainage and antibiotics.

Etiology

Subdural empyema is usually a complication of sinusitis (especially frontal, ethmoidal, or sphenoidal), but it can follow ear infections, cranial trauma or surgery, or, rarely, bacteremia. Pathogens are similar to those that cause brain abscess (see p. 1726). In children < 5 yr, the usual cause is bacterial meningitis; because childhood meningitis is now uncommon, childhood subdural empyema is uncommon.

Complications: Cortical venous thrombosis and brain abscess are common complications, and subdural empyema can rapidly spread to involve an entire cerebral hemisphere.

Symptoms and Signs

Fever, headache, lethargy, focal neurologic deficits (suggesting widespread involvement of one cerebral

hemisphere), and seizures evolve over several days. Meningeal signs, vomiting, and papilledema are common. Without treatment, coma and death occur rapidly.

Diagnosis

• MRI

Diagnosis is by contrast-enhanced MRI or CT. Blood and surgical specimens are cultured aerobically and anaerobically. Lumbar puncture provides little useful information and may precipitate transtentorial herniation. If subdural empyema is suspected (eg, based on symptom duration of several days, focal deficits, or risk factors) in patients with meningeal signs, lumbar puncture is contraindicated until neuroimaging excludes a mass lesion. In infants, a subdural tap may be diagnostic and may relieve pressure.

Treatment

• Surgical drainage

• Antibiotics

Emergency surgical drainage of the empyema and any underlying sinusitis should be done. Pending culture results, antibiotic coverage is the same as that for brain abscess except in young children, who may require antibiotics for any accompanying meningitis (see
Table 180-2 on p. 1740 and
Table 180-3 on p. 1741). Anticonvulsants and measures to reduce intracranial pressure may be needed.

Chapter 180. Meningitis

Introduction

(For brain infections, see Ch. 179 on p. 1726.)

Meningitis is inflammation of the meninges of the brain or spinal cord.

Meningitis is often infectious and is one of the most common CNS infections. Inflammation involves both the meninges and brain parenchyma (meningoencephalitis). Meningitis may become evident over hours or days (acute) or a longer period (subacute or chronic).

The most common types of acute meningitis are

• Acute bacterial meningitis

• Aseptic meningitis

Acute bacterial meningitis is a severe illness characterized by purulent CSF. It is rapidly progressive and, without treatment, fatal.

Aseptic meningitis is milder and typically self-limited; it is usually caused by viruses.

Symptoms and Signs

Many cases of infectious meningitis begin with a vague prodrome of viral symptoms. The classic meningitis triad of fever, headache, and nuchal rigidity develops over hours or days. Passive flexion of the neck is restricted and painful, but rotation and extension are typically not as painful. In severe cases, attempts at neck flexion may induce flexion of the hip or knee (Brudzinski's sign), and there may be resistance to passive extension of the knee while the hip is flexed (Kernig's sign). Neck stiffness and Brudzinski's and Kernig's signs are termed meningeal signs or meningismus; they occur because tension on nerve roots passing through inflamed meninges causes irritation.

Although brain parenchyma is not typically involved early in meningitis, lethargy, confusion, seizures, and focal deficits will develop if bacterial meningitis is left untreated.

Diagnosis

• Blood DNA PCR for bacterial pathogens

• CSF analysis

• Sometimes CT before lumbar puncture

Acute meningitis is a medical emergency that requires rapid diagnosis and treatment. After IV access is secured, blood samples are drawn for culture, CBC, and PCR of bacterial pathogens if available. Treatment is started empirically.

Lumbar puncture is done to obtain CSF for Gram stain, culture, cell count and differential, glucose concentration, protein content and other specialized tests. These tests must be done in a timely manner. However, patients with signs compatible with a mass lesion (eg, focal deficits, papilledema, deterioration in consciousness, seizures) require head CT before lumbar puncture because there is a small possibility that lumbar puncture can cause cerebral herniation if a brain abscess or other mass lesion is present.

CSF findings aid in the diagnosis of meningitis (see Table 180-1). Presence of bacteria on Gram stain or growth of bacteria in culture is diagnostic of bacterial meningitis. Gram stain is positive about 80% of the time in bacterial meningitis and usually differentiates among the common causative pathogens. CSF lymphocytosis and absence of pathogens

suggest aseptic meningitis but may represent partially treated bacterial meningitis.

Treatment

If patients appear ill and have findings of meningitis, antibiotics (see p. 1739) are started as soon as blood cultures are drawn. If patients do not appear very ill and the diagnosis is less certain, antibiotics can await CSF results.

Acute Bacterial Meningitis

(For neonatal meningitis, see p. 2830.)

Acute bacterial meningitis is a fulminant, often fatal pyogenic infection beginning in the meninges. Symptoms include headache, fever, and stiff neck. Without rapid treatment, obtundation and coma follow. Diagnosis is by CSF tests. Treatment requires antibiotics, often beginning empirically with a 3rd-or 4th-generation cephalosporin, vancomycin, and ampicillin; corticosteroids are usually given. Residual morbidity is common.

Etiology

Many bacteria can cause meningitis, but the most common are

• Group B streptococci (during the first 2 mo of life)

• *Neisseria meningitidis* (meningococci)

• *Streptococcus pneumoniae* (pneumococci)

Meningococci exist in the nasopharynx of about 5% of people and spread by respiratory droplets and close contact. Only a small fraction of carriers develop meningitis; what makes them susceptible is unknown. Meningococcal meningitis occurs most often during the first year of life. It also tends to occur in epidemics among closed populations (eg, in military barracks, college dormitories, and boarding schools).

Pneumococci are the most common cause of meningitis in adults. Especially at risk are alcoholics and people with chronic otitis, sinusitis, mastoiditis, CSF leaks, recurrent meningitis, pneumococcal pneumonia, sickle cell disease, or asplenia. Incidence of pneumococcal meningitis is decreasing because of routine vaccination.

Gram-negative organisms (most often *Escherichia coli, Klebsiella* sp, or *Enterobacter* sp) can cause meningitis in infants; in immunocompromised patients; or after CNS surgery, CNS trauma, bacteremia (eg, due to GU manipulation), or hospital-acquired infections. *Pseudomonas* sp occasionally causes meningitis in immunocompromised or colonized patients. *Haemophilus influenzae* type b meningitis, now uncommon because of widespread vaccination, can occur in immunocompromised patients or after head trauma in unvaccinated people.

Staphylococci can cause meningitis after penetrating head wounds or neurosurgical procedures (often as part of a mixed infection) or after bacteremia (eg, due to endocarditis).

Listeria typically cause meningitis in the very young, the very old, and patients of any age who are immunocompromised because of chronic renal failure, hepatic disorders, or corticosteroid or cytotoxic therapy after organ transplantation.

Bacteria typically reach the meninges by hematogenous spread from sites of colonization in the nasopharynx or other foci of infection (eg, pneumonia). Why some bacteria are more prone to colonize CSF is not clear, but binding pili and encapsulation appear to play a role. Receptors for pili and other bacterial surface components in the choroid plexus facilitate penetration into CSF.

Bacteria can also enter CSF by direct extension from nearby infections (eg, sinusitis, mastoiditis) or

through exterior openings in normally closed CSF pathways (eg, due to meningomyelocele, spinal dermal sinus, penetrating injuries, or neurosurgical procedures).

Pathophysiology

Bacterial surface components, complement, and inflammatory cytokines (eg, tumor

[Table 180-1. Cerebrospinal Fluid Abnormalities in Various Infections]

necrosis factor, IL-1) draw neutrophils into the CSF space. The neutrophils release metabolites that damage cell membranes including those of the vascular endothelium. The result is vasculitis and thrombophlebitis (which cause focal ischemia or infarction) and brain edema. Vasculitis also disrupts the blood-brain barrier, further increasing brain edema. The purulent exudate in the CSF blocks CSF reabsorption by the arachnoid villi, causing hydrocephalus. Brain edema and hydrocephalus increase intracranial pressure.

Systemic complications include

• Hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH)

• Disseminated intravascular coagulation (DIC)

• Septic shock

Occasionally, bilateral adrenal hemorrhagic infarction (Waterhouse-Friderichsen syndrome) results, particularly with meningococcal infection.

Symptoms and Signs

A respiratory illness or sore throat often precedes the more characteristic symptoms of fever, headache, stiff neck, and vomiting. Kernig's and Brudzinski's signs appear in about half of patients. Adults may become desperately ill within 24 h, and children even sooner. Seizures occur in about 30%. Cranial nerve abnormalities (eg, 3rd [oculomotor] or 7th [facial] cranial nerve palsy; occasionally, deafness) and other focal deficits occur in 10 to 20%. In patients > 2 yr, changes in consciousness progress through irritability, confusion, drowsiness, stupor, and coma. Opisthotonic posturing may occur.

Dehydration is common, and vascular collapse causes shock. Infection, particularly meningococcal, may be disseminated widely, to the joints, lungs, sinuses, and elsewhere. A petechial or purpuric rash commonly occurs in meningococcal meningitis. Examination of the head, ears, spine, and skin may reveal a source or route of infection. Spinal dimples, nevi, or tufts of hair suggest a spinal dermal sinus that communicates with the meninges and provides a portal for bacteria entry.

Young children: In children < 2 yr, meningeal signs may be absent. In those < 2 mo, symptoms and signs are often nonspecific, particularly in early disease. Fever, hypothermia, poor feeding, lethargy, vomiting, and irritability are common presenting symptoms. Seizures, a high-pitched cry, and bulging or tight fontanelles are possible but often occur late. Subdural effusions may develop after several days; typical signs are seizures, persistent fever, and enlarging head size.

Elderly: The elderly may also have nonspecific symptoms (eg, confusion with or occasionally without fever). Meningeal signs may be absent or mild. Arthritis may restrict neck motion, often in multiple directions, and should not be mistaken for meningismus.

Patients with partially treated meningitis: Patients seen early in the disease, before typical findings of meningitis appear, are sometimes diagnosed with otitis media or sinusitis and given oral antibiotics. Depending on the drug, the infection may be partially (but temporarily) suppressed. Patients may appear less ill and have milder meningeal signs and slower disease progression. This situation can significantly hamper recognition of meningitis.

Diagnosis

• CSF analysis

Acute bacterial meningitis is suspected in children < 2 yr with lethargy, progressive irritability, a high-pitched cry, a bulging fontanelle, meningeal signs, or hypothermia. Signs are often nonspecific, and threshold for suspecting meningitis must be low. Meningitis is suspected in patients > 2 yr with meningeal signs or unexplained alterations in consciousness, particularly in those with fever or risk factors.

Because acute bacterial meningitis, especially meningococcal, can be lethal within hours, it must be treated as soon as the diagnosis is suspected. Blood is drawn for culture, Gram stain, and bacterial DNA PCR if available. Prompt lumbar puncture with or without prior CT is required, but these procedures should not delay immediate treatment with corticosteroids and antibiotics.

CSF tests: CSF pressure may be elevated. Gram stain shows organisms in CSF in 80% of patients with acute bacterial meningitis. CSF contains a predominantly neutrophilic WBC count, usually between 1,000 µL and 10,000/µL. Glucose is usually < 40 mg/dL because of impaired CNS glucose transport and glucose consumption by neutrophils and bacteria. Protein is typically > 100 mg/dL. Cultures are positive in 90%; they may be falsely negative in patients who are partially treated. Latex agglutination tests can be used to detect antigens of meningococci, *H. influenzae* type b, pneumococci, group B streptococci, and *E. coli* K1 strains. However, these tests are not routinely done because they probably add little to other routine CSF tests. The limulus amebocyte lysate test can detect endotoxin in gram-negative meningitis. This test and the latex agglutination tests may be helpful when patients have received prior antibiotics (partial treatment), when patients are immunocompromised, or when other CSF tests do not identify the causative organism. Broad range bacterial PCR for 16S ribosomal DNA testing can be useful if CSF cultures detect no organisms. PCR testing is also available for meningococcus and pneumococcus.

Imaging tests: CT, when done, may be normal or show small ventricles, effacement of the sulci, and contrast enhancement over the convexities. MRI with gadolinium is more sensitive for subarachnoid inflammation. Scans should be scrutinized for evidence of brain abscess, sinusitis, mastoiditis, skull fracture, and congenital malformations. Evidence of venous infarctions or communicating hydrocephalus may appear after days or weeks.

Other tests: Peripheral blood tests include blood cultures (positive in 50%), cell count with differential, electrolytes, glucose, renal function, coagulation tests, and PCR for bacterial pathogens (where available). Serum Na is monitored for evidence of SIADH, and coagulation results are monitored for evidence of DIC. Urine and any nasopharyngeal or respiratory secretions and skin lesions are cultured.

Alternate diagnoses: Disorders that resemble bacterial meningitis can usually be differentiated by clinical presentation, neuroimaging, and routine CSF tests.

Viral meningitis can cause fever, headache, and stiff neck, but patients do not appear as ill, and CSF test results are different (see Table 180-1).

Viral encephalitis, especially herpes encephalitis, also causes fever, headache, confusion, seizure and coma, which can be confused with bacterial meningitis. MRI and CSF testing are helpful in distinguishing viral encephalitis from bacterial meningitis. Serum procalcitonin and C-reactive protein are elevated to a much greater degree with bacterial than with viral infections.

Subarachnoid hemorrhage causes severe headache and a stiff neck, but onset is explosive and fever is usually absent; CT shows hemorrhage, or the CSF contains RBCs or is xanthochromic.

Brain abscess can cause fever, headache, and impaired consciousness, but the neck is typically supple unless abscess contents have ruptured into the CSF space, causing a fulminant secondary meningitis.

Severe systemic infections (eg, sepsis, infective endocarditis) can impair cognition or consciousness by causing fever and compromising tissue perfusion; CSF is normal or contains a small number of WBCs, and the neck is supple.

Cerebellar tonsillar herniation can cause impaired consciousness (secondary to obstructive hydrocephalus) and neck stiffness but usually not fever, and it can be differentiated by CT or MRI.

Cerebral vasculitis (eg, due to SLE) and cerebral venous thrombosis can cause mild fever, headache, altered mental status, and mild to moderate meningeal inflammation, typically producing CSF test results similar to those of viral encephalitis.

Fungal meningitis or amebic *(Naegleria)* meningoencephalitis occasionally causes acute, fulminant meningitis with clinical findings and routine CSF test results similar to those of bacterial meningitis. Gram stain and routine cultures show no bacteria. In such cases, CSF is checked for cryptococcal polysaccharide antigen, *Histoplasma* polysaccharide antigen, and *Coccidioides immitis* complement fixation antibodies; CSF is also examined using India ink and cultured for fungi (see p. 1744). In amebic meningoencephalitis, ameboid movement can be detected in unspun wet mounts of CSF, and the amebas can be cultured.

TB meningitis is usually subacute or chronic but is occasionally acute; CSF characteristics are usually intermediate between those of acute bacterial and aseptic meningitis. Special stains (eg, acid-fast, immunofluorescent) and PCR are needed to identify TB.

Waterhouse-Friderichsen syndrome: This disorder should be suspected in any febrile patient who remains in shock despite adequate volume replacement and who has rapidly evolving purpura and evidence of DIC. With hemorrhagic necrosis of the adrenal glands, adrenocorticol insufficiency develops rapidly. A serum cortisol level < 13 µg/dL (in combination with an increased ACTH level) suggests glucocorticoid deficiency due to primary adrenal insufficiency. CT, MRI, or ultrasonography of the adrenal glands is done.

Prognosis

Immediate empirical treatment with corticosteroids, antibiotics, and supportive care have improved outcome and reduced mortality to < 10%. However, if meningitis is treated late or occurs in neonates, the elderly, or immunocompromised patients, death is common. A poor outcome is predicted by persistent leukopenia or development of Waterhouse-Friderichsen syndrome. Survivors occasionally have deafness, other cranial nerve deficits, cerebral infarction, recurrent seizures, or intellectual disability.

Treatment

• Corticosteroids

• Antibiotics (eg, ampicillin and ceftriaxone, with or without vancomycin)

If acute bacterial meningitis is suspected, corticosteroids and antibiotics are given as soon as blood cultures are drawn. If the diagnosis is unclear and the patient does not appear ill, antibiotics may be withheld pending CSF test results. Giving antibiotics before lumbar puncture slightly increases the probability of false-negative cultures, particularly with pneumococci, but does not affect other test results.

Corticosteroids: Dexamethasone 0.15 mg/kg IV q 6 h in children and 10 mg IV q 6 h in adults should be given with the first dose of antibiotics and continued for 4 days. Dexamethasone may prevent hearing loss and other neurologic sequelae by inhibiting release of proinflammatory cytokines triggered by antibiotic-induced bacterial lysis. Because corticosteroids impede vancomycin's penetration into CSF, vancomycin is given in a higher dose—15 to 20 mg/kg q 8 h.

In immunocompromised patients, the benefits of dexamethasone in reducing intracranial pressure must be weighed against the risk of worsening immunodeficiency.

Antibiotics: Choice of empiric antibiotics depends on the suspected pathogen and patient age (see Table 180-2; for antibiotic doses, see Table 180-3). Third-generation cephalosporins (eg, ceftriaxone, cefotaxime) are effective against

pathogens common in patients of all ages. Cefepime, a 4th-generation cephalosporin, can be substituted for a 3rd-generation cephalosporin in children and can be useful for *Pseudomonas* infection. However, because cephalosporin-resistant pneumococci are becoming increasingly prevalent, vancomycin, with or without rifampin, is usually added. Meropenem is also effective against *Pseudomonas* and many gram-negative bacteria. Ampicillin is added to cover *Listeria* sp. Aminoglycosides penetrate the CNS poorly but are still used empirically to cover gram-negative bacteria in neonates (see p. 2831). When meningitis due to a gram-negative anaerobe is a consideration (eg, because of otitis, sinusitis, or mastoiditis), meropenem should be added. For meningitis patients with a recent neurosurgical procedure or with an intraventricular shunt, vancomycin, meropenem, plus metronidazole provide coverage against staphylococci, gram-negative bacteria, and anaerobes.

Because herpes encephalitis can resemble bacterial meningitis at presentation, acyclovir is usually included with the initial empirical therapy. Similarly, during tick season, doxycycline may be added to cover CNS infection with Rocky Mountain spotted fever.

Reevaluation: As the results of blood, CSF, and other tests become available and the pathogen and drug susceptibility are identified, antibiotics are adjusted accordingly.

If no pathogen is identified in the CSF, addition of antibiotics for TB should be considered, especially if CSF glucose levels are very low.

If no bacteria grow in culture or are otherwise identified after 24 to 48 h, corticosteroids are stopped; corticosteroids continued for > 1 day without appropriate antibiotic coverage could worsen the infection. When initial CSF tests are inconclusive, a repeat lumbar puncture in 8 to 24 h (or sooner if the patient deteriorates) may help. If clinical and CSF findings continue to suggest aseptic meningitis, antibiotics are withheld. If the patient's condition is serious, especially if antibiotics have been given (possibly causing falsely sterile cultures), antibiotics should be continued.

Lumbar puncture should be repeated 24 to 48 h after starting antibiotics to confirm CSF sterility and conversion to lymphocytic predominance. Generally, antibiotics are continued for ≥ 1 wk after fever subsides and CSF is nearly normal (complete normalization may take weeks). Drug doses are not reduced when clinical improvement occurs because drug penetration commonly decreases as meningeal inflammation decreases.

Other measures: Supportive therapy includes treatment of fever, dehydration, electrolyte disorders, seizures, and shock.

If Waterhouse-Friderichsen syndrome is suspected, high-dose hydrocortisone (eg, 100 to 200 mg IV q 4 to 6 h or as a continuous infusion after an initial bolus) is given; treatment should not be delayed pending measurement of hormone levels.

Cerebral edema can be minimized by avoiding overhydration. If brain herniation is suspected, hyperventilation ($PaCO_2$, 25 to 30 mm Hg acutely), mannitol (0.25 to 1.0 g/kg IV), and additional dexamethasone (4 mg IV q 4 h) can be used; barbiturate-induced coma may be considered. Monitoring intracranial pressure may be helpful. If ventricles are enlarged, intracranial pressure may be monitored and CSF drained, but outcome is usually poor.

If infants up to 1 yr of age have subdural effusion, daily subdural taps through the cranial sutures usually help. No more than 20 mL/day of CSF should be removed from one side to avoid sudden shifts in intracranial contents. If effusion persists after 3 to 4 wk of

[**Table 180-2.** Antibiotic Therapy for Acute Bacterial Meningitis]

[**Table 180-3.** Common IV Antibiotic Dosages for Bacterial Meningitis*]

taps, surgical exploration for possible excision of a subdural membrane is indicated.

Patients with severe meningococcal meningitis may benefit from drotrecogin alfa (activated protein C),

which downregulates the inflammatory response. In patients with sepsis due to meningitis, intracranial bleeding occurs more frequently, with or without drotrecogin alfa treatment.

Prevention

Physical measures: Spread of meningitis is prevented by keeping patients in respiratory isolation (droplet precautions) for the first 24 h of therapy. Gloves, masks, and gowns are used.

Vaccinations: Certain types of bacterial meningitis can be prevented by vaccination.

A conjugated pneumococcal vaccine effective against 7 serotypes, including > 80% of organisms that cause meningitis, is recommended for all children (see p. 1177 and Table 268-10 on p. 2718).

Routine vaccination against *H. influenzae* type b is highly effective and begins at age 2 mo.

A quadrivalent meningococcal vaccine is given to children aged 2 to 10 yr with immunodeficiencies or functional asplenia, all children at age 11 to 12 yr (and older children, college students living in dormitories, and military recruits who have not had the vaccine previously), travelers to endemic areas, and laboratory personnel who routinely handle meningococcal specimens. Chemoprophylaxis is given to close contacts of patients with meningococcal meningitis. During an epidemic, the population at risk must be identified (eg, college students, a small town) and its size determined before proceeding to mass vaccination. The effort is expensive and requires public education and support, but it saves lives and reduces morbidity. NOTE: The meningococcal vaccine does not protect against serotype B meningococcal meningitis; this information should kept in mind when a vaccinated patient presents with symptoms of meningitis.

Chemoprophylaxis: Anyone who has face-to-face contact with the patient (eg, family, medical staff members) should receive postexposure chemoprophylaxis.

For meningococcal meningitis, chemoprophylaxis consists of one of the following:

• Rifampin 600 mg (for children > 1 mo, 10 mg/kg; for children < 1 mo, 5 mg/kg) po q 12 h for 4 doses

• Ceftriaxone 250 mg (for children < 15 yr, 125 mg) IM for 1 dose

• In adults, a fluoroquinolone (ciprofloxacin or levofloxacin 500 mg or ofloxacin 400 mg) po for 1 dose

Chemoprophylaxis against *H. influenzae* type b is rifampin 20 mg/kg po once/day (maximum: 600 mg/day) for 4 days. There is no consensus on whether children < 2 yr require prophylaxis for exposure at day care.

Chemoprophylaxis is not usually needed for contacts of patients with pneumococcal meningitis.

Aseptic Meningitis

Aseptic meningitis is inflammation of the meninges with CSF lymphocytic pleocytosis and no cause apparent after routine CSF stains and cultures. Viruses are the most common cause. Other causes may be infectious or noninfectious. Symptoms include fever, headache, and meningeal signs. Viral aseptic meningitis is usually self-limited. Treatment is usually symptomatic.

Etiology

There are many causes (see Table 180-4), which are typically classified as

• Infectious (eg, viruses, rickettsiae, spirochetes, parasites)

• Noninfectious (eg, intracranial tumors and cysts, drugs, systemic disorders)

Viruses: Enteroviruses, including echovirus, coxsackievirus, and enteroviruses 68 through 71, cause most cases of aseptic meningitis. They are transmitted through a fecaloral, food-borne route, entering the GI tract and spreading via the bloodstream.

The next most common causes of viral meningitis are herpes simplex virus type 2 (HSV-2), HIV, and the arthropod-borne viruses. Mumps virus is a common cause worldwide but has been minimized in the US by vaccination.

Mollaret's meningitis is a syndrome of self-limited, recurrent aseptic meningitis characterized by large atypical monocytes (once thought to be endothelial cells) in the CSF; it is caused by HSV-2 and associated with prior exposure to genital herpes; most patients are unaware of their exposure.

Viruses that cause encephalitis typically also cause a low-grade aseptic meningitis.

Bacteria: Bacteria may cause lymphocytic meningitis; they include spirochetes (in syphilis, Lyme disease, or leptospirosis) and rickettsiae (in typhus, Rocky Mountain spotted fever, or ehrlichiosis). CSF abnormalities may be transient or chronic.

Bacterial infections such as mastoiditis, sinusitis, brain abscess, and infective endocarditis can result in CSF with characteristics of aseptic meningitis because infection adjacent to the meninges can induce a sympathetic inflammatory response without bacteria being present.

Noninfectious causes: Meningeal inflammation may result from neoplastic infiltration, leakage of the contents of an intracranial cyst, intrathecal drugs, lead poisoning, and radiopaque agents. Infrequently, inflammation results from certain systemically administered drugs, presumably as a hypersensitivity reaction. The most common causative drugs are NSAIDs (especially ibuprofen), antimicrobials (especially sulfa drugs), and immune modulators (eg, IV immune globulins, OKT3 monoclonal antibodies, cyclosporine, vaccines).

Symptoms and Signs

Aseptic meningitis often follows a flu-like syndrome and usually causes fever and headache, but coryza is not prominent. Meningeal signs are less marked and slower to develop than in acute bacterial meningitis. Patients are usually not critically ill; systemic or nonspecific symptoms may predominate. Focal neurologic symptoms are absent. Patients with noninfectious meningeal inflammation are often afebrile.

Diagnosis

• CSF analysis

• Sometimes CT before lumbar puncture

The initial concern is whether patients presenting with headache, fever, and meningeal signs have acute bacterial meningitis requiring immediate antibiotic treatment. Viral or other aseptic meningitis should be considered when patients appear less acutely ill.

Head CT or MRI is done before lumbar puncture if a brain mass is suspected (eg, based on focal neurologic signs or papilledema). Idiopathic intracranial hypertension sometimes mimics aseptic meningitis.

Differentiating bacterial meningitis from aseptic meningitis: Because bacterial meningitis requires immediate treatment and aseptic meningitis usually does not, rapid identification of bacterial meningitis is important (and sometimes difficult).

CSF findings help make the distinction (see Table 180-1). CSF glucose is usually decreased and protein

is elevated in bacterial meningitis but not in aseptic meningitis. CSF WBCs are predominantly lymphocytes in aseptic meningitis; even a few CSF neutrophils (which may, however, be present in early viral meningitis) should prompt consideration of early bacterial meningitis. However, several types of bacterial meningitis have CSF characteristics that are similar to those of aseptic meningitis; they include partially treated bacterial meningitis, *Listeria* meningitis (which may be difficult to detect using Gram stain and may produce CSF monocytosis, which is more characteristic of aseptic meningitis), and TB meningitis. Clues to TB meningitis are clinical findings, elevated CSF protein, and mildly decreased CSF glucose (see p. 1744). CSF pressure is somewhat variable; although it is typically normal or mildly

[**Table 180-4.** Other Causes of CSF Inflammatory Response*]

elevated in aseptic meningitis and quite high in bacterial meningitis, it may be markedly elevated in aseptic meningitis.

Blood tests sometimes help. Serum levels of procalcitonin and C-reactive protein are much higher in bacterial infections than in viral ones.

Diagnosis of specific cause: In viral meningitis, PCR is the quickest way to identify the specific infectious agent, including enteroviruses, HSV-2, HIV, and cytomegalovirus. PCR is less reliable in West Nile virus infection, which is usually diagnosed based on IgM titers.

Tests are also done to diagnose nonviral causes of aseptic meningitis (eg, rickettsial infection, Lyme disease, syphilis). Drug-induced aseptic meningitis is a diagnosis of exclusion.

Treatment

• Supportive care

In most patients, the diagnosis is clear, and treatment requires only hydration, analgesics, and antipyretics. If listerial, partially treated, and early bacterial meningitis cannot be excluded, antibiotics effective against bacterial meningitis are given pending results of cultures or repeated CSF tests.

Drug-induced aseptic meningitis resolves when the causative drug is withdrawn.

Recurrent HSV-2 meningitis may be treated with acyclovir, famciclovir, or valacyclovir (see Table 151-2 on p. 1413).

Subacute and Chronic Meningitis

Meningeal inflammation that lasts > 2 wk (subacute meningitis) or > 1 mo (chronic meningitis) may have infectious or noninfectious causes (eg, cancer). Diagnosis requires CSF analysis, usually after CT or MRI. Treatment is directed at the cause.

Etiology

Subacute or chronic meningitis may have infectious or noninfectious causes and may be an aseptic meningitis (see Table 180-4). Infectious causes include fungal infections (most commonly with *Cryptococcus neoformans*), TB, Lyme disease, AIDS, *Actinomyces* infections, and syphilis; noninfectious causes include sarcoidosis, vasculitis, Behcet's syndrome, and cancers such as lymphomas, leukemia, melanomas, certain carcinomas, and gliomas (particularly glioblastoma, ependymoma, and medulloblastoma). Other causes include chemical reactions to certain intrathecal injections.

Use of immunosuppressants and the AIDS epidemic have increased the incidence of fungal meningitis. *Cryptococcus* sp (see p. 1329) is the most common cause in patients with AIDS, Hodgkin lymphoma, or lymphosarcoma and in those taking high-dose, long-term corticosteroids. *Coccidioides, Candida, Actinomyces, Histoplasma*, and *Aspergillus* spp are less common causes (see Ch. 142).

Symptoms and Signs

Most manifestations are similar to those of acute meningitis but evolve over weeks. Fever may be minimal. Headache, backache, and cranial nerve or spinal nerve root deficits are common. Communicating hydrocephalus may develop and cause dementia. Intracranial pressure may remain elevated and cause headache, vomiting, and decreased alertness for days or weeks. Without treatment, death can occur within a few weeks or months (eg, with TB or tumor), or symptoms can continue for years (eg, with Lyme disease).

Diagnosis

• CT or MRI

• CSF analysis

The diagnosis is suspected if meningeal symptoms or signs develop over > 2 wk, with or without symptoms of cerebral dysfunction, particularly if a potential cause of meningitis (eg, active TB, cancer) exists.

The diagnosis requires CSF analysis. CT or MRI is done to exclude mass lesions that cause slowly evolving cerebral dysfunction (eg, tumors, abscesses, subdural effusions) and to determine whether lumbar puncture can be done safely. CSF pressure is often elevated but may be normal. CSF cell count is elevated with a lymphocytic predominance; glucose is slightly or moderately reduced but may be significantly decreased in TB or fungal meningitis. CSF protein is high (see Table 180-1).

Other CSF tests (eg, special stains, fungal and acid-fast bacillus culture) are determined by the patient's risk factors. For example, TB is suspected in patients who are alcoholic, HIV-positive, or from areas where TB is endemic (see p. 1302). Identification of TB by microscopy has a notoriously low yield and requires acid-fast staining or immunofluorescence and an exhaustive microscopic search of CSF sediment, ideally from a large volume of CSF (30 to 50 mL), which may require 2 or 3 lumbar punctures (typically 20 to 30 mL can be withdrawn at a time). Positive cultures are the gold standard for diagnosis but also require 30 to 50 mL of CSF, and results take 2 to 6 wk. Although results differ among laboratories, PCR has a yield of about 50% in TB meningitis and can provide a specific diagnosis within days. Measurement of CSF tubulostearic acid by gas-liquid chromatography is specific but technically complex and not widely used.

Fungi may be detected microscopically in wet mounts or, for *Cryptococcus* sp, in India ink preparations (see also p. 1329). CSF cultures grow *Cryptococcus* and *Candida* spp in a few days and less common fungi in weeks. CSF cryptococcal antigen is highly specific and sensitive.

Neurosyphilis is diagnosed using the CSF Venereal Disease Research Laboratories (VDRL) test (see p. 1478). In Lyme disease (see p. 1268), diagnosis can be made by testing for serum antibodies against *Borrelia burgdorferi*. If serology is negative but clinical signs of meningitis are found, testing for intrathecal antibodies can be useful for diagnosis.

Diagnosis of neoplastic meningitis requires detecting cancer cells in CSF; detection depends on adequate CSF volume, frequency of collection (malignant cells may shed periodically; multiple samples increase the yield), sampling site (cisternal CSF is more often positive), and prompt fixation to preserve cell morphology. For 95% sensitivity, 30 to 50 mL of CSF (typically requiring several lumbar punctures) is collected and delivered to the laboratory promptly. For suspected neurosarcoidosis, ACE in CSF is measured; it is elevated in up to 24 to 50% of patients. For certain tumors, CSF tumor markers (eg, IL-10 for lymphoma; soluble CD27 for lymphoid cancers, such as acute lymphoblastic leukemia and non-Hodgkin lymphoma) can help with diagnosis or monitoring disease activity.

Some causes of subacute or chronic meningitis (eg, Behcet's syndrome) cannot be diagnosed by CSF analysis and must be diagnosed clinically.

Treatment

Treatment depends on the cause (see elsewhere in THE MANUAL).

Chapter 181. Neuro-Ophthalmologic and Cranial Nerve Disorders

Introduction

(See also Horner's Syndrome on p. 1618 and Chs. 47, 53, 69, and 168.)

Dysfunction of certain cranial nerves may affect the eye, pupil, optic nerve, or extraocular muscles and their nerves; thus, they can be considered cranial nerve disorders, neuroophthalmologic disorders, or both. Neuroophthalmologic disorders may also involve dysfunction of the central pathways that control and integrate ocular movement and vision. Cranial nerve disorders can also involve dysfunction of smell, vision, chewing, facial sensation or expression, taste, hearing, balance, swallowing, phonation, head turning and shoulder elevation, or tongue movements (see Table 181-1). One or more cranial nerves may be affected.

Causes and symptoms of neuro-ophthalmologic and cranial nerve disorders overlap. Both types of disorders can result from tumors, inflammation, trauma, systemic disorders, and degenerative or other processes, causing such symptoms as vision loss, diplopia, ptosis, pupillary abnormalities, periocular pain, facial pain, or headache.

Diagnosis

Evaluation includes the following:

• Detailed questioning about symptoms

• Examination of the visual system (see also p. 537)

• Tests to detect nystagmus (see Sidebar 46-1 on p. 414)

• Examination of the cranial nerves (see p. 1587)

Visual system examination includes ophthalmoscopy and testing of visual acuity, visual fields (see p. 539), pupils (see Table 181-2), and eye movements (ocular motility—see Table 181-3). As part of this testing, the 2nd, 3rd, 4th, and 6th cranial nerves are examined (see also p. 1587). Neuroimaging with CT or MRI is also usually required.

The following parts of the visual examination are of particular interest in diagnosing neuroophthalmologic and cranial nerve disorders:

Pupils are inspected for size, equality, and regularity. Normally, the pupils constrict promptly (within 1 sec) and equally during accommodation and during exposure to direct light and to light directed at the other pupil (consensual light reflex). Testing pupillary response to consensual light via a swinging flashlight test can determine whether a defect is present. Normally, the degree of pupillary constriction does not change as the flashlight is swung from eye to eye.

- If a relative afferent defect (deafferented pupil, afferent pupillary defect, or Marcus Gunn pupil) is present, the pupil paradoxically dilates when the flashlight swings to the side of the defect. A deafferented pupil constricts in response to consensual but not to direct light.

- If an efferent defect is present, the pupil responds sluggishly or does not respond to both direct and consensual light.

Eye movements are checked by having the patient hold the head steady while tracking the examiner's finger as it moves to the far right,

[**Table 181-1.** Cranial Nerves]

left, upward, downward, diagonally to either side, and inward toward the patient's nose (to assess accommodation). However, such examination may miss mild paresis of ocular movement sufficient to cause diplopia.

Diplopia may indicate a defect in bilateral coordination of eye movements (eg, in neural pathways) or in the 3rd (oculomotor), 4th (trochlear), or 6th (abducens) cranial nerve. If diplopia persists when one eye is closed (monocular diplopia), the cause is probably a nonneurologic eye disorder (see p. 550). If diplopia disappears when either eye is closed (binocular diplopia), the cause is probably a disorder of ocular motility. The 2 images are furthest apart when the patient looks in the direction served by the paretic eye muscle (eg, to the left when the left lateral rectus muscle

[**Table 181-2.** Common Pupillary Abnormalities]

is paretic). The eye that, when closed, eliminates the more peripheral image is paretic. Placing a red glass over one eye can help identify the paretic eye. When the red glass covers the paretic eye, the more peripheral image is red (see also p. 551).

Treatment

Treatment of neuro-ophthalmologic and cranial disorders depends on the cause.

Conjugate Gaze Palsies

A conjugate gaze palsy is inability to move both eyes in a single horizontal (most commonly) or vertical direction.

Gaze palsies most commonly affect horizontal gaze; some affect upward gaze, and fewer affect downward gaze.

Horizontal gaze palsies: Conjugate horizontal gaze is controlled by neural input from the cerebral hemispheres, cerebellum, vestibular nuclei, and neck. Neural input from these sites converges at the horizontal gaze center (paramedian pontine reticular formation) and is integrated into a final command to the adjacent 6th cranial nerve nucleus, which controls the lateral rectus on the same side, and, via the medial longitudinal fasciculus (MLF), to the contralateral 3rd cranial nerve nucleus and the medial rectus it controls. Inhibitory signals to opposing eye muscles occur simultaneously.

[**Table 181-3.** Common Disturbances of Ocular Motility]

The most common and devastating impairment of horizontal gaze results from pontine lesions that affect the horizontal gaze center and the 6th cranial nerve nucleus. Strokes are a common cause, resulting in loss of horizontal gaze ipsilateral to the lesion. In palsies due to stroke, the eyes may not move in response to any stimulus (eg, voluntary or vestibular). Milder palsies may cause only nystagmus or inability to maintain fixation.

Another common cause is a lesion in the contralateral cerebral hemisphere rostral to the frontal gyrus. These lesions are typically caused by a stroke. The resulting palsy usually abates with time. Horizontal conjugate gaze mediated by brain stem reflexes (eg, in response to cold-water caloric stimulation) is preserved.

Vertical gaze palsies: Upward and downward gaze depends on input from fiber paths that ascend from the vestibular system through the MLF on both sides to the 3rd and 4th cranial nerve nuclei, the interstitial nucleus of Cajal, and the rostral interstitial nucleus of the MLF. A separate system descends, presumably from the cerebral hemispheres, through the midbrain pretectum to the 3rd and 4th cranial nerve nuclei. The rostral interstitial nucleus of the MLF integrates the neural input into a final command for vertical gaze.

Vertical gaze becomes more limited with aging.

Vertical gaze palsies commonly result from midbrain lesions, usually infarcts and tumors. Parinaud's syndrome (dorsal midbrain syndrome), a conjugate upward vertical gaze palsy, may result from a pineal tumor or, less commonly, a tumor or infarct of the midbrain pretectum. This syndrome is characterized by impaired upward gaze, lid retraction (Collier's sign), downward gaze preference (setting-sun sign), convergence-retraction nystagmus, and dilated pupils (about 6 mm) that respond poorly to light but better to accommodation (light-near dissociation).

Downward gaze palsies: Impaired downward gaze with preservation of upward gaze usually indicates progressive supranuclear palsy (see p. 1771); other causes are rare.

Internuclear Ophthalmoplegia

Internuclear ophthalmoplegia is characterized by paresis of eye adduction in horizontal gaze but not in convergence. It can be unilateral or bilateral.

During horizontal gaze, the medial longitudinal fasciculus (MLF) on each side of the brain stem enables abduction of one eye to be coordinated with adduction of the other. The MLF connects the following structures:

• 6th cranial nerve nucleus (which controls the lateral rectus, responsible for abduction)

• Adjacent horizontal gaze center (paramedian pontine reticular formation)

• Contralateral 3rd cranial nerve nucleus (which controls the medial rectus, responsible for adduction)

The MLF also connects the vestibular nuclei with the 3rd cranial nerve nuclei.

Internuclear ophthalmoplegia results from a lesion in the MLF. In young people, the disorder is commonly caused by multiple sclerosis and may be bilateral. In the elderly, internuclear ophthalmoplegia is typically caused by stroke and is unilateral. Occasionally, the cause is neurosyphilis, Lyme disease, tumor, or drug intoxication (eg, with tricyclic antidepressants).

If a lesion in the MLF blocks signals from the horizontal gaze center to the 3rd cranial nerve, the eye on the affected side cannot adduct (or adducts weakly) past the midline. The affected eye adducts normally in convergence because convergence does not require signals from the horizontal gaze center. This finding distinguishes internuclear ophthalmoplegia from 3rd cranial nerve palsy, which impairs adduction in convergence (this palsy also differs because it causes limited vertical eye movement, ptosis, and pupillary abnormalities).

During horizontal gaze to the side opposite the affected eye, images are horizontally displaced, causing diplopia; nystagmus often occurs in the abducting eye. Sometimes vertical bilateral nystagmus occurs during attempted upward gaze.

Treatment is directed at the underlying disorder.

One-and-a-half syndrome: This uncommon syndrome occurs if a lesion affects the horizontal gaze center and the MLF on the same side. The eyes cannot move horizontally to either side except the eye on the side opposite the lesion can abduct; convergence is unaffected. Causes include multiple sclerosis, infarction, hemorrhage, and tumor.

With treatment (eg, radiation therapy for a tumor, treatment of multiple sclerosis), improvement may occur but is often limited after infarction.

Third Cranial Nerve Disorders

Third cranial nerve disorders can impair ocular motility, pupillary function, or both. Symptoms and signs include diplopia, ptosis, and paresis of eye adduction and of upward and downward gaze. If the pupil is affected, it is dilated and light reflexes are impaired. If the pupil is affected or

patients are increasingly unresponsive, CT is done as soon as possible.

Etiology

Third cranial (oculomotor) nerve disorders that cause palsies and affect the pupil commonly result from aneurysms (especially of the posterior communicating artery) and transtentorial brain herniation (see Fig. 174-1 on p. 1657) and less commonly from meningitis affecting the brain stem (eg, TB meningitis). The most common cause of palsies that spare the pupil, particularly partial palsies, is ischemia of the 3rd cranial nerve (usually due to diabetes) or of the midbrain. Occasionally, a posterior communicating artery aneurysm causes complete oculomotor palsy and spares the pupil.

Symptoms and Signs

Diplopia and ptosis (drooping of the upper eyelid) occur. The affected eye may deviate slightly out and down in straight-ahead gaze; adduction is slow and may not proceed past the midline. Upward gaze is impaired. When downward gaze is attempted, the superior oblique muscle causes the eye to adduct slightly and rotate. The pupil may be normal or dilated; its response to direct or and consensual light may be sluggish or absent (efferent defect). Mydriasis (pupil dilation) may be an early sign.

Diagnosis

• Clinical evaluation

• CT or MRI

Differential diagnosis includes midbrain lesions that disrupt the oculomotor fascicle (Claude's syndrome, Benedict's syndrome), leptomeningeal tumor or infection, cavernous sinus disease (giant carotid aneurysm, fistula, or thrombosis), intraorbital structural lesions (eg, orbital mucormycosis) that restrict ocular motility, ocular myopathies (eg, due to hyperthyroidism or mitochondrial disorders), and disorders of the neuromuscular junction (eg, due to myasthenia gravis or botulism). Differentiation may be clinical. Exophthalmos or enophthalmos, a history of severe orbital trauma, or an obviously inflamed orbit suggests an intraorbital structural disorder. Graves' orbitopathy (ophthalmopathy) should be considered in patients with bilateral ocular paresis, paresis of upward gaze or abduction, exophthalmos, lid retraction, lid lag during downward gaze (Graefe's sign), and a normal pupil.

CT or MRI is required. If a patient has a dilated pupil and a sudden, severe headache (suggesting ruptured aneurysm) or is increasingly unresponsive (suggesting herniation), CT is done immediately. If ruptured aneurysm is suspected and CT does not show blood or is not available rapidly, other tests, such as lumbar puncture, magnetic resonance angiography, CT angiography, or cerebral angiography, are indicated. Cavernous sinus disease and orbital mucormycosis require immediate MRI imaging for timely treatment.

Fourth Cranial Nerve Palsy

Fourth cranial nerve palsy impairs the superior oblique muscle, causing paresis of vertical gaze, mainly in adduction.

Fourth cranial (trochlear) nerve palsy is often idiopathic. Few causes have been identified. Causes include closed head injury (common), which may cause unilateral or bilateral palsies, and infarction due to small-vessel disease (eg, in diabetes). Rarely, this palsy results from aneurysms, tumors (eg, tentorial meningioma, pinealoma), or multiple sclerosis.

Because the superior oblique muscle is paretic, the eyes do not adduct normally. Patients see double images, one above and slightly to the side of the other; thus, going down stairs, which requires looking down and inward, is difficult. However, tilting the head to the side opposite the palsied muscle can compensate and eliminate the double images.

Examination may detect subtle impaired ocular motility, causing symptoms but not signs.

Oculomotor exercises or prism glasses may help restore concordant vision.

Sixth Cranial Nerve Palsy

Sixth cranial nerve palsy affects the lateral rectus muscle, impairing eye abduction. The eye may be slightly adducted when the patient looks straight ahead. The palsy may be secondary to nerve infarction, Wernicke's encephalopathy, trauma, infection, or increased intracranial pressure, or it may be idiopathic. Determining the cause requires MRI and often lumbar puncture and evaluation for vasculitis.

Etiology

Sixth cranial (abducens) nerve palsy may result from small-vessel disease, particularly in diabetics as part of a disorder called mononeuritis multiplex (multiple mononeuropathy). It may result from compression of the nerve by lesions in the cavernous sinus (eg, nasopharyngeal tumors), orbit, or base of the skull. The palsy may also result from increased intracranial pressure, head trauma, or both. Other causes include meningitis, meningeal carcinomatosis, Wernicke's encephalopathy, aneurysm, vasculitis, multiple sclerosis, pontine stroke, and, rarely, low CSF pressure headache (eg, after lumbar puncture). Children with respiratory infection may have recurrent palsy. However, the cause of an isolated 6th cranial nerve palsy is often not identified.

Symptoms and Signs

Symptoms include binocular horizontal diplopia when looking to the side of the paretic eye. Because the tonic action of the medial rectus muscle is unopposed, the eye is slightly adducted when the patient looks straight ahead. The eye abducts sluggishly, and even when abduction is maximal, the lateral sclera is exposed. With complete paralysis, the eye cannot abduct past midline.

Palsy resulting from nerve compression by a thrombus (eg, due to head trauma or stroke), tumor, or aneurysm in the cavernous sinus causes severe head pain, chemosis (conjunctival edema), anesthesia in the distribution of the 1st division of the 5th cranial nerve, optic nerve compression with vision loss, and paralysis of the 3rd, 4th, and 6th cranial nerves. Both sides are typically affected, although unevenly.

Diagnosis

• MRI

• If vasculitis is suspected, ESR, antinuclear antibodies, and rheumatoid factor

A 6th nerve palsy is usually obvious, but the cause is not. If retinal venous pulsations are seen during ophthalmoscopy, increased intracranial pressure is unlikely. CT is often done because it is often immediately available. However, MRI is the test of choice; MRI provides greater resolution of the orbits, cavernous sinus, posterior fossa, and cranial nerves. If imaging results are normal but meningitis or increased intracranial pressure is suspected, lumbar puncture is done.

If vasculitis is suspected clinically, evaluation begins with measurement of ESR, antinuclear antibodies, and rheumatoid factor. In children, if increased intracranial pressure is excluded, respiratory infection is considered.

Treatment

In many patients, 6th cranial nerve palsies resolve once the underlying disorder is treated. Idiopathic palsy usually abates within 2 mo.

Trigeminal Neuralgia

(Tic Douloureux)

Trigeminal neuralgia is severe paroxysmal, lancinating facial pain due to a disorder of the 5th cranial nerve. Diagnosis is clinical. Treatment is usually with carbamazepine or gabapentin; sometimes surgery is required.

Trigeminal neuralgia affects mainly adults, especially the elderly.

Etiology

Trigeminal neuralgia is usually caused by an intracranial artery (eg, anterior inferior cerebellar artery, ectatic basilar artery) or, less often, a venous loop that compresses the 5th cranial (trigeminal) nerve at its root entry zone into the brain stem. Other less common causes include compression by a tumor and occasionally a multiple sclerosis plaque at the root entry zone, but these are distinguished usually by accompanying sensory and other deficits. Other disorders that cause similar symptoms (eg, multiple sclerosis) are sometimes considered to be trigeminal neuralgia and sometimes not. Recognizing the cause is what is important.

The mechanism is unclear. One theory suggests that nerve compression causes local demyelination, which may result in ectopic impulse generation and/or disinhibition of central pain pathways involving the spinal trigeminal nucleus.

Symptoms and Signs

Pain occurs along the distribution of one or more sensory divisions of the trigeminal nerve, most often the maxillary. The pain is paroxysmal, lasting seconds up to 2 min, but attacks may recur rapidly. It is lancinating, excruciating, and sometimes incapacitating. Pain is often precipitated by stimulating a facial trigger point (eg, by chewing, brushing the teeth, or smiling). Sleeping on that side of the face is often intolerable.

Diagnosis

• Clinical evaluation

Symptoms are almost pathognomonic. Thus, some other disorders that cause facial pain can be differentiated clinically:

• Chronic paroxysmal hemicrania (Sjaastad syndrome) is differentiated by longer (5 to 8 min) attacks of pain and its dramatic response to indomethacin.

• Postherpetic pain is differentiated by its constant duration (without paroxysms), typical antecedent rash, scarring, and predilection for the ophthalmic division.

• Migraine, which may cause atypical facial pain, is differentiated by pain that is more prolonged and often throbbing.

Neurologic examination is normal in trigeminal neuralgia. Thus, neurologic deficits (usually loss of facial sensation) suggest that the trigeminal neuralgia-like pain is caused by another disorder (eg, tumor, stroke, multiple sclerosis plaque, vascular malformation, other lesions that compress the trigeminal nerve or disrupt its brain stem pathways.

Treatment

• Usually anticonvulsants

Carbamazepine 200 mg po tid or qid is usually effective for long periods; it is begun at 100 mg po bid, increasing the dose by 100 to 200 mg/day until pain is controlled (maximum daily dose 1200 mg). Hepatic enzymes and CBC should be checked after 2 wk, then every 3 to 6 mo. If carbamazepine is ineffective or has adverse effects, one of the following may be tried:

- Oxcarbazepine 150 to 300 mg po bid
- Gabapentin 300 to 600 mg po tid (300 mg po once on day 1, 300 mg po bid on day 2, 300 mg po tid on day 3, then increasing dose as needed to 600 mg po tid)
- Phenytoin 100 to 200 mg po bid (beginning with 100 mg po bid, then increasing as needed)
- Baclofen 10 to 30 mg po tid (beginning with 5 to 10 mg po tid, then increasing as needed by about 5 mg/day)
- Amitriptyline 25 to 150 mg po taken at bedtime (beginning with 25 mg, then increasing by 25-mg increments each week as needed)

Peripheral nerve block provides temporary relief.

If pain is severe despite these measures, neuroablative treatments are considered; however, efficacy may be temporary, and improvement may be followed by recurrent pain that is more severe than the preceding episodes. In a posterior fossa craniectomy, a small pad can be placed to separate the pulsating vascular loop from the trigeminal root. In radiosurgery, a gamma knife can be used to cut the proximal trigeminal nerve. Electrolytic or chemical lesions or balloon compression of the trigeminal (gasserian) ganglion can be made via a percutaneous stereotaxically positioned needle. Occasionally, the trigeminal nerve fibers between the gasserian ganglion and brain stem are cut. Sometimes, as a last resort to relieve intractable pain, the trigeminal nerve is destroyed.

Hemifacial Spasm

Hemifacial spasm refers to unilateral painless, synchronous contractions of facial muscles due to dysfunction of the 7th cranial (facial) nerve and/or its motor nucleus. Hemifacial spasm results from nerve compression by a pulsating blood vessel, similar to that in trigeminal neuralgia.

Diagnosis is clinical. Focal seizures, blepharospasm, and tics cause similar symptoms and should be considered.

Treatment is similar to that of trigeminal neuralgia except botulinum toxin (botulinum toxin type A or botulinum toxin type B) can also be used effectively.

Bell's Palsy

Bell's palsy is sudden, idiopathic, unilateral peripheral 7th cranial nerve palsy. Symptoms are hemifacial paresis of the upper and lower face. There are no specific tests for diagnosis. Treatment may include corticosteroids, antiviral drugs (eg, acyclovir), lubrication of the eye, and intermittent use of an eye patch.

Etiology

Cause is unknown, but the mechanism is presumably swelling of the 7th cranial (facial) nerve due to an immune or viral disorder. Recent evidence suggests herpes simplex virus infection. The nerve is compressed, resulting in ischemia and paresis, because the nerve passes through a narrow opening (internal acoustic meatus) in the temporal bone.

The orbicularis oculi and frontalis muscles are paretic when the lesion is distal to the 7th cranial nerve nucleus (ie, peripheral) but much less so when the lesion is proximal to the nucleus (ie, central). The effects differ because the orbicularis oculi and frontalis muscles are controlled by the 7th cranial nerve nuclei (central part of the facial nerve), which receive input from both left and right hemispheres. In contrast, the lower facial muscles (below the zygomatic arch) receive input from mainly the peripheral part of the facial nerve, distal to the 7th cranial nerve nuclei, which receives input from only one hemisphere. Thus, the muscles are paretic regardless of the location of the lesion along the 7th cranial nerve.

Symptoms and Signs

Pain behind the ear often precedes facial paresis. Paresis, often with complete paralysis, develops within hours and is usually maximal within 48 to 72 h. Patients may report a numb or heavy feeling in the face. The affected side becomes flat and expressionless; ability to wrinkle the forehead, blink, and grimace is limited or absent (see
Plate 68). In severe cases, the palpebral fissure widens and the eye does not close, often irritating the conjunctiva and drying the cornea.

Sensory examination is normal, but the external auditory canal and a small patch behind the ear (over the mastoid) may be painful to the touch. If the nerve lesion is proximal to the geniculate ganglion, salivation, taste, and lacrimation may be impaired, and hyperacusis may be present.

Diagnosis

• Clinical evaluation

• Testing if indicated by clinical findings

There are no specific diagnostic tests. Thus, Bell's palsy is a diagnosis of exclusion. It can be distinguished from a central 7th cranial nerve lesion (eg, due to hemispheric stroke or tumor), which causes weakness primarily of the lower face; patients with central lesions can usually furrow their brow and close their eyes tightly. Other disorders that cause peripheral 7th cranial nerve palsies and must be excluded include the following:

• Geniculate herpes (Ramsay Hunt syndrome, which is due to herpes zoster)

• Middle ear or mastoid infections

• Sarcoidosis

• Lyme disease

• Petrous bone fractures

• Carcinomatous or leukemic nerve invasion

• Chronic meningitis

• Cerebellopontine angle or glomus jugulare tumors

Other disorders that cause peripheral 7th cranial nerve palsy typically develop more slowly than Bell's palsy and may have other distinguishing symptoms or signs.

In Bell's palsy, MRI may show contrast enhancement of the 7th cranial nerve at or near the geniculate ganglion. However, its enhancement may reflect other pathology, such as sarcoidosis or meningeal tumor. If the paralysis progresses over weeks to months, the likelihood of tumor (eg, most commonly schwannoma) compressing the 7th cranial nerve increases. MRI can also help exclude other structural disorders causing 7th cranial nerve palsy. CT, usually negative in Bell's palsy, is done if a fracture is suspected or if MRI is not immediately available and stroke is possible. Acute and convalescent serologic tests for Lyme disease are done if patients have been in a geographic area where ticks are endemic. For all patients, a chest x-ray is taken and serum ACE is measured to check for sarcoidosis. Viral titers are not helpful.

Prognosis

The extent of nerve damage determines outcome. If some function remains, full recovery typically occurs

within several months. Nerve conduction studies and electromyography predict outcome. The likelihood of complete recovery after total paralysis is 90% if nerve branches in the face retain normal excitability to supramaximal electrical stimulation and is only about 20% if electrical excitability is absent.

Regrowth of nerve fibers may be misdirected, innervating lower facial muscles with periocular fibers and vice versa. The result is contraction of unexpected muscles during voluntary facial movements (synkinesia) or crocodile tears during salivation. Chronic disuse of the facial muscles may lead to contractures.

Treatment

• Possibly corticosteroids, antiviral drugs, or both

• Supportive measures

No treatment has proved effective for idiopathic Bell's palsy. Corticosteroids, if begun within 48 h after onset, may slightly reduce duration and degree of residual paralysis. Prednisone 60 to 80 mg po once/day is given for 1 wk, then decreased gradually over the 2nd wk. Antiviral drugs effective against herpes simplex virus (eg, valacyclovir 1 g po tid for 7 to 10 days, famciclovir 500 mg po tid for 5 to 10 days, acyclovir 400 mg po 5 times/day for 10 days) are also often given.

Corneal drying must be prevented by frequent use of natural tears, isotonic saline, or methylcellulose drops and by intermittent use of tape or a patch to help close the eye, particularly during sleep. Tarsorrhaphy is occasionally required.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is recurrent attacks of severe pain in the 9th cranial nerve distribution (posterior pharynx, tonsils, back of the tongue, middle ear). Diagnosis is clinical. Treatment is usually with carbamazepine or gabapentin.

Glossopharyngeal neuralgia sometimes results from nerve compression by an aberrant, pulsating artery similar to that in trigeminal neuralgia and hemifacial spasm. Rarely, the cause is a tumor in the cerebellopontine angle or the neck. Often, no cause is identified. The disorder is rare, more commonly affecting men, usually after age 40.

Symptoms and Signs

As in trigeminal neuralgia, paroxysmal attacks of unilateral brief, excruciating pain occur spontaneously or are precipitated by certain movements (eg, chewing, swallowing, talking, sneezing). The pain, lasting seconds to a few minutes, usually begins in the tonsillar region or at the base of the tongue and may radiate to the ipsilateral ear. Occasionally, increased vagus nerve activity causes sinus arrest with syncope; episodes may be very infrequent.

Diagnosis

• Clinical evaluation, often including response to anesthetics

• MRI

Diagnosis is clinical. Glossopharyngeal neuralgia is distinguished from trigeminal neuralgia by the location of the pain. Also, in glossopharyngeal neuralgia, swallowing or touching the tonsils with an applicator tends to precipitate pain, and applying lidocaine to the throat temporarily eliminates spontaneous or evoked pain. MRI is done to exclude tonsillar, pharyngeal, and cerebellopontine angle tumors and metastatic lesions in the anterior cervical triangle. Local nerve blocks done by an ENT physician can help distinguish between carotidynia, superior laryngeal neuralgia, and pain caused by tumors.

Treatment

• Usually anticonvulsants

Treatment is the same as that for trigeminal neuralgia (see p. 1754). If oral drugs are ineffective, topical cocaine applied to the pharynx may provide temporary relief, and surgery to decompress the nerve from a pulsating artery may be necessary. If pain is restricted to the pharynx, surgery can be restricted to the extracranial part of the nerve. If pain is widespread, surgery must involve the intracranial part of the nerve.

Chapter 182. Craniocervical Junction Abnormalities

Craniocervical junction abnormalities are congenital or acquired abnormalities of the occipital bone, foramen magnum, or first 2 cervical vertebrae that decrease the space for the lower brain stem and cervical cord. These abnormalities can result in neck pain; syringomyelia; cerebellar, lower cranial nerve, and spinal cord deficits; and vertebrobasilar ischemia. Diagnosis is by MRI or CT. Treatment often involves reduction, followed by stabilization via surgery or an external device.

Neural tissue is flexible and susceptible to compression. Craniocervical junction abnormalities can cause or contribute to cervical spinal cord or brain stem compression; some abnormalities and their clinical consequences include the following:

- Fusion of the atlas (C1) and occipital bone: Spinal cord compression if the anteroposterior diameter of the foramen magnum behind the odontoid process is < 19 mm
- Basilar invagination (upward bulging of the occipital condyles): A short neck and compression that can affect the cerebellum, brain stem, lower cranial nerves, and spinal cord
- Atlantoaxial subluxation or dislocation (displacement of the atlas anteriorly in relation to the axis): Acute or chronic spinal cord compression
- Klippel-Feil malformation (fusion of cervical vertebrae): Deformity and limited motion of the neck but usually no neurologic consequences
- Platybasia (flattening of the skull base so that the angle formed by the intersection of the clival and anterior fossa planes is > 135°), seen on lateral skull imaging: No symptoms or cerebellar or spinal cord deficits or normal-pressure hydrocephalus

Etiology

Craniocervical junction abnormalities can be congenital or acquired.

Congenital: Congenital abnormalities may be specific structural abnormalities or general or systemic disorders that affect skeletal growth and development. Many patients have multiple abnormalities.

Structural abnormalities include the following:

- Os odontoideum (anomalous bone that replaces all or part of the odontoid process)
- Atlas assimilation (congenital fusion of the atlas and occipital bone)
- Congenital Klippel-Feil malformation (eg, with Turner's or Noonan's syndrome), often associated with atlanto-occipital anomalies
- Atlas hypoplasia
- Chiari malformations (descent of the cerebellar tonsils or vermis into the cervical spinal canal, sometimes associated with platybasia—see p. 2992)

General or systemic disorders that affect skeletal growth and development and involve the craniocervical junction include the following:

- Achondroplasia (impaired epiphyseal bone growth, resulting in shortened, malformed bones) sometimes causes the foramen magnum to narrow or fuse with the atlas and thus may compress the spinal cord or brain stem.
- Down syndrome, Morquio's syndrome (mucopolysaccharidosis IV), or osteogenesis imperfecta can

cause atlantoaxial subluxation or dislocation.

Acquired: Acquired causes include injuries and disorders.

- Injuries may involve bone, ligaments, or both and are usually caused by vehicle or bicycle accidents, falls, and particularly diving; some injuries are immediately fatal.

- RA (the most common disease cause) and Paget's disease of the cervical spine can cause atlantoaxial dislocation or subluxation, basilar invagination, or platybasia.

- Metastatic tumors that affect bone can cause atlantoaxial dislocation or subluxation.

- Slowly growing craniocervical junction tumors (eg, meningioma, chordoma) can impinge on the brain stem or spinal cord.

Symptoms and Signs

Symptoms and signs can occur after a minor neck injury or spontaneously and may vary in progression. Presentation varies by degree of compression and by structures affected. The most common manifestations are

- Neck pain, often with headache

- Symptoms and signs of spinal cord compression

Neck pain often spreads to the arms and may be accompanied by headache (commonly, occipital headache radiating to the skull vertex); it is attributed to compression of the C2 root and the greater occipital nerve and to local musculoskeletal dysfunction. Neck pain and headache usually worsen with head movement and can be precipitated by coughing or bending forward. If patients with Chiari malformation have hydrocephalus, being upright may aggravate the hydrocephalus and result in headaches.

Spinal cord compression involves the upper cervical cord. Deficits include spastic paresis in the arms, legs, or both, caused by compression of motor tracts. Joint position and vibration senses (posterior column function) are commonly impaired. Tingling down the back, often into the legs, with neck flexion (Lhermitte's sign) may occur. Uncommonly, pain and temperature senses (spinothalamic tract function) are impaired in a stocking-glove pattern.

Neck appearance, range of motion, or both can be affected by some abnormalities (eg, platybasia, basilar invagination, Klippel-Feil malformation). The neck may be short, webbed (with a skinfold running approximately from the sternocleidomastoid to the shoulder), or in an abnormal position (eg, torticollis in Klippel-Feil malformation). Range of motion may be limited.

Brain compression (eg, due to platybasia, basilar invagination, or craniocervical tumors) may cause brain stem, cranial nerve, and cerebellar deficits. Brain stem and cranial nerve deficits include sleep apnea, internuclear ophthalmoplegia (ipsilateral weakness of eye adduction plus contralateral horizontal nystagmus in the abducting eye with lateral gaze), downbeat nystagmus (fast component downward), hoarseness, dysarthria, and dysphagia. Cerebellar deficits usually impair coordination (see p. 1777).

Vertebrobasilar ischemia can be triggered by changing head position. Symptoms may include intermittent syncope, drop attacks, vertigo, confusion or altered consciousness, weakness, and visual disturbance.

Syringomyelia (cavity in the central part of the spinal cord—see p. 1812) is common in patients with Chiari malformation. It may cause segmental flaccid weakness and atrophy, which first appear or are most severe in the distal upper extremities; pain and temperature senses may be lost in a capelike distribution over the neck and proximal upper extremities, but light touch is preserved.

Diagnosis

• MRI or CT of the brain and upper spinal cord

A craniocervical abnormality is suspected when patients have pain in the neck or occiput plus neurologic deficits referable to the lower brain stem, upper cervical spinal cord, or cerebellum. Lower cervical spine disorders can usually be distinguished clinically (based on level of spinal cord dysfunction) and by neuroimaging.

Neuroimaging: If a craniocervical abnormality is suspected, MRI or CT of the upper spinal cord and brain, particularly the posterior fossa and craniocervical junction, is done. Acute or suddenly progressive deficits are an emergency, requiring immediate imaging. Sagittal MRI best identifies associated neural lesions (eg, hindbrain, cerebellar, spinal cord, and vascular abnormalities; syringomyelia) and soft-tissue lesions. CT shows bone structures more accurately than MRI and may be done more easily in an emergency.

If MRI and CT are unavailable, plain x-rays—lateral view of the skull showing the cervical spine, anteroposterior view, and oblique views of the cervical spine—are taken.

If MRI is unavailable or inconclusive and CT is inconclusive, CT myelography (CT after intrathecal injection of a radiopaque dye) is done. If MRI or CT suggests vascular abnormalities, magnetic resonance angiography or vertebral angiography is done.

Treatment

• Reduction and immobilization

• Sometimes surgical decompression, fixation, or both

If neural structures are compressed, treatment consists of reduction (traction or changes in head position to realign the craniocervical junction and thus relieve neural compression). After reduction, the head and neck are immobilized. *Acute or suddenly progressive spinal cord compression requires emergency reduction.*

For most patients, reduction involves skeletal traction with a crown halo ring and weight of up to about 4 kg. Reduction with traction may take 5 to 6 days. If reduction is achieved, the neck is immobilized in a halo vest for 8 to 12 wk; then x-rays must be taken to confirm stability.

If reduction does not relieve neural compression, surgical decompression, using a ventral or a dorsal approach, is necessary. If instability persists after decompression, posterior fixation (stabilization) is required. For some abnormalities (eg, due to RA), external immobilization alone is rarely successful; if it is unsuccessful, posterior fixation or anterior decompression and stabilization are required.

Several different methods of instrumentation (eg, plates or rods with screws) can be used for temporary stabilization until bones fuse and stability is permanent. In general, all unstable areas must be fused.

Bone disease: Radiation therapy and a hard cervical collar often help patients with metastatic bone tumors. Calcitonin, mithramycin, and bisphosphonates may help patients with Paget's disease.

Chapter 183. Movement and Cerebellar Disorders

Introduction

Voluntary movement requires interaction of the corticospinal (pyramidal) tracts, basal ganglia, and cerebellum (the center for motor coordination). The pyramidal tracts pass through the medullary pyramids to connect the cerebral cortex to lower motor centers of the brain stem and spinal cord. The basal ganglia (caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra) form the extrapyramidal system. They are located deep in the forebrain and direct their output mainly rostrally through the thalamus to the cerebral cortex. Most neural lesions that cause movement disorders occur in the extrapyramidal system; thus, movement disorders are also called extrapyramidal disorders.

Classification

Movement disorders are classified as those with decreased or slow purposeful movements (hypokinesia) or those with excessive voluntary or abnormal involuntary movements (hyperkinesia). Although disorders of the cerebellum also impair gait and movement, they are classified separately (see p. 1777).

Hypokinesia: Most hypokinetic disorders are parkinsonian disorders, which are characterized by slow and decreased movement, muscular rigidity, resting tremor, and postural instability (see p. 1765).

Hyperkinesia: There are many hyperkinetic disorders (see Fig. 183-1 and Table 183-1). They can be subclassified as rhythmic or non-rhythmic.

Rhythmic disorders are primarily tremors—regular alternating or oscillatory movements, which can occur mainly at rest (as resting tremor) or during attempted movement (as intention tremor).

Nonrhythmic disorders are characterized as slow (eg, athetosis), sustained (eg, dystonias), or rapid. Rapid disorders are characterized as suppressible (eg, tics) or nonsuppressible (eg, hemiballismus, chorea, myoclonus). Athetosis and chorea often occur together as choreoathetosis. Chorea occurs in Huntington's disease (see p. 1763). Tic disorders include Tourette's syndrome (see p. 2902).

Chorea, Athetosis, and Hemiballismus

Chorea is nonrhythmic, jerky, rapid, nonsuppressible involuntary movements, mostly of distal muscles or the face; movements may merge imperceptibly into purposeful or semipurposeful acts that mask the involuntary movements. Athetosis is nonrhythmic, slow, writhing, sinuous movements predominantly in distal muscles, often alternating with postures of the proximal limbs to produce a continuous, flowing stream of movement. Hemiballismus is usually a unilateral, nonrhythmic, rapid, nonsuppressible, violent, flinging movement of the proximal arm.

[**Fig. 183-1.** Classification of hyperkinesias.]

Chorea and athetosis often occur together (as choreoathetosis). They are manifestations of overactivity in certain pathways of the basal ganglia. Huntington's disease (see p. 1763) is the most common degenerative disease causing chorea. Other causes include thyrotoxicosis, paraneoplastic syndromes, SLE affecting the CNS, other autoimmune disorders, and drugs (eg, antipsychotics). Rheumatic fever sometimes leads to Sydenham's chorea (see p. 2862). A tumor or infarct of the caudate nucleus can cause acute unilateral chorea (hemichorea). Chorea may occur as an isolated symptom in patients > 60 (as senile chorea); this chorea tends to be symmetric and does not cause dementia.

The cause is treated or corrected if possible. Sydenham's chorea and chorea due to infarcts of the caudate nucleus often lessen over time. Chorea due to thyrotoxicosis usually lessens when thyroid dysfunction is corrected. In Huntington's disease, drugs that suppress dopaminergic activity, such as antipsychotics (eg, risperidone), and dopamine-depleting drugs (eg, reserpine, tetrabenazine) can be used. However, improvement may be limited.

Chorea gravidarum occurs during pregnancy, often in patients who had rheumatic fever. Chorea usually begins during the 1st trimester and resolves spontaneously by or after delivery. Treatment is sedation with barbiturates; other sedatives may harm the fetus. Rarely, a similar disorder occurs in women taking oral contraceptives.

Hemiballismus is caused by a lesion, usually an infarct, around the contralateral subthalamic nucleus. Although disabling, hemiballismus is usually self-limited, lasting 6 to 8 wk. Treatment with antipsychotics is often effective.

Dystonias

Dystonias are sustained involuntary muscle contractions, often distorting body posture. Dystonias can be primary or secondary, and they can be generalized, focal, or segmental. Diagnosis is clinical. Treatment of generalized dystonia is often with a combination of anticholinergic drugs, muscle relaxants, and benzodiazepines. Treatment of focal or segmental dystonias is often with botulinum toxin; more generalized or refractory cases may benefit from surgery.

Dystonia may be primary (idiopathic) or secondary to degenerative or metabolic CNS disorders (eg, Wilson's disease, Hallervorden-Spatz disease, various lipidoses, multiple sclerosis, cerebral palsy, stroke, brain hypoxia) or drugs (most often phenothiazines, thioxanthenes, butyrophenones, and antiemetics).

Generalized dystonia (dystonia musculorum deformans): This rare dystonia is progressive and characterized by movements that result in sustained, often bizarre postures. It is often hereditary, usually as an autosomal dominant disorder with partial penetrance; asymptomatic siblings of patients often have a forme fruste of

[Table 183-1. Hyperkinetic Disorders]

the disorder. The causative gene is usually *DYT1*, causing DYT1 dystonia.

Symptoms usually begin in childhood with inversion and plantar fixation of the foot while walking. The dystonia may affect only the trunk or a leg but sometimes affects the whole body. Patients with the most severe form may become twisted into grotesque fixed postures and ultimately confined to a wheelchair. Symptoms that begin during adulthood usually affect only the face or arms. Mental function is usually preserved.

Focal dystonias: These dystonias affect a single body part. They typically start in a person's 30s or 40s and affect women more often. Initially, spasms may be periodic, occurring randomly or during stress; they are triggered by certain movements of the affected body part and disappear during rest. Over days, weeks, or many years, spasms may progress; they may be triggered by movements of unaffected body parts and may continue during rest. Eventually, the affected body part remains distorted, sometimes in a painful position, resulting in severe disability. Symptoms vary depending on the specific muscles involved.

Occupational dystonia consists of focal dystonic spasms initiated by performing skilled acts (eg, writer's or typist's cramp, the yips in golfers).

Spasmodic dystonia consists of a strained, hoarse, or creaky voice due to abnormal involuntary contraction of laryngeal muscles.

Torticollis begins with a pulling sensation followed by sustained torsion and deviation of the head and neck. The cause is often unknown but, in some cases, is probably genetic. In early stages, it can be voluntarily overcome. Patients may discover sensory or tactile tricks that make the spasm stop, such as touching the face on the side contralateral to the deviation. Torticollis can also be caused by dopamine-blocking drugs (eg, haloperidol).

Segmental dystonias: These dystonias affect ≥ 2 contiguous body parts.

Meige's disease (blepharospasm-oromandibular dystonia) consists of involuntary blinking, jaw grinding, and grimacing, usually beginning in late middle age. It may mimic the buccal-lingual-facial movements of tardive dyskinesia.

Diagnosis

Diagnosis is clinical.

Treatment

• For generalized dystonia, anticholinergics, muscle relaxants, or both

• For focal dystonia, botulinum toxin

Treatment is often unsatisfactory. For generalized dystonia, a high-dose anticholinergic drug (trihexyphenidyl 2 to 10 mg po tid, benztropine 3 to 15 mg po once/day) is most commonly used, often with a muscle relaxant (usually baclofen), a benzodiazepine (eg, clonazepam), or both. Generalized dystonia that is severe or does not respond to drugs may be treated with deep brain stimulation of the globus pallidus interna, which requires surgery.

For focal or segmental dystonias or for generalized dystonia that severely affects specific body parts, the treatment of choice is purified botulinum toxin type A injected into the affected muscles by an experienced practitioner. Botulinum toxin weakens muscular contractions, but it does not alter the abnormal neural stimulus. Toxin injection is particularly effective for blepharospasm and torticollis. Dosage varies greatly. Treatments must be repeated every 3 to 6 mo.

Fragile X-Associated Tremor/Ataxia Syndrome

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a genetic disorder affecting mostly men and causing tremor, ataxia, and dementia.

FXTAS affects about 1/3000 men. A premutation (an increased number of CGG repeats) occurs in the fragile X mental retardation (*FMR1*) gene on the X chromosome; if the mutation is full, > 200 repeats occur, causing fragile X syndrome. People with the premutation are considered carriers. Daughters (but not sons) of men with the premutation inherit the premutation. Their children (grandchildren of men with the gene) have a 50% chance of inheriting the premutation, which can expand into a full mutation when passed from mother to child (and thus cause fragile X syndrome). FXTAS develops in about 30% of men with the premutation and in < 5% of women with the premutation. Risk of developing FXTAS increases with age.

Symptoms and Signs

Symptoms usually develop in older age; average age of onset in 60 yr. The more CGG repeats, the more severe are the symptoms.

Tremor that resembles essential tremor is a common early symptom, usually followed by ataxia within 2 yr. Other symptoms may include slow movements, stiffness, and decreased facial expression, similar to Parkinson's disease.

Cognitive impairment, including loss of short-term memory, slowed thought, and difficulty problem-solving, varies. These symptoms often progress to dementia. Depression, anxiety, impatience, hostility, and mood lability may develop.

Sensation and reflexes in the feet may be lost. Dysautonomia (eg, orthostatic hypotension) may occur. In later stages, bladder and bowel control may be lost. Life expectancy after motor symptoms is reported to range from about 5 to 25 yr.

In women with the premutation, symptoms are usually less severe, possibly because the presence of

another X chromosome is protective. Symptoms more often suggest multiple sclerosis or fibromyalgia than FXTAS. These women have an increased risk of early menopause, infertility, and ovarian dysfunction.

Diagnosis

• Genetic testing

Grandfathers of children who have fragile X syndrome should be asked whether they have neurologic symptoms associated with FXTAS. MRI can detect the characteristic brightness in the middle cerebellar peduncles, which is not always present in FXTAS but is rarely caused by other disorders. Diagnosis is confirmed by genetic testing.

Treatment

Tremor can often be relieved with many of the drugs used to control tremors due to Parkinson's disease (see p. 1767).

Huntington's Disease

(Huntington's Chorea; Chronic Progressive Chorea; Hereditary Chorea)

Huntington's disease is an autosomal dominant disorder characterized by chorea and progressive cognitive deterioration, usually beginning in middle age. Diagnosis is by genetic testing. Treatment is supportive. First-degree relatives are encouraged to have genetic testing.

Huntington's disease affects both sexes equally. The caudate nucleus atrophies, the inhibitory medium spiny neurons in the corpus striatum degenerate, and levels of the neurotransmitters γ-aminobutyric acid (GABA) and substance P decrease.

Huntington's disease results from a gene mutation causing abnormal repetition of the DNA sequence CAG that codes for the amino acid glutamine. The resulting gene product, a large protein called huntingtin, has an expanded stretch of polyglutamine residues, which leads to disease via unknown mechanisms. The more CAG repetitions, the earlier the disease begins and the more severe the effects. The number of repeats can increase with successive generations and, over time, lead to a more severe phenotype within a family tree.

Symptoms and Signs

Symptoms and signs develop insidiously, starting at about age 35 to 50 but can develop before adulthood. Dementia or psychiatric disturbances (eg, depression, apathy, irritability, anhedonia, antisocial behavior, full-blown bipolar or schizophreniform disorder) develop before or simultaneously with the movement disorder. Abnormal movements appear; they include myoclonic jerks or irregular movements of the extremities, a lilting gait (like a puppet's), facial grimacing, ataxia, and inability to sustain a motor act (motor impersistence) such as tongue protrusion.

The disorder progresses, making walking impossible, swallowing difficult, and dementia severe. Most patients eventually require institutionalization. Death usually occurs 13 to 15 yr after symptoms begin. The cause is usually pneumonia or coronary artery disease.

Diagnosis

• Clinical evaluation, confirmed by genetic testing

• MRI to rule out other causes

Diagnosis is based on typical symptoms and signs plus a positive family history and is confirmed by genetic testing. Neuroimaging is done to exclude other disorders; in advanced Huntington's disease, MRI and CT coronal views show boxcar ventricles (ie, squared-off edges due to atrophy of the caudate head).

Treatment

• Supportive measures

• Genetic counseling

Because the disease is progressive, end-of-life care should be discussed early (see p. 3480).

Treatment is supportive. Chorea and agitation may be partially suppressed by antipsychotics (eg, chlorpromazine 25 to 300 mg po tid, haloperidol 5 to 45 mg po bid); dose is increased until intolerable or undesirable adverse effects (eg, lethargy, parkinsonism) occur. Alternatively, tetrabenazine may be used. The dose is started at 12.5 mg po once/day; dosage is increased (to 12.5 mg bid in the 2nd wk, 12.5 mg tid in the 3rd wk, up to a total of 100 mg/day divided into 3 doses) until intolerable adverse effects (eg, sedation, akathisias, parkinsonism, depression) occur or chorea resolves.

Experimental therapies aim to reduce glutamatergic neurotransmission via the *N*-methyl-D-aspartate receptor and bolster mitochondrial energy production. Treatment to supplement GABA in the brain has been ineffective.

People who have 1st-degree relatives with the disease should have genetic testing and counseling (see also p. 2598) because people are likely to have children before symptoms appear. If such people are interested in testing, they are referred to centers that have expertise in dealing with the complex ethical and psychologic issues involved.

Myoclonus

Myoclonus is a brief, shocklike contraction of a muscle or group of muscles. Diagnosis is clinical and by selective testing. Treatment includes correction of reversible causes and sometimes oral drugs (eg, clonazepam, valproate).

Physiologic myoclonus may occur as a person falls asleep (nocturnal myoclonus). Myoclonus can result from other disorders and certain drugs (see Table 183-2). The most common causes are hypoxia, drug toxicity, and metabolic disturbances; other causes include degenerative disorders affecting the basal ganglia and some dementias.

[**Table 183-2.** Causes of Myoclonus]

Myoclonus may be focal, segmental (contiguous areas), multifocal (noncontiguous areas), or generalized.

Symptoms and Signs

Myoclonus can vary in amplitude, frequency, and distribution. Muscle jerks may be induced by a stimulus (eg, sudden noise, movement, light, visual threat). Myoclonus that occurs when patients are suddenly startled (startle myoclonus) may be an early symptom of Creutzfeldt-Jacob disease. Myoclonus due to severe closed head trauma or hypoxicischemic brain damage may worsen with purposeful movements (action myoclonus) or may occur spontaneously when movement is limited because of injury.

Myoclonus due to metabolic disturbances may be multifocal, asymmetric, and stimulus-induced; it usually involves facial or proximal limb muscles. If the disturbance persists, generalized myoclonic jerks and, ultimately, seizures may occur.

Diagnosis

Diagnosis is clinical. Testing is done based on clinically suspected causes.

Treatment

• Correction of metabolic disturbance

• Drug therapy to relieve symptoms

Treatment begins with correction of underlying metabolic disturbances.

For symptom relief, clonazepam 0.5 to 2 mg po tid is often effective. Valproate 250 to 500 mg po bid or levetiracetam 250 to 500 mg po once/day to bid may be effective; rarely, other anticonvulsants help. Doses of clonazepam or valproate may need to be lower in the elderly. Many forms of myoclonus respond to the serotonin precursor 5-hydroxytryptophan (initially, 25 mg po qid, increased to 150 to 250 mg po qid), which must be used with the oral decarboxylase inhibitor carbidopa (50 mg every morning and 25 mg at noon or 50 mg every evening and 25 mg at bedtime).

Parkinson's Disease

Parkinson's disease is an idiopathic, slowly progressive, degenerative CNS disorder characterized by resting tremor, muscular rigidity, slow and decreased movement, and postural instability. Diagnosis is clinical. Treatment is with levodopa plus carbidopa, other drugs, and, for refractory symptoms, surgery.

Parkinson's disease affects about 0.4% of people > 40 yr, 1% of people ≥ 65 yr, and 10% of people ≥ 80 yr. The mean age at onset is about 57 yr. Rarely, Parkinson's disease begins in childhood or adolescence (juvenile parkinsonism).

Parkinsonism refers to symptoms that are similar to those of Parkinson's disease but caused by another condition.

Etiology

Synuclein is a presynaptic neuronal and glial cell protein, which can form insoluble fibrils in Lewy bodies. Although there are rare cases of Parkinson's disease without Lewy bodies, the pathologic hallmark of Parkinson's disease remains synuclein-filled Lewy bodies in the nigrostriatal system. However, synucleinopathy can occur in many other parts of the nervous system, including the dorsal motor nucleus of the vagus nerve, basal nucleus of Meynert, hypothalamus, neocortex, olfactory bulb, sympathetic ganglia, and myenteric plexus of the GI tract. Lewy bodies appear in a temporal sequence, and many experts believe that Parkinson's disease is a relatively late development in a systemic synucleinopathy, which may also include Lewy body dementia. Patients with Parkinson's disease may also have Alzheimer's disease. Parkinson's disease, Lewy body dementia, and Alzheimer's disease share several features (see p. 1673); further research is needed to clarify their relationship to each other, including the relative contributions of synucleinopathy.

In Parkinson's disease, pigmented neurons of the substantia nigra, locus ceruleus, and other brain stem dopaminergic cell groups are lost. Loss of substantia nigra neurons, which project into the caudate nucleus and putamen, depletes dopamine in these areas.

A genetic predisposition is likely, at least in some cases. About 15 to 20% of patients have a family history of Parkinson's disease. Several abnormal genes have been identified. Inheritance is autosomal dominant for some genes and autosomal recessive for others.

Symptoms and Signs

In most patients, the disease begins insidiously.

A resting tremor of one hand is often the first symptom. The tremor is characterized as follows:

• Slow and coarse

• Maximal at rest, lessening during movement, and absent during sleep

- Amplitude increased by emotional tension or fatigue

- Often involving the wrist and fingers in movements similar to those used to manipulate small objects or pills (pill-rolling tremor)

Usually, the hands, arms, and legs are most affected, in that order. The jaw and tongue may also be affected, but not the voice. Tremor may become less prominent as the disease progresses.

Rigidity develops without tremor in many patients. When a clinician moves a rigid joint, sudden, rhythmic jerks due to variations in the intensity of the rigidity occur, producing a ratchet-like effect (cogwheel rigidity).

Slow movements (bradykinesia) are typical as rigidity progresses. Movement also becomes decreased (hypokinesia) and difficult to initiate (akinesia).

Rigidity and hypokinesia may contribute to muscular aches and sensations of fatigue. The face becomes masklike, with an open mouth, drooling, and reduced blinking. Early on, patients may appear depressed because facial expression is lacking and movements are decreased and slowed. Speech becomes hypophonic, with characteristic monotonous, stuttering dysarthria. Hypokinesia and impaired control of distal musculature cause micrographia (writing in very small letters) and make activities of daily living increasingly difficult. Without warning, voluntary movement, including walking, may suddenly halt (called freezing).

Postural instability develops, resulting in gait abnormalities. Patients have difficulty starting to walk, turning, and stopping; the gait becomes shuffling with short steps, and the arms are held flexed to the waist and do not swing with the stride. Steps may inadvertently quicken, and patients may break into a run to keep from falling (festination). A tendency to fall forward (propulsion) or backward (retropulsion) when the center of gravity is displaced results from loss of postural reflexes. Posture becomes stooped.

Dementia can occur.

Sleep disorders are common. Insomnia may result from nocturia or from the inability to turn in bed. Rapid eye movement (REM) sleep behavior disorder may develop; in it, violent bursts of physical activity occur during REM sleep. Sleep deprivation may contribute to depression, exacerbate cognitive impairment, or cause excessive daytime sleepiness.

Neurologic symptoms unrelated to parkinsonism commonly develop because synucleinopathy occurs in other areas of the central, peripheral, and autonomic nervous systems. It may have the following effects:

- Almost universal sympathetic denervation of the heart, contributing to orthostatic hypotension

- Esophageal dysmotility, contributing to dysphagia and increased risk of aspiration

- Lower bowel dysmotility, contributing to constipation

- Urinary hesitancy and/or urgency (common)

- Anosmia (common)

Seborrheic dermatitis is also common.

Postencephalitic parkinsonism causes forced, sustained deviation of the head and eyes (oculogyric crises), other dystonias, autonomic instability, depression, and personality changes.

Diagnosis

• Mainly by clinical evaluation

Diagnosis is clinical. Parkinson's disease is suspected in patients with characteristic unilateral resting tremor, decreased movement, or rigidity. The tremor disappears (or attenuates) during finger-to-nose coordination testing.

During the neurologic examination, patients cannot perform rapidly alternating or rapid successive movements well. Sensation and strength are usually normal. Reflexes are normal but may be difficult to elicit because of marked tremor or rigidity. Patients may not suppress eye closure when the frontal muscle is tapped between the eyes (glabellar reflex; if persistent, called Myerson's sign).

Slowed and decreased movement due to Parkinson's disease must be differentiated from decreased movement and spasticity due to lesions of the corticospinal tracts. Unlike Parkinson's disease, corticospinal tract lesions cause paresis (weakness or paralysis), preferentially in distal antigravity muscles; hyperreflexia; and extensor plantar responses (Babinski's sign). Spasticity due to corticospinal tract lesions increases muscle tone and deep tendon reflex responses; muscle tone increases in proportion to rate and degree of stretch placed on a muscle until resistance suddenly melts away (clasp-knife phenomenon). Rigidity in Parkinson's disease differs because resistance does not change through the entire range of motion (moving the limb is similar to bending a lead pipe).

Diagnosis is confirmed by the presence of other characteristic signs (eg, infrequent blinking, lack of facial expression, impaired postural reflexes, characteristic gait abnormalities). Tremor without other characteristic signs suggests early disease or another diagnosis. In the elderly, decreased spontaneous movements or a short-stepped gait may result from depression or dementia; such cases may be difficult to distinguish from Parkinson's disease.

To differentiate Parkinson's disease from secondary parkinsonism, clinicians note whether levodopa results in dramatic improvement, suggesting Parkinson's disease. Causes of parkinsonism can be identified by the following:

• Taking a thorough history, including occupational, drug, and family history

• Checking for neurologic deficits characteristic of disorders other than Parkinson's disease (such as neurodegenerative disorders)

• Neuroimaging when indicated

Treatment

• Carbidopa/levodopa (mainstay of treatment)

• Amantadine, monoamine oxidase type B (MAO-B) inhibitors, or anticholinergic drugs used first as monotherapy or late with levodopa

• Dopamine agonists at any stage

• Catechol *O*-methyltransferase (COMT) inhibitors sometimes used with levodopa

• Surgery if drugs are ineffective

• Exercise and adaptive measures

Many oral drugs are commonly used to relieve symptoms of Parkinson's disease (see Table 183-3). Traditionally, levodopa has been the first drug used. However, some experts believe that early use of levodopa hastens development of adverse effects and inconsistency of drug response; they prefer to delay levodopa, particularly in younger patients, if possible and to use MAO-B inhibitors, anticholinergic drugs, amantadine, or dopamine agonists first if drug treatment is necessary. Levodopa is then delayed until symptoms interfere with daily activities despite use of other treatments.

Doses are often reduced in the elderly. Drugs that cause or worsen symptoms, particularly antipsychotics, are avoided.

Levodopa: Levodopa, the metabolic precursor of dopamine, crosses the blood-brain barrier into the basal ganglia, where it is decarboxylated to form dopamine. Coadministration of the peripheral decarboxylase inhibitor carbidopa prevents levodopa catabolism, thus lowering the levodopa dosage requirements and minimizing adverse effects. Levodopa is most effective at relieving bradykinesia and rigidity, although tremor is often substantially reduced. Mildly affected patients who take levodopa may return to nearly normal, and bedbound patients may become ambulatory.

Levodopa has central adverse effects; occasional hallucinations or delirium occurs, most often in the elderly and patients with dementia. The dose that causes dyskinesias tends to decrease as treatment continues. In some patients, the lowest dose that reduces parkinsonian symptoms also causes dyskinesias.

Dosage of carbidopa/levodopa is increased every 4 to 7 days as tolerated until maximum benefit is reached. Adverse effects may be minimized by increasing the dose gradually and by giving the drug with or after meals; however, high-protein meals may impair absorption of levodopa. If peripheral adverse effects predominate, increasing the amount of carbidopa may help. Most patients with Parkinson's disease require 400 to 1000 mg/day of levodopa in divided doses every 2 to 5 h. A dissolvable immediate-release oral form of carbidopa/levodopa can be taken without water; this form is useful for patients who have difficulty swallowing. Doses are the same as for immediate-release carbidopa/levodopa.

Occasionally, levodopa must be used to maintain motor function despite levodopa-induced hallucinations or delirium. Psychosis can sometimes be treated with oral quetiapine or clozapine; these drugs aggravate parkinsonian symptoms much less than other antipsychotics (eg, risperidone, olanzapine) or not at all. Haloperidol should be avoided. Quetiapine can be started at 25 mg once/day or bid and increased in 25-mg increments every 1 to 3 days up to 800 mg/day as tolerated. Use of clozapine is limited because agranulocytosis occurs in 1% of patients. When clozapine is used, the dose is 12.5 to 50 mg once/day to 12.5 to 25 mg bid. CBC is done weekly for 6 mo and every 2 wk thereafter.

After 2 to 5 yr of treatment, most patients experience fluctuations in their response to levodopa (on-off effect). Whether dyskinesias and the on-off effect result from levodopa or the underlying disease is controversial. Eventually, the period of improvement after each dose shortens, and drug-induced dyskinesias result in swings from intense akinesia to uncontrollable hyperactivity. Traditionally, such swings are managed by keeping the levodopa dose as low as possible and using dosing intervals as short as every 1 to 2 h. Alternative methods include adjunctive use of dopamineagonists, controlled-release levodopa/carbidopa, COMT and/or MAO inhibitors, and amantadine.

Amantadine: This drug is useful as monotherapy for early, mild parkinsonism in 50% of patients and later can be used to augment levodopa's effects. It may augment dopaminergic activity, anticholinergic effects, or both. If used as monotherapy, amantadine often loses its effectiveness after several months. Amantadine may ameliorate dyskinesias secondary to long-term use of levodopa.

Dopamine agonists: These drugs directly activate dopamine receptors in the basal ganglia. Oral drugs include bromocriptine, pramipexole, and ropinirole.

Oral dopamine agonists can be used as monotherapy but, as such, are rarely sufficient for more than a few years. They may be useful at all stages of the disease. Using these drugs early in treatment, with small doses of levodopa, may delay emergence of dyskinesias and on-off effects, possibly because dopamine agonists stimulate dopamine receptors longer than levodopa does. This type of stimulation is more physiologic and may better preserve the receptors. Dopamine agonists are particularly useful in later stages when response to levodopa decreases or on-off effects are prominent.

Rotigotine was recently withdrawn from the market because of problems with consistent drug delivery.

Adverse effects may limit use of dopamine agonists. Reducing the levodopa dose may minimize adverse

effects of dopamine agonists. Agonists can cause compulsive gambling, hypersexuality, or overeating in 1 to 2% of patients, requiring a change in drug or a reduction in dose. Bromocriptine is rarely used because cardiac valvular fibrosis and pleural fibrosis are concerns. Pergolide, another dopamine agonist, was recalled because it increases risk of cardiac valvular fibrosis.

Apomorphine is an injectable dopamine agonist used as rescue therapy when off effects are severe. Onset of action is rapid (5 to 10 min), and duration is short (60 to 90 min). Apomorphine 2 to 6 mg sc can be given up to 5 times/day as needed. A 2-mg test dose is given first to check for orthostatic hypotension. BP is checked in the standing and supine positions before treatment and 20, 40, and 60 min afterward. Other adverse effects are similar to those of other dopamine agonists. Nausea can be prevented by starting trimethobenzamide 300 mg po tid 3 days before apomorphine and continuing it for the first 2 mo of treatment.

Selective monoamine oxidase type B (MAO-B) inhibitors: Selegiline inhibits one of the 2 major enzymes that break down dopamine in the brain, thereby prolonging the action of each dose of levodopa. In some patients with mild on-off effects, selegiline helps prolong levodopa's effect. Used initially as monotherapy, selegiline can delay the initiation of levodopa by about 1 yr. Selegiline may slow progression of Parkinson's disease by potentiating residual brain dopamine in early disease or by reducing oxidative metabolism of brain dopamine. A dose of 5 mg po bid does not cause hypertensive crisis (sometimes triggered by consuming tyramine in foods, such as some cheeses, during MAO inhibitor therapy); this adverse effect is common with nonselective MAO inhibitors, which block A and B isoenzymes. Although virtually free of adverse effects, selegiline can potentiate levodopa-induced dyskinesias, mental and psychiatric adverse effects, and nausea, requiring reduction in the levodopa dose. Selegiline is also available in a formulation designed for buccal absorption (zydis-selegiline).

Rasagiline, an MAO-B inhibitor that is not metabolized to amphetamine, is effective and well-tolerated in early and late disease. Whether rasagiline's effects are purely symptomatic or also neuroprotective is unclear, but recent studies suggest rasagiline may alter disease progression.

Anticholinergic drugs: These drugs can be used as monotherapy in early disease and later to supplement levodopa. Commonly used anticholinergic drugs include benztropine and trihexyphenidyl. Antihistamines with anticholinergic effects (eg, diphenhydramine 25 to 50 mg po bid to qid, orphenadrine 50 mg po once/day to qid) are occasionally useful for treating tremor. Anticholinergic tricyclic antidepressants (eg, amitriptyline 10 to 150 mg po at bedtime), if used for depression, may be useful as an adjunct to levodopa. Doses of anticholinergic drugs are increased very slowly. Adverse effects are particularly troublesome in the elderly; if possible, they should not be given anticholinergic drugs.

Catechol *O*-methyltransferase (COMT) inhibitors: These drugs (eg, entacapone, tolcapone) inhibit the breakdown of dopamine and therefore appear to be useful adjuncts to levodopa. A combination of levodopa, carbidopa, and entacapone can be used. For each dose of levodopa taken, 200 mg of entacapone is given, to a maximum of 200 mg 8 times/day. Tolcapone, a potent COMT inhibitor, is less commonly used because of rare reports of liver toxicity.

Surgery: If drugs are ineffective and disease is advanced, surgery is considered. For patients with levodopa-induced dyskinesias or significant motor fluctuations, deep brain stimulation of the subthalamic nucleus or globus pallidus interna is often recommended. For patients with tremor only, stimulation of the ventralis intermediate nucleus of the thalamus is sometimes recommended; however, because most patients also have other symptoms, stimulation of the subthalamic nucleus, which relieves tremor as well as other symptoms, is usually preferable.

Physical measures: Maximizing activity is a goal. Patients should do daily activities to the extent possible. If they cannot, physical or occupational therapy, which may involve a

[Table 183-3. Some Commonly Used Oral Antiparkinsonian Drugs]

regular exercise program, may help condition them physically. Therapists may teach patients adaptive strategies and help them make appropriate adaptations in the home (eg, installing grab bars to reduce the risk of falls).

Because the disease, antiparkinsonian drugs, and inactivity can lead to constipation, patients should consume a high-fiber diet, exercise when possible, and drink adequate amounts of fluids. Dietary supplements (eg, psyllium) and stimulant laxatives (eg, bisacodyl 10 to 20 mg po once/day) can help.

Parkinsonism

Parkinsonism refers to symptoms that are similar to those of Parkinson's disease but caused by another condition.

Parkinsonism results from drugs, disorders other than Parkinson's disease, or exogenous toxins (see Table 183-4). The mechanism is blockage of or interference with dopamine's action in the basal ganglia. The most common cause is ingestion of drugs that block dopamine receptors (eg, phenothiazine, thioxanthene, butyrophenone, antipsychotic drugs, reserpine).

[**Table 183-4.** Some Causes of Parkinsonism]

Parkinsonism causes the same symptoms as Parkinson's disease (eg, resting tremor, rigidity, bradykinesia, postural instability—see p. 1765).

Diagnosis

• Clinical evaluation, response to levodopa therapy, and, for differential diagnosis, sometimes neuroimaging

To differentiate Parkinson's disease from secondary parkinsonism, clinicians note whether levodopa results in dramatic improvement, suggesting Parkinson's disease. Causes of parkinsonism can be identified by the following:

• A thorough history, including occupational, drug, and family history

• Evaluation for neurologic deficits characteristic of disorders other than Parkinson's disease (such as neurodegenerative disorders)

• Neuroimaging when indicated

Treatment

• Treatment of the cause

The cause is corrected or treated if possible, sometimes resulting in amelioration or disappearance of symptoms. Drugs used to treat Parkinson's disease are often ineffective or have only transient benefit. But amantadine or an anticholinergic drug (eg, benztropine) may ameliorate parkinsonism secondary to use of antipsychotic drugs.

Physical measures to maintain mobility and independence are useful (as for Parkinson's disease, see p. 1768). Good nutrition is essential.

Progressive Supranuclear Palsy

(Steele-Richardson-Olszewski Syndrome)

Progressive supranuclear palsy is a rare, degenerative CNS disorder causing loss of voluntary eye movements, bradykinesia, muscular rigidity with progressive axial dystonia, pseudobulbar palsy, and dementia.

The cause of progressive supranuclear palsy is unknown. Neurons in the basal ganglia and brain stem degenerate; neurofibrillary tangles containing an abnormally phosphorylated tau protein are also present.

Multiple lacunar strokes may occur in the basal ganglia and deep white matter.

Symptoms and Signs

Symptoms usually begin in late middle age. The first symptom may be difficulty looking up without extending the neck or difficulty climbing up and down stairs. Voluntary eye movements, particularly vertical, are difficult, but reflexive eye movements are unaffected. Movements are slowed, muscles become rigid, and axial dystonia develops. Patients tend to fall backward. Dysphagia and dysarthria with emotional lability (pseudobulbar palsy) is common; these deficits occur in a stepwise progression as occurs with multiple strokes. Dementia eventually occurs. Many patients become incapacitated within about 5 yr and die within about 10 yr.

Diagnosis

Diagnosis is clinical.

Treatment

• Supportive care

Treatment is unsatisfactory. Occasionally, levodopa, dopamine agonists and/or amantadine partially relieve rigidity.

Because the disorder is fatal, patients should be encouraged to prepare advance directives soon after the disorder is diagnosed. These directives should indicate what kind of medical care people want at the end of life (see p. 3471).

Tremor

Tremors are involuntary, rhythmic, alternating, or oscillatory movements of interrelated muscle groups. They typically involve the hands, head, facial structures, vocal cords, trunk, or legs. Tremors can be characterized by

• Frequency of oscillation (rapid or slow)

• Amplitude of movement (fine or coarse)

• Movements or postures that evoke them (eg, rest, action, certain positions)

Pathophysiology

Tremors are considered a movement disorder. Movement is controlled by interaction of the corticospinal (pyramidal) tracts, basal ganglia, and cerebellum. The basal ganglia consist of the caudate nucleus, putamen, globus pallidus, and substantia nigra, which together form the extrapyramidal system.

Most neural lesions that cause movement disorders occur in the extrapyramidal system; thus, movement disorders are also called extrapyramidal disorders. Neural dysfunction or lesions responsible for tremor may result from injury, ischemic or metabolic insult, or a neurodegenerative disorder. Sometimes tremor is an inherited condition (eg, essential tremor).

Classification: Tremor is classified primarily based on when it occurs:

• **Resting tremors** are maximal at rest and decrease with activity; they occur at a frequency of 3 to 6 cycles/sec (Hz).

• **Postural tremors** are maximal when a limb is maintained in a fixed position against gravity (eg, holding the arms out); they occur at a frequency of 5 to 18 Hz.

• **Intention tremors** are maximal during movement toward a target, as in finger-to-nose testing; they occur at a frequency of 3 to 10 Hz.

Tremor can also be classified based on whether it is within the range of normal (physiologic tremor), a primary disorder (essential tremor, Parkinson's disease), or a pathologic sign of CNS injury (eg, poststroke).

Etiology

Physiologic tremor: Physiologic tremor is the most common cause of tremor in otherwise healthy people; it is present normally but usually causes such small movements that it is noticeable only when enhanced by certain drugs or conditions (eg, anxiety; stress; fatigue; thyrotoxicosis; use of caffeine, phosphodiesterase inhibitors, β-adrenergic agonists, or corticosteroids).

Nonphysiologic tremor: There are many causes (see Table 183-5), but the most common are

• Essential tremor

• Parkinson's disease

• Cerebral or cerebellar injury (eg, from a stroke or multiple sclerosis)

• Hereditary disorders involving the cerebellum (eg, spinocerebellar ataxia)

Drugs can cause or aggravate different types of tremor (see Table 183-6). Low doses of some sedatives (eg, alcohol) may relieve some tremors (eg, essential and physiologic tremor); higher doses may cause or exacerbate tremor.

[**Table 183-5.** Some Causes of Tremor]

Evaluation

Because the diagnosis of tremor is largely clinical, a meticulous history and physical examination are essential.

History: History of present illness should cover acuity of onset (eg, gradual, abrupt), age at onset, body parts affected, provoking factors (eg, movement, rest, standing), and alleviating or exacerbating factors (eg, alcohol, caffeine, stress, anxiety). If onset is abrupt, patients should be asked about potential triggering events (eg, recent trauma, use of a new drug).

Review of systems should seek symptoms of causative disorders, including double vision (multiple sclerosis), recent onset of motor weakness or dysarthria (stroke), headaches and fevers (brain abscess or tumor), muscle rigidity and slow movement (Parkinson's disease), weight loss and heat intolerance (hyperthyroidism), sensory deficits (peripheral neuropathy), and agitation and hallucinations (alcohol withdrawal).

Past medical history should cover conditions associated with tremor (see Table 183-5).

[**Table 183-6.** Some Drug Causes of Tremor by Type]

Family history should include questions about tremor in 1st-degree relatives. The drug profile should be reviewed for causative drugs (see Table 183-6), and patients should be asked specifically about caffeine intake and alcohol and recreational drug use (particularly recent discontinuation).

Physical examination: Vital signs should be reviewed for tachycardia, hypertension, or fever. General examination should note any cachexia, psychomotor agitation, and presence or absence of facial expressions. The thyroid should be palpated for nodules or thyromegaly, and any signs of exophthalmus

or lid lag should be noted.

Focused examination of the tremor should note distribution and frequency of the tremor while the affected body parts are at rest and fully supported (eg, in the patient's lap), while the patient assumes certain postures (eg, holding the arms outstretched), and while the patient is walking or doing tasks with the affected body part. The examiner should note whether the tremor changes during mental distraction tasks (eg, serial subtraction of 7 from 100). The quality of the voice should be observed while the patient sustains a long note.

A complete and extensive neurologic examination is mandatory and should include cranial nerve evaluation, motor and sensory function testing, gait testing, assessment of deep tendon reflexes, and evaluation of cerebellar maneuvers (eg, finger-to-nose, shin-to-heel, rapid alternating hand movements). The examiner should test muscles for rigidity by moving the limbs through their range of motion.

Red flags: The following findings are of particular concern:

• Abrupt onset

• Onset in people < 50 and with no family history of tremor

• Other neurologic deficits (eg, change in mental status, motor weakness, cranial nerve palsy, ataxic gait, dysarthria)

• Tachycardia and agitation

Interpretation of findings: Clinical findings help suggest a cause (see also Table 183-5).

Tremor type and onset are useful clues. Resting tremors usually indicate Parkinson's disease, particularly when they are unilateral or when tremor is isolated to the chin, voice, or leg.

Intention tremors suggest a cerebellar disorder but may result from multiple sclerosis or Wilson's disease.

Postural tremor suggests physiologic or essential tremor if onset is gradual or a toxic or metabolic disorder if onset is sudden.

Severe essential tremor is often confused with Parkinson's disease but can usually be distinguished by specific characteristics (see Table 183-7). Occasionally, the 2 syndromes can overlap (mixed essential tremor-Parkinson's disease).

Sudden onset or stepwise progression suggests stroke, multiple sclerosis, or psychogenic etiology. Sudden onset after drug use suggests a drug cause. Onset of tremor with agitation, tachycardia, and hypertension within 24 to 72 h of hospitalization may suggest alcohol withdrawal.

Gait is observed. Gait abnormalities suggest multiple sclerosis, stroke, Parkinson's disease, or a cerebellar disorder. The gait is often normal in patients with essential tremor. It is characteristically narrow-based and shuffling in Parkinson's disease and wide-based and ataxic in cerebellar disorders. The gait may have histrionic or inconsistent qualities in patients with psychogenic tremor.

Complex tremor that decreases with mental distraction or whose frequency entrains to a volitional tapping rhythm in an unaffected body part (maintaining 2 different volitional movement frequencies simultaneously in 2 different body parts is difficult) suggests a psychogenic tremor.

Testing: In most patients, history and physical examination are sufficient to identify the likely etiology. However, MRI or CT of the brain should be done if

• Tremor onset is acute.

• Progression is rapid.

• Neurologic signs suggest stroke, a demyelinating disorder, or a structural lesion.

[**Table 183-7.** Some Characteristics Differentiating Parkinson's Disease from Essential Tremor]

For certain patients (based on history and physical examination findings), thyroid-stimulating hormone (TSH) and thyroxine (T_4) are measured to check for hyperthyroidism, Ca and parathyroid hormone are measured to check for hyperparathyroidism, and glucose testing is done to rule out hypoglycemia.

In patients with toxic encephalopathy, the underlying condition is usually readily apparent, but measurement of BUN and ammonia levels can help confirm the diagnosis. Measurement of free metanephrines in plasma is indicated in patients with unexplained refractory hypertension; serum ceruloplasmin and urinary copper levels should be measured in patients who are < 40 and have tremor and no family history of benign tremor.

Although electromyography (EMG) can differentiate true tremor from other movement disorders (eg, myoclonus, clonus, epilepsia partialis continua), it is rarely required. However, EMG may help establish peripheral neuropathy as a potential cause of tremor if a neuropathy is clinically suspected.

Treatment

Physiologic tremors: No treatment is necessary unless symptoms are bothersome.

Physiologic tremors enhanced by alcohol withdrawal or thyrotoxicosis respond to treatment of the underlying condition.

Oral benzodiazepines (eg, diazepam 2 to 10 mg, lorazepam 1 to 2 mg, oxazepam 10 to 30 mg) given tid or qid may be useful for people with tremor and chronic anxiety, but continuous use should be avoided. Propranolol 20 to 80 mg po qid (and other β-blockers) is often effective for tremor enhanced by drugs or acute anxiety (eg, stage fright). Primidone 50 to 250 mg po tid may be tried if β-blockers are ineffective or poorly tolerated. For some patients, a small amount of alcohol is effective.

Essential tremors: Propranolol 20 to 80 mg po qid (or other β-blockers) is often effective, as is primidone 50 to 250 mg po tid.

Cerebellar tremors: No effective drug is available; physical measures (eg, weighting the affected limbs or teaching patients to brace the proximal limb during activity) sometimes help.

Parkinsonian tremors: The underlying disorder is treated, usually with anticholinergic drugs or other antiparkinson drugs such as amantadine, dopamine agonists, and levodopa.

Disabling tremor: For patients with severe, disabling, drug-refractory essential tremor, surgical management with stereotactic thalamotomy or chronic thalamic deep brain stimulation may be done. Similarly, in Parkinson's disease, tremor substantially lessens after thalamic or subthalamic nucleus deep brain stimulation. Although these techniques are widely available, they should be used only after all drug treatment options have been tried.

Geriatrics Essentials

Many elderly patients attribute development of tremor to normal aging and may not seek medical attention. Although essential tremor is more prevalent among the elderly, a thorough history and physical examination are required to rule out other causes.

Comparatively lower doses of drugs may exacerbate tremor in the elderly, and adjusting doses of chronically used drugs (eg, amiodarone, metoclopramide, SSRIs, thyroxine) to the lowest effective dose should be considered. Similarly, elderly patients are more vulnerable to adverse effects of drugs used to treat tremor (eg, anticholinergic drugs); thus, drugs should be used cautiously in the elderly, usually at lower dosages than are otherwise considered optimal.

Tremor can significantly affect functional ability in the elderly, particularly if they have other physical or cognitive impairments. Physical and occupational therapy can provide simple coping strategies, and assistive devices may help maintain quality of life.

Key Points

- The most common causes of tremor include physiologic tremor, essential tremor, and Parkinson's disease.
- Tremor can be classified as resting, postural, or intention.
- History and physical examination can typically identify the etiology of tremor.
- Abrupt onset of tremor or tremor in patients who are < 50 and do not have a family history of benign tremor requires prompt, in-depth evaluation.

Cerebellar Disorders

Cerebellar disorders have numerous causes, including congenital malformations, hereditary ataxias, and acquired conditions. Symptoms vary with the cause but typically include ataxia (impaired muscle coordination). Diagnosis is clinical and often by imaging and sometimes genetic testing. Treatment is usually supportive unless the cause is acquired and reversible.

The cerebellum has 3 parts:

- **Archicerebellum (vestibulocerebellum):** It includes the flocculonodular lobe, which is located in the medial zone. It helps maintain equilibrium and coordinate eye, head, and neck movements; it is closely interconnected with the vestibular nuclei.
- **Midline vermis (paleocerebellum):** It helps coordinate trunk and leg movements. Vermis lesions result in abnormalities of stance and gait.
- **Lateral hemispheres (neocerebellum):** They control quick and finely coordinated limb movements, predominantly of the arms.

There is growing consensus that, in addition to coordination, the cerebellum controls some aspects of memory, learning, and cognition.

Ataxia is the archetypal sign of cerebellar dysfunction, but many other motor abnormalities may occur (see Table 183-8).

Etiology

Congenital malformations: Such malformations are almost always sporadic, often occurring as part of complex malformation syndromes (eg, Dandy-Walker malformation—see p. 2992) that affect other parts of the CNS. Malformations manifest early in life and are nonprogressive. Manifestations vary markedly depending on the structures involved; ataxia is usually present.

Hereditary ataxias: Hereditary ataxias may be autosomal recessive or autosomal dominant. Autosomal recessive ataxias include Friedreich's ataxia (the most prevalent), ataxia-telangiectasia, abetalipoproteinemia, ataxia with isolated vitamin E deficiency, and cerebrotendinous xanthomatosis.

Friedreich's ataxia results from a gene mutation causing abnormal repetition of the DNA sequence GAA in the gene that codes for the mitochondrial protein frataxin. Decreased frataxin levels lead to mitochondrial iron overload and impaired mitochondrial function. Gait unsteadiness begins between ages 5 and 15; it is followed by upper-extremity ataxia, dysarthria, and paresis, particularly of the lower

extremities. Mental function often declines. Tremor, if present, is slight. Reflexes and vibration and position senses are lost. Talipes, scoliosis, and progressive cardiomyopathy are common.

Spinocerebellar ataxias (SCAs) are the main autosomal dominant ataxias. Classification of these ataxias has been revised many times recently as knowledge about genetics increases. Currently, at least 28 different gene loci are recognized; at least 10 involve expanded DNA sequence repeats. Some involve a repetition of the DNA sequence CAG that codes for the amino acid glutamine, similar to that in Huntington's disease. Manifestations vary. Some of the most common SCAs affect multiple areas in the central and peripheral nervous systems; neuropathy, pyramidal signs, and restless leg syndrome, as well as ataxia, are common. Some SCA usually cause only cerebellar ataxia. SCA3, formerly known as

[**Table 183-8.** Signs of Cerebellar Disorders]

Machado-Joseph disease, may be the most common dominantly inherited SCA. Symptoms include ataxia and possibly dystonia, facial twitching, ophthalmoplegia, and peculiar bulging eyes.

Acquired conditions: Acquired ataxias may result from nonhereditary neurodegenerative disorders (eg, multiple system atrophy—see p. 1618), systemic disorders, or toxin exposure, or they may be idiopathic. Systemic disorders include alcoholism (alcoholic cerebellar degeneration), celiac sprue, hypothyroidism, and vitamin E deficiency. Toxins include carbon monoxide, heavy metals, lithium, phenytoin, and certain solvents.

In children, primary brain tumors (medulloblastoma, cystic astrocytoma) may be the cause; the midline cerebellum is the most common site of such tumors. Rarely, in children, reversible diffuse cerebellar dysfunction follows viral infections.

Diagnosis

Diagnosis is clinical and includes a thorough family history and search for acquired systemic disorders. Neuroimaging, typically MRI, is done. Genetic testing is done if family history is suggestive.

Treatment

Some systemic disorders (eg, hypothyroidism, celiac sprue) and toxin exposure can be treated; occasionally, surgery for structural lesions (tumor, hydrocephalus) is beneficial. However, treatment is usually only supportive.

Chapter 184. Demyelinating Disorders

Introduction

Myelin sheaths cover many nerve fibers in the central and peripheral nervous system; they accelerate axonal transmission of neural impulses. Disorders that affect myelin interrupt nerve transmission; symptoms may reflect deficits in any part of the nervous system.

Myelin formed by oligodendroglia in the CNS differs chemically and immunologically from that formed by Schwann cells peripherally. Thus, some myelin disorders (eg, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, some other peripheral nerve polyneuropathies—see p. 1799) tend to affect primarily the peripheral nerves, and others affect primarily the CNS (see Table 184-1). The most commonly affected areas in the CNS are the brain, spinal cord, and optic nerves.

Demyelination is often secondary to an infectious, ischemic, metabolic, or hereditary disorder. In primary demyelinating disorders, cause is unknown, but an autoimmune mechanism is suspected because the disorder sometimes follows a viral infection or viral vaccination.

Demyelination tends to be segmental or patchy, affecting multiple areas simultaneously or sequentially. Remyelination often occurs, with repair, regeneration, and complete recovery of neural function. However, extensive myelin loss is usually followed by axonal degeneration and often cell body degeneration; both may be irreversible.

Demyelination should be considered in any patient with unexplained neurologic deficits. Primary demyelinating disorders are suggested by the following:

- Diffuse or multifocal deficits
- Sudden onset, particularly in young adults
- Onset within weeks of an infection or vaccination
- Deficits that wax and wane
- Symptoms suggesting a specific demyelinating disorder (eg, unexplained optic neuritis or internuclear ophthalmoplegia suggesting multiple sclerosis)

Specific tests and treatment depend on the specific disorder.

Multiple Sclerosis

Multiple sclerosis (MS) is characterized by disseminated patches of demyelination in the brain and spinal cord. Common symptoms include visual and oculomotor abnormalities, paresthesias, weakness, spasticity, urinary dysfunction, and mild cognitive impairment. Typically, neurologic deficits are multiple, with remissions and exacerbations gradually producing disability. Diagnosis is by history of remissions and exacerbations plus clinical signs, test results, lesions seen on MRI, or other criteria (depending on symptoms) to objectively demonstrate ≥ 2 separate neurologic abnormalities. Treatment includes corticosteroids for acute exacerbations, immunomodulatory drugs to prevent exacerbations, and supportive measures.

[**Table 184-1.** Disorders that Can Cause CNS Demyelination]

MS is believed to involve an immunologic mechanism. One postulated cause is infection by a latent virus (possibly a human herpesvirus such as Epstein-Barr virus), which, when activated, triggers a secondary immune response. An increased incidence among certain families and presence of human leukocyte antigen (HLA) allotypes (HLA-DR2) suggests genetic susceptibility. MS is more common among people who spend their first 15 yr of life in temperate climates (1/2000) than in those who spend them in the

tropics (1/10,000). One explanation is that lower levels of vitamin D are associated with an increased risk of MS, and vitamin D levels correlate with the degree of sun exposure, which is lower in temperate climates. Cigarette smoking also appears to increase risk. Age at onset ranges from 15 to 60 yr, typically 20 to 40 yr; women are affected somewhat more often.

Neuromyelitis optica (Devic disease), previously considered a variant of MS, is now recognized as a separate disorder (see p. 1783).

Pathophysiology

Localized areas of demyelination (plaques) occur, with destruction of oligodendroglia, perivascular inflammation, and chemical changes in lipid and protein constituents of myelin in and around the plaques. Axonal damage is possible, but cell bodies and axons tend to be relatively preserved. Fibrous gliosis develops in plaques that are disseminated throughout the CNS, primarily in white matter, particularly in the lateral and posterior columns (especially in the cervical regions), optic nerves, and periventricular areas. Tracts in the midbrain, pons, and cerebellum are also affected. Gray matter in the cerebrum and spinal cord can be affected but to a much lesser degree.

Symptoms and Signs

MS is characterized by varied CNS deficits, with remissions and recurring exacerbations. Exacerbations average about 3/yr, but frequency varies greatly. Although MS may progress and regress unpredictably, there are typical patterns of progression:

- Relapsing-remitting pattern: Exacerbations alternate with remissions, when partial or full recovery occurs or symptoms are stable. Remissions may last months or years. Exacerbations can occur spontaneously or can be triggered by an infection such as influenza.

- Primary progressive pattern: The disease progresses gradually with no remissions, although there may be temporary plateaus during which the disease does not progress. Unlike in the relapsing-remitting pattern, there are no clear exacerbations.

- Secondary progressive pattern: This pattern begins with relapses alternating with remissions, followed by gradual progression of the disease.

- Progressive relapsing pattern: The disease progresses gradually, but progression is interrupted by sudden, clear relapses. This pattern is rare.

The most common initial symptoms are the following:

- Paresthesias in one or more extremities, in the trunk, or on one side of the face

- Weakness or clumsiness of a leg or hand

- Visual disturbances (eg, partial loss of vision and pain in one eye due to retrobulbar optic neuritis, diplopia due to ocular palsy, scotomas)

Other common early symptoms include slight stiffness or unusual fatigability of a limb, minor gait disturbances, difficulty with bladder control, vertigo, and mild affective disturbances; all usually indicate scattered CNS involvement and may be subtle. Excess heat (eg, warm weather, a hot bath, fever) may temporarily exacerbate symptoms and signs.

Mild cognitive impairment is common. Apathy, poor judgment, or inattention may occur. Affective disturbances, including emotional lability, euphoria, or, most commonly, depression, are common. Depression may be reactive or partly due to cerebral lesions of MS. A few patients have seizures.

Cranial nerves: Unilateral or asymmetric optic neuritis and bilateral internuclear ophthalmoplegia are typical. Optic neuritis causes loss of vision (ranging from scotomas to blindness), eye pain, and

sometimes abnormal visual fields, a swollen optic disk, or a partial or complete afferent pupillary defect (see p. 622).

Internuclear ophthalmoplegia results if there is a lesion in the medial longitudinal fasciculus connecting the 3rd, 4th, and 6th nerve nuclei. During horizontal gaze, adduction of one eye is decreased, with nystagmus of the other (abducting) eye; convergence is intact.

Rapid, small-amplitude eye oscillations in straight-ahead (primary) gaze (pendular nystagmus) are uncommon but characteristic of MS. Vertigo is common. Intermittent unilateral facial numbness or pain (resembling trigeminal neuralgia), palsy, or spasm may occur. Mild dysarthria may occur, caused by bulbar weakness, cerebellar damage, or disturbance of cortical control. Other cranial nerve deficits are unusual but may occur secondary to brain stem injury.

Motor: Weakness is common. It usually reflects corticospinal tract damage in the spinal cord, affects the lower extremities preferentially, and is bilateral and spastic. Deep tendon reflexes (eg, knee and ankle jerks) are usually increased, and an extensor plantar response (Babinski's sign) and clonus are often present. Spastic paraparesis produces a stiff, imbalanced gait; in advanced cases, it may confine patients to a wheelchair. Painful flexor spasms in response to sensory stimuli (eg, bedclothes) may occur late. Cerebral or cervical spinal cord lesions may result in hemiparesis, which sometimes is the presenting symptom.

Cerebellar: In advanced MS, cerebellar ataxia plus spasticity may be severely disabling; other cerebellar manifestations include slurred speech, scanning speech (slow enunciation with a tendency to hesitate at the beginning of a word or syllable), and Charcot's triad (intention tremor, scanning speech, and nystagmus).

Sensory: Paresthesias and partial loss of any type of sensation are common and often localized (eg, to one or both hands or legs). Various painful sensory disturbances (eg, burning or electric shocklike pains) can occur spontaneously or in response to touch, especially if the spinal cord is affected.

An example is Lhermitte's sign, an electric shocklike pain that radiates down the spine or into the legs when the neck is flexed. Objective sensory changes tend to be transient and difficult to demonstrate.

Spinal cord: Involvement commonly causes bladder dysfunction (eg, urinary urgency or hesitancy, partial retention of urine, mild urinary incontinence). Constipation, erectile dysfunction in men, and genital anesthesia in women may occur. Frank urinary and fecal incontinence may occur in advanced MS.

Progressive myelopathy, a variant of MS, causes spinal cord motor weakness but no other deficits.

Diagnosis

• Clinical criteria

• Brain and spinal MRI

• Sometimes CSF IgG levels and evoked potentials

MS is suspected in patients with optic neuritis, internuclear ophthalmoplegia, or other symptoms that suggest MS, particularly if deficits are multifocal or intermittent. Most diagnostic criteria for MS require a history of exacerbations and remissions plus objective demonstration by examination or testing of ≥ 2 separate neurologic abnormalities. Brain and spinal MRI is done. MRI plus clinical findings may be diagnostic, but if they are inconclusive, additional testing may be necessary to objectively demonstrate separate neurologic abnormalities. Such testing usually begins with CSF analysis and, if necessary, includes evoked potentials.

MRI is the most sensitive imaging test for MS and can exclude other treatable disorders that may mimic MS, such as nondemyelinating lesions at the junction of the spinal cord and medulla (eg, subarachnoid cyst, foramen magnum tumors). Gadolinium-contrast enhancement can distinguish actively inflamed from

older plaques. Alternatively, contrast-enhanced CT can be done. The sensitivity of MRI and CT is increased by giving twice the dose of contrast agent (which is standard practice) and delaying scanning (double-dose delayed scanning).

CSF examination, including opening pressure, cell count and differential, protein, glucose, Ig, oligoclonal bands, and usually myelin basic protein and albumin, is done. IgG is usually increased as a percentage of CSF components, such as protein (normally < 11%) or CSF albumin (normally < 27%). IgG levels correlate with disease severity. Oligoclonal bands can usually be detected by agarose electrophoresis of CSF. Myelin basic protein may be elevated during active demyelination. CSF lymphocyte count and protein content may be slightly increased.

Other tests include evoked potentials (delays in electrical responses to sensory stimulation—see p. 1597), which are often more sensitive for MS than symptoms or signs. Visual evoked responses are sensitive and particularly helpful in patients with no confirmed cranial lesions (eg, those with lesions only in the spinal cord). Somatosensory evoked potentials and brain stem auditory evoked potentials are sometimes also measured. Sometimes systemic disorders (eg, SLE) and infections (eg, Lyme disease) can mimic MS and should be excluded with specific blood tests. Blood tests to measure an IgG antibody specific for neuromyelitis optica (NMO-IgG) may be done to differentiate that disorder from MS.

Prognosis

The course is highly varied and unpredictable. In most patients, especially when MS begins with optic neuritis, remissions can last months to > 10 yr. However, some patients, particularly men with onset in middle age, have frequent exacerbations and are rapidly incapacitated. Cigarette smoking may accelerate the course. Life span is shortened only in very severe cases.

Treatment

- Corticosteroids for acute exacerbations
- Immunomodulators to prevent exacerbations
- Baclofen or tizanidine for spasticity
- Gabapentin or tricyclic antidepressants for pain
- Supportive care

Goals include shortening acute exacerbations, decreasing frequency of exacerbations, and relieving symptoms; maintaining the patient's ability to walk is particularly important.

Disease-modifying drugs: Acute exacerbations that cause objective deficits sufficient to impair function (eg, loss of vision, strength, or coordination) are treated with brief courses of corticosteroids (eg, prednisone 60 to 100 mg po once/day tapered over 2 to 3 wk, methylprednisolone 500 to 1000 mg IV once/day for 3 to 5 days). Some evidence indicates that IV corticosteroids shorten acute exacerbations, slow progression, and improve MRI measures of disease. Immunomodulatory therapy, such as interferons (IFNs) or glatiramer, decreases the frequency of acute exacerbations and delays eventual disability. Typical regimens include interferon beta-1b 8 million IU sc every other day, interferon beta-1a 6 million IU (30 µg) IM weekly, and interferon beta-1a 44 µg sc 3 times weekly. Common adverse effects of IFNs include flu-like symptoms and depression (which tend to decrease over time), development of neutralizing antibodies after months of therapy, and cytopenias. Glatiramer acetate 20 mg sc once/day may be used.

The immunosuppressant mitoxantrone, 12 mg/m^2 IV q 3 mo for 24 mo, may be helpful, particularly for progressive MS that is refractory to other treatments. Natalizumab, an anti-α_4 integrin antibody, inhibits passage of leukocytes across the blood-brain barrier; given as a monthly infusion, it reduces number of exacerbations and new brain lesions but may increase the risk of progressive multifocal leukoencephalopathy. If immunomodulatory drugs are ineffective, monthly IV immune globulin may help.

Immunosuppressants other than mitoxantrone (eg, methotrexate, azathioprine, mycophenolate, cyclophosphamide, cladribine) have been used for more severe, progressive MS but are controversial. Plasma exchange and hematopoietic stem cell transplantation may be somewhat useful for severe, intractable disease.

Symptom control: Other treatments can be used to control specific symptoms:

- Spasticity is treated with escalating doses of baclofen 10 to 20 mg po tid to qid or tizanidine 4 to 8 mg po tid. Gait training and range-of-motion exercises can help weak, spastic limbs.

- Painful paresthesias are usually treated with gabapentin 100 to 600 mg po tid; alternatives include tricyclic antidepressants (eg, amitriptyline 25 to 75 mg po at bedtime, desipramine 25 to 100 mg po at bedtime if amitriptyline has intolerable anticholinergic effects), carbamazepine 200 mg po tid, and opioids.

- Depression is treated with counseling and antidepressants.

- Bladder dysfunction is treated based on its underlying mechanism (see p. 2352).

- Fatigue can be treated with amantadine 100 mg po tid or modafinil 100 to 300 mg po once/day.

Supportive care: Encouragement and reassurance help. Regular exercise (eg, stationary biking, treadmill, swimming, stretching) is recommended, even for patients with advanced MS, because it conditions the heart and muscles, reduces spasticity, prevents contractures, and has psychologic benefits. Vitamin D supplements (800 to 1000 units daily) may decrease the risk of disease progression. Vitamin D also reduces the risk of osteoporosis, particularly in patients at increased risk because mobility is decreased or they take corticosteroids. Patients should maintain as normal and active a life as possible but should avoid overwork, fatigue, and exposure to excess heat. Cigarette smoking should be stopped. Vaccination does not appear to increase risk of exacerbations. Debilitated patients require measures to prevent pressure ulcers and UTIs; intermittent urinary self-catheterization may be necessary.

Neuromyelitis Optica

(Devic Disease)

Neuromyelitis optica affects only the eyes and spinal cord. It causes acute optic neuritis, sometimes bilateral, plus demyelination of the cervical or thoracic spinal cord. Neuromyelitis optica was previously considered to be a variant of multiple sclerosis (MS) but is now recognized as a different disorder.

Symptoms include visual loss, paraparesis or quadriparesis, and incontinence.

Diagnosis

- Brain and spinal cord MRI

- Visual evoked potentials

Diagnosis usually includes brain and spinal cord MRI and visual evoked potentials. Blood tests to measure an IgG antibody specific for neuromyelitis optica (NMO-IgG) may be done to differentiate it from MS.

Treatment

- Corticosteroids and immunomodulatory or immunosuppressive treatments

There is no cure. However, treatment can prevent, slow, or decrease the severity of exacerbations. Methylprednisolone and azathioprine are often used. Plasma exchange may help people who do not

respond to corticosteroids. Rituximab, an anti-B-cell antibody, reduces IgG production and has been shown to be disease-stabilizing.

Treatment of symptoms is similar to that for MS (see above). Baclofen or tizanidine may relieve muscle spasms.

Chapter 185. Peripheral Nervous System and Motor Unit Disorders

Introduction

The peripheral nervous system refers to parts of the nervous system outside the brain and spinal cord. It includes the cranial nerves and spinal nerves from their origin to their end. The anterior horn cells, although technically part of the CNS, are sometimes discussed with the peripheral nervous system because they are part of the motor unit.

Motor neuron dysfunction results in muscle weakness or paralysis. Sensory neuron dysfunction results in abnormal or lost sensation. Some disorders are progressive and fatal.

Anatomy

A motor unit consists of an anterior horn cell, its motor axon, the muscle fibers it innervates, and the connection between them (neuromuscular junction). The anterior horn cells are located in the gray matter of the spinal cord and thus are technically part of the CNS. In contrast to the motor system, the cell bodies of the afferent sensory fibers lie outside the spinal cord, in dorsal root ganglia.

Nerve fibers outside the spinal cord join to form anterior (ventral) motor roots and posterior (dorsal) sensory root nerve roots. The ventral and dorsal roots combine to form a spinal nerve. Thirty of the 31 pairs of spinal nerves have dorsal and ventral roots; C1 has no sensory root (see Fig. 186-1 on p. 1805).

The spinal nerves exit the vertebral column via an intervertebral foramen. Because the spinal cord is shorter than the vertebral column, the more caudal the spinal nerve, the further the foramen is from the corresponding cord segment. Thus, in the lumbosacral region, nerve roots from lower cord segments descend within the spinal column in a near-vertical sheaf, forming the cauda equina. Just beyond the intervertebral foramen, spinal nerves branch into several parts.

Branches of the cervical and lumbosacral spinal nerves anastomose peripherally into plexuses, then branch into nerve trunks that terminate up to 1 m away in peripheral structures. The intercostal nerves are segmental.

The term peripheral nerve refers to the part of a spinal nerve distal to the root and plexus. Peripheral nerves are bundles of nerve fibers. They range in diameter from 0.3 to 22 µm. Schwann cells form a thin cytoplasmic tube around each fiber and further wrap larger fibers in a multilayered insulating membrane (myelin sheath).

Physiology

The myelin sheath enhances impulse conduction. The largest and most heavily myelinated fibers conduct quickly; they convey motor, touch, and proprioceptive impulses. The less myelinated and unmyelinated fibers conduct more slowly; they convey pain, temperature, and autonomic impulses. Because nerves are metabolically active tissues, they require nutrients, supplied by blood vessels called the vasa nervorum.

Etiology

Disorders can result from damage to or dysfunction of the cell body, myelin sheath, axons, or neuromuscular junction. Disorders can be genetic or acquired (due to toxic, metabolic, traumatic, infectious, or inflammatory conditions—see Table 185-1). Peripheral neuropathies may affect one nerve (mononeuropathy), several discrete nerves (multiple mononeuropathy, or mononeuritis multiplex), or multiple nerves diffusely (polyneuropathy). Some conditions involve a plexus (plexopathy) or nerve root (radiculopathy). More than one site can be affected; eg, in the most common variant of Guillain-Barre syndrome, multiple segments of cranial nerves, usually the 2 facial nerves, may be affected.

Pathophysiology

Because sensory and motor cell bodies are in different locations, a nerve cell body disorder typically affects either the sensory or motor component but rarely both.

Damage: Damage to the myelin sheath (demyelination—see p. 1779) slows nerve conduction. Demyelination affects mainly heavily myelinated fibers, causing large-fiber sensory dysfunction (buzzing and tingling sensations), motor weakness, and diminished reflexes. The hallmark of acquired demyelinating polyneuropathy is severe motor weakness with minimal atrophy.

Because the vasa nervorum do not reach the center of a nerve, centrally located fascicles are most vulnerable to vascular disorders (eg, vasculitis, ischemia). These disorders result in smallfiber sensory dysfunction (sharp pain and burning sensations), motor weakness proportional to atrophy, and less severe reflex abnormalities than in other nerve disorders. The distal two thirds of a limb is affected most. Initially, deficits tend to be asymmetric because the vasculitic or ischemic process is random. However, multiple infarcts may later coalesce, causing symmetric deficits (multiple mononeuropathy).

Toxic-metabolic or genetic disorders usually begin symmetrically. Immune-mediated processes may be symmetric or, early in rapidly evolving processes, asymmetric.

Damage to the axon transport system for cellular constituents, especially microtubules and microfilaments, causes significant axon dysfunction. First affected are the smaller fibers (because they have greater metabolic requirements) at the most distal part of the nerve. Then, axonal degeneration slowly ascends, producting

[**Table 185-1.** Causes of Peripheral Nervous System Disorders]

the characteristic distal-to-proximal pattern of symptoms (stocking-glove sensory loss, weakness).

Recovery: Damage to the myelin sheath (eg, by injury or Guillain-Barre syndrome) can often be repaired by surviving Schwann cells in about 6 to 12 wk.

After axonal damage, the fiber regrows within the Schwann cell tube at about 1 mm/day once the pathologic process ends. However, regrowth may be misdirected, causing aberrant innervation (eg, of fibers in the wrong muscle, of a touch receptor at the wrong site, or of a temperature instead of a touch receptor).

Regeneration is virtually impossible when the cell body dies and is unlikely when the axon is completely lost.

Evaluation

• Deficits defined by history and examination

• Attention to clinical clues to peripheral nervous system disorders

• Usually, nerve conduction velocity studies and electromyography

Clinical evaluation: History should focus on type of symptom, onset, progression, and location, as well as information about potential causes (eg, family history, toxic exposures, past medical disorders). Physical and neurologic examination should further define the type of deficit (eg, motor deficit, type of sensory deficit, combination). Sensation (using pinprick and light touch for small fibers and vibration for large fibers), proprioception, motor strength, and deep tendon reflexes are evaluated (see p. 1589). Cranial nerve as well as central and peripheral nerve function is evaluated. Whether motor weakness is proportional to the degree of atrophy is noted, as are type and distribution of reflex abnormalities. Autonomic function is evaluated (see p. 1615).

Physicians should suspect a peripheral nervous system disorder based on the pattern and type of neurologic deficits, especially if deficits are in the territories of nerve roots, spinal nerves, plexuses,

specific peripheral nerves, or a combination. These disorders are also suspected in patients with mixed sensory and motor deficits, with multiple foci, or with a focus that is incompatible with a single anatomic site in the CNS.

Physicians should also suspect peripheral nervous system disorders in patients with generalized or diffuse weakness but no sensory deficits; in these cases, peripheral nervous system disorders may be overlooked because they are not the most likely cause of such symptoms. Clues that a peripheral nervous system disorder may be the cause of generalized weakness include the following:

- Patterns of generalized weakness that suggest a specific cause (eg, predominant ptosis and diplopia, which suggest early myasthenia gravis)
- Symptoms and signs other than weakness that suggest a specific disorder or group of disorders (eg, cholinergic effects, which suggest organophosphate poisoning)
- Deficits in a stocking-glove distribution, which suggest diffuse axonal disorders or polyneuropathy
- Fasciculations
- Hypotonia
- Muscle wasting without hyperreflexia
- Weakness that is progressive, chronic, and unexplained

Clues that the cause may not be a peripheral nervous system disorder include hyperreflexia and hypertonia. These deficits suggest an upper motor neuron disorder as the cause of weakness. Hyporeflexia is consistent with peripheral nervous system deficits but is non-specific.

Although many exceptions are possible, certain clinical clues may also suggest possible causes of peripheral nervous system deficits (see Table 185-2).

Clinical assessment narrows diagnostic possibilities and guides further testing.

Testing: Usually, nerve conduction velocity studies and electromyography (collectively called electrodiagnostic testing) are done (see p. 1597). These tests help identify level of involvement (nerve, plexus, root) and distinguish demyelinating disorders (very slow conduction) from axonal disorders. Other testing depends on whether a CNS lesion must be ruled out.

Patients with weakness but no sensory deficits are evaluated for weakness.

Treatment

- Treatment of underlying disorder
- Supportive care, often by a multidisciplinary team

Treatment is directed at the underlying disorder when possible. Otherwise, treatment is supportive. A multidisciplinary team approach helps patients cope with progressive neurologic disability:

- Physical therapists may help patients maintain muscle function.
- Occupational therapists can recommend adaptive braces and walking devices to help with activities of daily living.
- Speech and language therapists may provide alternative communication devices.

- If pharyngeal weakness develops, nurses feed patients with extreme care.

- A gastroenterologist may recommend percutaneous endoscopic gastrostomy.

- If respiratory weakness develops, pulmonary specialists are needed to determine whether noninvasive respiratory support (eg, bilevel positive airway pressure) or

[**Table 185-2.** Clinical Clues to Causes of Peripheral Nervous System* Disorders]

tracheostomy with full ventilatory support should be used.

Early in fatal disorders, health care practitioners must talk frankly with patients, family members, and caregivers to determine the level of intervention acceptable (see p. 3480). These decisions should be reviewed and confirmed at various stages of the disorder.

Disorders of Neuromuscular Transmission

Disorders of neuromuscular transmission affect the neuromuscular junction. They may involve

- Postsynaptic receptors (eg, in myasthenia gravis—see p. 1793)

- Presynaptic release of acetylcholine (eg, in botulism)

- Breakdown of acetylcholine within the synapse (eg, due to drugs or neurotoxic chemicals)

Common features of these disorders include fluctuating fatigue and muscle weakness with no sensory deficits.

Eaton-Lambert syndrome: This disorder is due to impaired acetylcholine release from presynaptic nerve terminals (see p. 1055).

Botulism: Also due to impaired release of acetylcholine from presynaptic nerve terminals, botulism develops when toxin produced by *Clostridium botulinum* spores irreversibly binds to the terminal cholinergic nerve endings (see p. 1290). The result is severe weakness, sometimes with respiratory compromise. Other systemic symptoms may include mydriasis, dry mouth, constipation, urinary retention, and tachycardia due to unopposed sympathetic nervous system activity (anticholinergic syndrome). These systemic findings are absent in myasthenia gravis.

In botulism, electromyography (EMG) detects a mild decremental response to low-frequency (2- to 3-Hz) repetitive nerve stimulation but a pronounced incremental response after 10 sec of exercise or with rapid (50-Hz) repetitive nerve stimulation.

Drugs or toxic chemicals: Cholinergic drugs, organophosphate insecticides, and most nerve gases block neuromuscular transmission by excessive acetylcholine action that depolarizes postsynaptic receptors. Miosis, bronchorrhea, and myasthenic-like weakness (cholinergic syndrome) result.

Aminoglycoside and polypeptide antibiotics decrease presynaptic acetylcholine release and sensitivity of the postsynaptic membrane to acetylcholine. At high serum levels, these antibiotics may increase neuromuscular block in patients with latent myasthenia gravis. Long-term penicillamine treatment may cause a reversible syndrome that clinically and electromyographically resembles myasthenia gravis. Excessive Mg po or IV (with blood levels approaching 8 to 9 mg/dL) can also induce severe weakness resembling a myasthenic syndrome.

Treatment consists of eliminating the drug or toxic chemical and providing necessary respiratory support and intensive nursing care. Atropine 0.4 to 0.6 mg po tid decreases bronchial secretions in patients with cholinergic excess. Higher doses (eg, 2 to 4 mg IV q 5 min) may be necessary for organophosphate insecticide or nerve gas poisoning.

Disorders With Neuromuscular Manifestations

Stiff-person syndrome: The syndrome affects the CNS but has neuromuscular manifestations. It often occurs in patients with type 1 diabetes. It may be autoimmune and can occur as a paraneoplastic syndrome (most often with breast, lung, or colon cancer or with Hodgkin lymphoma). Autoantibodies against several proteins involved in GABA (γ-aminobutyric acid)-glycine synapses are present, affecting primarily inhibitory neurons that originate in the anterior horn of the spinal cord.

Progressive stiffness develops insidiously in the trunk and abdomen and, to a lesser degree, in the legs and arms. Patients are otherwise normal, and examination detects only muscle hypertrophy and stiffness. EMG shows only the electrical activity of normal contraction.

Only symptomatic therapy is available. Diazepam is the only drug that consistently relieves muscle stiffness. Results of plasmapheresis are inconsistent.

Isaacs' syndrome: This syndrome, generally thought to be a channelopathy, sometimes occurs as a paraneoplastic syndrome. It may also occur in other disorders (eg, myasthenia gravis, thymoma, cancer, amyloidosis) or can be inherited. Cause is unknown. Abnormalities are thought to originate in a peripheral nerve because they are abolished by curare but usually persist after general anesthesia.

The limbs are most affected. The sine qua non is myokymia—continuous muscle twitching described as bag-of-worms movements. Other symptoms include carpopedal spasms, intermittent cramps, increased sweating, and pseudomyotonia (impaired relaxation after a strong muscle contraction but without the typical waxing-and-waning EMG abnormality of true myotonia). Carbamazepine or phenytoin may relieve these symptoms.

Guillain-Barre Syndrome

(Acute Idiopathic Polyneuritis; Acute Inflammatory Demyelinating Polyradiculoneuropathy)

Guillain-Barre syndrome is an acute, usually rapidly progressive inflammatory polyneuropathy characterized by muscular weakness and mild distal sensory loss. Cause is thought to be autoimmune. Diagnosis is clinical. Treatment includes plasmapheresis, γ-globulin, and, for severe cases, mechanical ventilation.

Guillain-Barre syndrome is the most common acquired inflammatory neuropathy. Although the cause is not fully understood, it is thought to be autoimmune. There are several variants. In some, demyelination predominates; others affect the axon.

In about two thirds of patients, the syndrome begins 5 days to 3 wk after a banal infectious disorder, surgery, or vaccination. Infection is the trigger in > 50% of patients; common pathogens include *Campylobacter jejuni,* enteric viruses, herpesviruses (including cytomegalovirus and Epstein-Barr virus), and *Mycoplasma* sp. A cluster of cases followed the swine flu vaccination program in 1975.

Symptoms and Signs

Flaccid weakness predominates in most patients; it is always more prominent than sensory abnormalities and may be most prominent proximally. Relatively symmetric weakness with paresthesias usually begins in the legs and progresses to the arms, but it occasionally begins in the arms or head. In 90% of patients, weakness is maximal at 3 wk. Deep tendon reflexes are lost. Sphincters are usually spared. Facial and oropharyngeal muscles are weak in > 50% of patients with severe disease. Dehydration and undernutrition may result. Respiratory paralysis severe enough to require endotracheal intubation and mechanical ventilation occurs in 5 to 10%.

A few patients (possibly with a variant form) have significant, life-threatening autonomic dysfunction causing BP fluctuations, inappropriate ADH secretion, cardiac arrhythmias, GI stasis, urinary retention, and pupillary changes. An unusual variant (Fisher variant) may cause only ophthalmoparesis, ataxia, and areflexia.

Diagnosis

• Clinical evaluation

• Electrodiagnostic testing

• CSF analysis

Diagnosis is primarily clinical. Similar acute weakness can result from myasthenia gravis, botulism, poliomyelitis (mainly outside the US), tick paralysis, West Nile virus infection, and metabolic neuropathies, but these disorders can usually be distinguished as follows:

• Myasthenia gravis is intermittent and worsened by exertion.

• Botulism may cause fixed dilated pupils (in 50%) and prominent cranial nerve dysfunction with normal sensation.

• Poliomyelitis usually occurs in epidemics.

• Tick paralysis causes ascending paralysis but spares sensation.

• West Nile virus causes headache, fever, and asymmetric flaccid paralysis but spares sensation.

• Metabolic neuropathies occur with a chronic metabolic disorder.

Tests for infectious disorders and immune dysfunction, including tests for hepatitis and HIV and serum protein electrophoresis, are done.

If Guillain-Barre syndrome is suspected, patients should be admitted to a hospital for electrodiagnostic testing, CSF analysis, and monitoring by measuring forced vital capacity every 6 to 8 h. Initial electrodiagnostic testing detects slow nerve conduction velocities and evidence of segmental demyelination in two thirds of patients; however, normal results do not exclude the diagnosis and should not delay treatment.

CSF analysis may detect albuminocytologic dissociation (increased protein but normal WBC count), but it may not appear for up to 1 wk and does not develop in 10% of patients.

Prognosis

This syndrome is fatal in < 2%. Most patients improve considerably over a period of months, but about 30% of adults and even more children have some residual weakness at 3 yr. Patients with residual defects may require retraining, orthopedic appliances, or surgery.

After initial improvement, 3 to 10% of patients develop chronic inflammatory demyelinating polyneuropathy (CIDP—see p. 1790).

Treatment

• Intensive supportive care

• Plasmapheresis or IV immune globulin

Guillain-Barre syndrome is a medical emergency, requiring constant monitoring and support of vital functions, typically in an ICU. Forced vital capacity should be measured frequently so that respiration can be assisted if necessary; if vital capacity is < 15 mL/kg, endotracheal intubation is indicated. Inability to lift the head off the pillow by flexing the neck is another danger sign; it frequently develops simultaneously with phrenic nerve (diaphragm) weakness.

If oral fluid intake is difficult, IV fluids are given as needed to maintain a urine volume of at least 1 to 1.5 L/day. Extremities should be protected from trauma and from the pressure of bed rest. Heat therapy helps relieve pain, making early physical therapy possible. Immobilization, which may cause ankylosis and contractures, should be avoided. Passive full-range joint movement should be started immediately, and active exercises should be initiated when acute symptoms subside. Heparin 5000 units sc bid helps prevent deep venous thrombosis in bedbound patients.

Given early, immune globulin (γ-globulin) 400 mg/kg IV once/day for 5 consecutive days is the treatment of choice; it has some benefit up to 1 mo from disease onset.

Plasmapheresis (see p. 1044) helps when done early in the syndrome; it is used if γ-globulin is ineffective. Plasmapheresis is relatively safe, shortens the disease course and hospital stay, and reduces mortality risk and incidence of permanent paralysis. Plasmapheresis removes any previously administered γ-globulin, negating its benefits.

Corticosteroids do not improve the outcome and should not be used.

Chronic Inflammatory Demyelinating Polyneuropathy

(Chronic Acquired Demyelinating Polyneuropathy; Chronic Relapsing Polyneuropathy)

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated polyneuropathy characterized by symmetric weakness of proximal and distal muscles and by progression continuing > 2 mo.

Progression for > 2 mo differentiates CIDP from Guillain-Barre syndrome, which is monophasic and self-limited. CIDP develops in 3 to 10% of patients with Guillain-Barre syndrome.

Diagnosis

• CSF analysis and electrodiagnostic tests

Testing includes CSF analysis and electrodiagnostic tests. Results are similar to those in Guillain-Barre syndrome: CSF protein level is increased, and electrodiagnostic testing detects demyelination. Nerve biopsy, which can detect demyelination, is seldom needed.

Treatment

• Corticosteroids

• Sometimes plasmapheresis or IV immune globulin

Unlike Guillain-Barre syndrome, CIDP responds to corticosteroids. Azathioprine may be added to decrease corticosteroid dependence. However, in severe or rapidly progressive cases, plasmapheresis or IV immune globulin may be preferred. Immunosuppressants (eg, azathioprine) may be helpful. Treatment may be needed for a long time.

Hereditary Neuropathies

Hereditary neuropathies include a variety of congenital degenerative peripheral neuropathies.

Hereditary neuropathies are classified as sensorimotor, sensory, or motor (see Motor Neuron Disorders on p. 1791). Causes of secondary hereditary neuropathies include Refsum's disease, porphyria, and Fabry's disease.

Sensorimotor neuropathies: There are 3 main types (I, II, and III); all begin in childhood. Some less common types begin at birth and result in greater disability.

Types I and II (Charcot-Marie-Tooth disease, peroneal muscular atrophy) are the most common; they are usually autosomal dominant disorders. Type I results from a duplication (extra copy) of the peripheral myelin protein-22 gene (*PMP22*), located on the short arm of chromosome 17. These disorders are characterized by weakness and atrophy, primarily in peroneal and distal leg muscles. Patients may also have other degenerative disorders (eg, Friedreich's ataxia) or a family history of them. Patients with type I present in middle childhood with footdrop and slowly progressive distal muscle atrophy, causing stork leg deformity. Intrinsic muscle wasting in the hands begins later. Vibration, pain, and temperature sensation decreases in a stocking-glove pattern. Deep tendon reflexes are absent. High pedal arches or hammertoes may be the only signs in family members who are carriers. Nerve conduction velocities are slow, and distal latencies are prolonged. Segmental demyelination and remyelination occur. Enlarged peripheral nerves may be palpated. The disease progresses slowly and does not affect life span. Type II evolves more slowly; weakness usually develops later in life. Patients have relatively normal nerve conduction velocities but low amplitude sensory nerve action potentials and compound muscle action potentials. Biopsies detect axonal (wallerian) degeneration.

Type III (hypertrophic interstitial neuropathy, Dejerine-Sottas disease), a rare autosomal recessive disorder, begins in childhood with progressive weakness and sensory loss and absent deep tendon reflexes. Although initially it resembles Charcot-Marie-Tooth disease, the motor weakness progresses more quickly. Demyelination and remyelination occur, producing enlarged peripheral nerves and onion bulbs, detected by nerve biopsy.

Sensory neuropathies: Hereditary sensory neuropathies are rare. Loss of distal pain and temperature sensation is more prominent than loss of vibratory and position sense. The main complication is foot mutilation due to pain insensitivity, resulting in a high risk of infections and osteomyelitis.

Diagnosis

The characteristic distribution of motor weakness, foot deformities, and family history suggests the diagnosis, which should be confirmed by electrophysiologic testing. Genetic analysis is available, but there are no specific treatments.

Treatment

• Supportive care

Bracing helps correct footdrop; orthopedic surgery to stabilize the foot may help. Physical therapy (to strengthen muscles) and occupational therapy may help; vocational counseling may help prepare young patients to maintain vocational skills despite disease progression.

Hereditary Motor Neuropathy With Liability to Pressure Palsies

In hereditary motor neuropathy with liability to pressure palsies (HNPP), nerves become increasingly sensitive to pressure and stretch.

In HNPP, nerves lose their myelin sheath and do not conduct nerve impulses normally. Inheritance is usually autosomal dominant. The cause is loss of one copy of peripheral myelin protein-22 gene (*PMP22*), located on the short arm of chromosome 17. Two copies of the gene are needed for normal function. Incidence of HNPP is estimated to be 2 to 5/100,000.

Usually, symptoms start during adolescence or young adulthood, but they may start at any age. Peroneal nerve palsy with footdrop, ulnar nerve palsy, and carpal tunnel syndrome commonly develop. The pressure palsies can be mild or severe and last from minutes to months. Numbness and weakness occur in affected areas.

Diagnosis

HNPP should be suspected in patients with any of the following:

• Recurrent compression mononeuropathies

• Multiple mononeuropathy of unknown origin

• Symptoms suggesting recurrent demyelinating polyneuropathy

• A family history of carpal tunnel syndrome

Electrodiagnostic testing and genetic testing aid in diagnosis; rarely, biopsy is required.

Treatment

• Supportive care

Treatment involves avoiding or modifying activities that cause symptoms. Wrist splints and elbow pads can reduce pressure, prevent reinjury, and allow the nerve to repair the myelin over time. Surgery is rarely indicated.

Motor Neuron Disorders

Motor neuron disorders (MNDs) are characterized by steady, relentless, progressive degeneration of corticospinal tracts, anterior horn cells, bulbar motor nuclei, or a combination. Symptoms vary in severity and may include muscle weakness and atrophy, fasciculations, emotional lability, and respiratory muscle weakness. Diagnosis involves nerve conduction velocity studies, electromyography, and exclusion of other disorders via MRI and laboratory tests. Treatment is supportive.

MNDs may involve the CNS as well as the peripheral nervous system. Usually, etiology is unknown. Nomenclature and symptoms vary according to the part of the motor system most affected. Myopathies have similar features but are disorders of the muscle membrane, contractile apparatus, or organelles (see p. 3008).

MNDs can be classified as upper and lower; some disorders (eg, amyotrophic lateral sclerosis) have features of both. They are more common among men, most often during their 50s.

Symptoms and Signs

Upper MNDs (eg, primary lateral sclerosis) affect neurons of the motor cortex, which extend to the brain stem (corticobulbar tracts) or spinal cord (corticospinal tracts). Generally, symptoms consist of stiffness, clumsiness, and awkward movements, usually affecting first the mouth, throat, or both, then spreading to the limbs.

Lower MNDs affect the anterior horn cells or cranial nerve motor nuclei or their efferent axons to the skeletal muscles. In bulbar palsies, only the cranial nerve motor nuclei in the brain stem (bulbar nuclei) are affected. Patients usually present with facial weakness, dysphagia, and dysarthria. When anterior horn cells of spinal (not cranial) nerves are affected, as in spinal muscular atrophies (see p. 1803), symptoms usually include muscle weakness and atrophy, fasciculations (visible muscle twitches), and muscle cramps, initially in a hand, a foot, or the tongue. Poliomyelitis, an enteroviral infection that attacks anterior horn cells, and postpolio syndrome are also lower MNDs (see p. 1426).

Physical findings help differentiate upper from lower MNDs (see Table 185-3) and weakness due to lower MNDs from that due to myopathy (see Table 185-4).

Amyotrophic lateral sclerosis (ALS): ALS (Lou Gehrig disease, Charcot's syndrome) is the most common MND.

Most patients present with random, asymmetric symptoms, consisting of cramps, weakness, and muscle atrophy of the hands (most commonly) or feet. Weakness progresses to the forearms, shoulders, and lower limbs. Fasciculations, spasticity, hyperactive deep tendon reflexes, extensor plantar reflexes, clumsiness, stiffness of movement, weight loss, fatigue, and difficulty controlling facial expression and tongue movements soon follow. Other symptoms include hoarseness, dysphagia, slurred speech, increased saliva production, and a tendency to choke on liquids. Late in the disorder, a pseudobulbar affect occurs, with inappropriate, involuntary, and uncontrollable excesses of laughter or crying. Sensory systems, consciousness, cognition, voluntary eye movements, sexual function, and urinary and anal sphincters are usually spared.

Death is usually caused by failure of the respiratory muscles; 50% of patients die within 3 yr of onset, 20% live 5 yr, and 10% live 10 yr. Survival for > 30 yr is rare. In the bulbar variant, deterioration and death occur more rapidly.

Progressive bulbar palsy: The muscles innervated by cranial nerves and corticobulbar tracts are predominantly affected, causing progressive difficulty with chewing, swallowing, and talking; nasal voice; reduced gag reflex; fasciculations and weak movement of the facial muscles and tongue; and weak palatal movement. A pseudobulbar affect, with emotional lability may occur if the corticobulbar tract is affected. Commonly, the disorder spreads, affecting extrabulbar segments; then it is called bulbar-variant ALS.

[**Table 185-3.** Distinguishing Upper from Lower Motor Neuron Lesions]

[**Table 185-4.** Distinguishing the Cause of Muscle Weakness: Lower Motor Neuron Dysfunction vs Myopathy*]

Patients with dysphagia have a very poor prognosis; respiratory complications due to aspiration frequently result in death within 1 to 3 yr.

Progressive muscular atrophy: In many cases, especially those with childhood onset, inheritance is autosomal recessive. Other cases are sporadic. The disorder can develop at any age. Anterior horn cell involvement occurs alone or is more prominent than corticospinal involvement, and progression tends to be more benign than that of other MNDs.

Fasciculations may be the earliest manifestation. Muscle wasting and marked weakness begin in the hands and progress to the arms, shoulders, and legs, eventually becoming generalized. Patients may survive ≥ 25 yr.

Primary lateral sclerosis and progressive pseudobulbar palsy: Muscle stiffness and signs of distal motor weakness gradually increase, affecting the limbs in primary lateral sclerosis and the lower cranial nerves in progressive pseudobulbar palsy. Fasciculations and muscle atrophy may follow many years later. These disorders usually take several years to result in total disability.

Diagnosis

• Electrodiagnostic tests

• MRI of brain and, if no cranial nerve involvement, cervical spine

• Laboratory tests to check for other, more treatable causes

Diagnosis is suggested by progressive, generalized motor weakness without significant sensory abnormalities. Other disorders that cause pure muscle weakness should be ruled out:

• Disorders of neuromuscular transmission

• Various myopathies (including noninflammatory and drug-induced)

- Spinal muscular atrophies (mostly in children)
- Polymyositis
- Dermatomyositis
- Thyroid and adrenal disorders
- Electrolyte abnormalities (eg, hypokalemia, hypercalcemia, hypophosphatemia)
- Various infections (eg, syphilis, Lyme disease, hepatitis C)

When cranial nerves are affected, a treatable cause is less likely. Upper and lower motor neuron signs plus weakness in facial muscles strongly suggest ALS.

Electrodiagnostic tests should be done to check for evidence of disorders of neuromuscular transmission or demyelination. Such evidence is not present in MNDs; nerve conduction velocities are usually normal until late in the disease. Needle electromyography (EMG) is the most useful test, showing fibrillations, positive waves, fasciculations, and sometimes giant motor units, even in unaffected limbs.

Brain MRI is required. When there is no clinical or EMG evidence of cranial nerve motor weakness, MRI of the cervical spine is indicated to exclude structural lesions.

Laboratory tests are done to check for other, treatable causes. Tests include CBC, electrolytes, creatine kinase, and thyroid function tests. Serum and urine protein electrophoresis with immunofixation for monoclonal antibodies is done to check for a paraprotein that is rarely associated with MNDs. Discovering an underlying paraproteinemia may indicate that the MND is paraneoplastic, and treatment of the paraproteinemia may ameliorate the MND. Antimyelin-associated glycoprotein (MAG) antibodies are associated with a demyelinating motor neuropathy, which may mimic ALS. A 24-h urine collection is done to check for heavy metals in patients who may have been exposed to them. Lumbar puncture should be done; elevated WBCs or protein levels in CSF strongly suggest an alternative diagnosis.

Serum Venereal Disease Research Laboratories (VDRL) tests, ESR, and measurement of certain antibodies (rheumatoid factor, Lyme titer, HIV, hepatitis C virus, antinuclear [ANA], anti-Hu [to check for anti-Hu paraneoplastic syndrome]) are indicated only if suggested by risk factors or history. Genetic testing (eg, for superoxide dismutase gene mutation or genetic abnormalities that cause spinal muscular atrophies) and enzyme measurements (eg, hexosaminidase A) should not be done unless patients are interested in genetic counseling; disorders detected by these tests have no known specific treatments.

Treatment

- Supportive care
- Riluzole for bulbar-variant ALS

There is no specific treatment. However, an antiglutamate drug, riluzole 50 mg po bid, prolongs life in patients with progressive bulbar palsy. A multidisciplinary team approach helps patients cope with progressive neurologic disability.

The following drugs may help reduce symptoms:

- For spasticity, baclofen
- For cramps, quinine or phenytoin
- To decrease saliva production, a strong anticholinergic drug (eg, glycopyrrolate, amitriptyline, benztropine, trihexyphenidyl, transdermal hyoscine, atropine)

• For pseudobulbar affect, amitriptyline and fluvoxamine

In patients with progressive bulbar palsy, surgery to improve swallowing has had limited success.

Myasthenia Gravis

Myasthenia gravis involves episodic muscle weakness and easy fatigability caused by autoantibody- and cell-mediated destruction of acetylcholine receptors. It is more common among young women but may occur at any age. Symptoms worsen with muscle activity and lessen with rest. Diagnosis is by antibody testing to acetylcholine receptor (AChR), electromyography, and IV edrophonium challenge, which briefly lessens the weakness. Treatment includes anticholinesterase drugs, immunosuppressants, corticosteroids, plasmapheresis, and possibly thymectomy.

Myasthenia gravis develops most commonly in women aged 20 to 40. It results from an autoimmune attack on postsynaptic acetylcholine receptors, which disrupts neuromuscular transmission. The trigger for autoantibody production is unknown, but the disorder is associated with abnormalities of the thymus, thyrotoxicosis, and other autoimmune disorders. The role of the thymus in myasthenia is unclear, but 65% of patients have thymic hyperplasia, and 10% have a thymoma. About half of the thymomas are malignant. Precipitating factors include infection, surgery, and certain drugs (eg, aminoglycosides, quinine, Mg sulfate, procainamide, Ca channel blockers).

Some patients with generalized myasthenia have no antibodies to acetylcholine receptors (AChR) in serum. About half of these patients have antibodies to muscle-specific receptor tyrosine kinase (MuSK), a surface membrane enzyme that helps AChR molecules aggregate during development of the neuromuscular junction. Anti-MuSK antibodies do not occur in patients with AChR antibodies or with isolated ocular myasthenia. The clinical significance of anti-MuSK antibodies is still under study, but patients with them may be less responsive to anticholinesterase drugs and require more aggressive early immunotherapy than patients who have AChR antibodies.

Uncommon forms: Ocular myasthenia gravis involves only extraocular muscles. It represents about 15% of cases.

Congenital myasthenia is a rare autosomal recessive disorder that begins in childhood; it results from structural abnormalities in the postsynaptic receptor rather than an autoimmune disorder. Ophthalmoplegia is common.

Neonatal myasthenia affects 12% of infants born to women with myasthenia gravis. It is due to IgG antibodies that passively cross the placenta. It causes generalized muscle weakness, which resolves in days to weeks as antibody titers decline. Thus, treatment is usually supportive.

Symptoms and Signs

The most common symptoms are ptosis, diplopia, and muscle weakness after use of the affected muscle. Weakness resolves when the affected muscles are rested but recurs when they are used again. Ocular muscles are affected initially in 40% of patients and eventually in 85%. Only ocular muscles are affected in 15%. Hand grip may alternate between weak and normal (milkmaid's grip). Neck muscles may become weak. If generalized myasthenia is going to develop after ocular symptoms, it usually does so within the first 3 yr. Proximal limb weakness is common. Some patients present with bulbar symptoms (eg, altered voice, nasal regurgitation, choking, dysphagia). Sensation and deep tendon reflexes are normal. Manifestations fluctuate in intensity over hours to days.

Myasthenic crisis, a severe generalized quadriparesis or life-threatening respiratory muscle weakness, occurs in about 10% of patients. It is often due to a supervening infection that reactivates the immune system. Once respiratory insufficiency begins, respiratory failure may occur rapidly.

Diagnosis

• Bedside anticholinesterase test

• AChR antibody levels, electromyography, or both

Diagnosis is suggested by symptoms and signs and confirmed by tests. An anticholinesterase test, done at bedside and using the short-acting (< 5 min) drug edrophonium, is positive in most patients who have myasthenia with overt weakness. A muscle with obvious weakness is tested. Patients are asked to exercise the affected muscle until fatigue occurs (eg, to hold the eyes open until ptosis occurs or to count aloud until slurred speech develops); then, edrophonium 2 mg IV is given. If no adverse reaction (eg, bradycardia, atrioventricular block) occurs within 30 sec, another 8 mg is given. Rapid (< 2 min) recovery of muscle function is a positive result. However, a positive result is not definitive for myasthenia gravis because such improvement may occur in other neuromuscular disorders. Also, results may be equivocal. During the test, weakness due to cholinergic crisis may worsen. Resuscitation equipment and atropine (as an antidote) must be available during the test.

Even if the anticholinesterase test is unequivocally positive, serum AChR antibody levels, electromyography (EMG), or both are required to confirm the diagnosis. AChR antibodies are present in 80 to 90% of patients with generalized myasthenia but in only 50% with the ocular form. Antibody levels do not correlate with disease severity. About half of patients without AChR antibodies test positive for anti-MuSK antibodies.

EMG using repetitive stimuli (2 to 3/sec) shows a significant decrease in amplitude of the compound muscle action potential response in 60% of patients. Single-fiber EMG can detect such a decrease in > 95%.

Once myasthenia is diagnosed, CT or MRI of the thorax should be done to check for a thymoma. Other tests should be done to screen for autoimmune disorders frequently associated with myasthenia gravis (eg, vitamin B_{12} deficiency, hyperthyroidism, RA, SLE).

Patients in myasthenic crisis should be evaluated for an infectious trigger. Bedside pulmonary function tests (eg, forced vital capacity) help detect impending respiratory failure.

Treatment

• Anticholinesterase drugs and plasmapheresis to relieve symptoms

• Corticosteroids, immunosuppressants, and thymectomy to lessen the autoimmune reaction

• Supportive care

In patients with congenital myasthenia, anticholinesterase drugs and immunomodulating treatments are not beneficial and should be avoided. Patients with respiratory failure require intubation and mechanical ventilation.

Symptomatic treatment: Anticholinesterase drugs are the mainstay of symptomatic treatment but do not alter the underlying disease process. Moreover, they rarely relieve all symptoms, and myasthenia may become refractory to these drugs. Pyridostigmine is begun at 30 to 60 mg po q 3 to 4 h and titrated up to a maximum of 180 mg/dose based on symptoms. When parenteral therapy is necessary (eg, because of dysphagia), neostigmine (1 mg = 60 mg of pyridostigmine) may be substituted. Anticholinesterase drugs can cause abdominal cramps and diarrhea, which are treated with oral atropine 0.4 to 0.6 mg (given with pyridostigmine) or propantheline 15 mg tid to qid.

Cholinergic crisis is muscular weakness caused by a dose of neostigmine or pyridostigmine that is too high. A mild crisis may be difficult to differentiate from worsening myasthenia. Severe cholinergic crisis can usually be differentiated because it, unlike myasthenia gravis, results in increased lacrimation and salivation, tachycardia, and diarrhea.

The approach to deterioration in patients who have been responding well to treatment is controversial.

Some experts believe an edrophonium test is useful because strength improves only during myasthenic crisis. Others recommend initiating respiratory support and stopping anticholinesterase drugs for several days.

Immunomodulating treatment: Immunosuppressants interrupt the autoimmune reaction and slow the disease course, but they do not relieve symptoms rapidly. After being given IV immune globulin 400 mg/kg once/day for 5 days, 70% of patients improve in 1 to 2 wk. Effects may last 1 to 2 mo.

Corticosteroids are necessary as maintenance therapy for many patients but have little immediate effect in myasthenic crisis. Over one half of patients worsen acutely after starting high-dose corticosteroids. Initially, prednisone 20 mg po once/day is given; dose is increased by 5 mg q 2 to 3 days up to 60 or 70 mg, which is then given every other day. Improvement may take several months; then, the dose should be reduced to the minimum necessary to control symptoms.

Azathioprine 2.5 to 3.5 mg/kg po once/day may be as effective as corticosteroids, although significant benefit may not occur for many months. Cyclosporine 2 to 2.5 mg/kg po bid may allow the corticosteroid dose to be reduced. These drugs require the usual precautions. Other drugs that may be beneficial include methotrexate, cyclophosphamide, and mycophenolate mofetil.

Thymectomy is an option for most patients with generalized myasthenia if they are < 60 yr and should be done in all patients with a thymoma. Subsequently, in 80%, remission occurs or the maintenance drug dose can be lowered.

Plasmapheresis may be useful during myasthenia crisis and, for patients unresponsive to drugs, before thymectomy.

Nerve Root Disorders

(Radiculopathies)

Nerve root disorders result in segmental radicular deficits (eg, pain or paresthesias in a dermatomal distribution, weakness of muscles innervated by the root). Diagnosis may require neuroimaging, electrodiagnostic studies, and systemic testing for underlying disorders. Treatment depends on the cause but includes symptomatic relief with NSAIDs and other analgesics.

Nerve root disorders (radiculopathies) are precipitated by chronic pressure on a root in or adjacent to the spinal column. The most common cause is a herniated intervertebral disk. Bone changes due to RA or osteoarthritis, especially in the cervical and lumbar areas, may also compress isolated nerve roots. Less commonly, carcinomatous meningitis causes patchy multiple root dysfunction. Rarely, mass spinal lesions (eg, epidural abscesses and tumors, spinal meningiomas, neurofibromas) may manifest with radicular symptoms instead of the usual spinal cord dysfunction (see p. 1805). Diabetes can cause a painful thoracic or extremity radiculopathy by causing ischemia of the nerve root. Infectious disorders, such as those due to fungi (eg, histoplasmosis) and spirochetes (eg, Lyme disease, syphilis), sometimes affect nerve roots. Herpes zoster infection usually causes a painful radiculopathy with dermatomal sensory loss and characteristic rash, but it may cause a motor radiculopathy with myotomic weakness and reflex loss. Cytomegalovirus-induced polyradiculitis is a complication of AIDS.

Symptoms and Signs

Radiculopathies tend to cause characteristic radicular syndromes of pain and segmental neurologic deficits based on the cord level of the affected root (see Table 185-5). Muscles innervated by the affected motor root become weak and atrophy; they also may be flaccid with fasciculations. Sensory root involvement causes sensory impairment in a dermatomal distribution. Corresponding segmental deep tendon reflexes may be diminished or absent. Electric shock-like pains may radiate along the affected nerve root's distribution.

Pain may be exacerbated by movements that transmit pressure to the nerve root through the

subarachnoid space (eg, moving the spine, coughing, sneezing, doing the Valsalva maneuver). Lesions of the cauda equina, which affect multiple lumbar and sacral roots, cause radicular symptoms in both legs and may impair sphincter and sexual function.

[**Table 185-5.** Symptoms of Common Radiculopathies by Cord Level]

Findings indicating spinal cord compression include a sensory level (an abrupt change in sensation below a horizontal line across the spine), flaccid paraparesis or quadriparesis, reflex abnormalities below the site of compression, early-onset hyporeflexia followed later by hyperreflexia, and sphincter dysfunction.

Diagnosis

• Neuroimaging

• Sometimes electrodiagnostic tests

Radicular symptoms require MRI or CT of the affected area. Myelography is sometimes used if multiple levels are affected. The area imaged depends on symptoms and signs; if the level is unclear, electrodiagnostic studies should be done to localize the affected root, but electrodiagnostic studies cannot identify the cause.

If imaging does not detect an anatomic abnormality, CSF analysis is done to check for infectious or inflammatory causes, and fasting plasma glucose is measured to check for diabetes.

Treatment

• Treatment of the cause and of pain

Specific causes are treated. Acute pain requires appropriate analgesics (eg, acetaminophen, NSAIDs, sometimes opioids). NSAIDs are particularly useful for disorders that involve inflammation. Muscle relaxants, sedatives, and topical treatments rarely provide additional benefit. Chronic pain can be difficult to manage (see p. 1630); acetaminophen and NSAIDs are often only partly effective, and chronic use of NSAIDs has substantial risks. Opioids have a high risk of addiction. Tricyclic antidepressants and anticonvulsants may be effective, as may physical therapy and consultation with a mental health practitioner. For a few patients, alternative medical treatments (eg, transdermal electrical nerve stimulation, spinal manipulation, acupuncture, medicinal herbs) may be tried if all other treatments are ineffective.

Herniated Nucleus Pulposus

(Herniated, Ruptured, or Prolapsed Intervertebral Disk)

Herniated nucleus pulposus is prolapse of an intervertebral disk through a tear in the surrounding annulus fibrosus. The tear causes pain; when the disk impinges on an adjacent nerve root, a segmental radiculopathy with paresthesias and weakness in the distribution of the affected root results. Diagnosis is by CT, MRI, or CT myelography. Treatment of mild cases is with analgesics as needed. Bed rest is rarely indicated. Patients with progressive or severe neurologic deficits, intractable pain, or sphincter dysfunction may require immediate or elective surgery (eg, diskectomy, laminectomy).

Spinal vertebrae are separated by cartilaginous disks consisting of an outer annulus fibrosus and an inner nucleus pulposus. When degenerative changes (with or without trauma) result in protrusion or rupture of the nucleus through the annulus fibrosus in the lumbosacral or cervical area, the nucleus is displaced posterolaterally or posteriorly into the extradural space. Radiculopathy occurs when the herniated nucleus compresses or irritates the nerve root. Posterior protrusion may compress the cord or cauda equina, especially in a congenitally narrow spinal canal (spinal stenosis). In the lumbar area, > 80% of disk ruptures affect L5 or S1 nerve roots; in the cervical area, C6 and C7 are most commonly affected. Herniated disks are common.

Symptoms and Signs

Herniated disks often cause no symptoms, or they may cause symptoms and signs in the distribution of affected nerve roots. Pain usually develops suddenly, and back pain is typically relieved by bed rest. In contrast, nerve root pain caused by an epidural tumor or abscess begins more insidiously, and back pain is worsened by bed rest.

In patients with lumbosacral herniation, straight-leg raises stretch the lower lumbar roots and exacerbate back or leg pain (bilateral if disk herniation is central); straightening the knee while sitting also causes pain.

Cervical herniation causes pain during neck flexion or tilting. Cervical cord compression, if chronic, manifests with spastic paresis of the lower limbs and, if acute, causes quadriparesis.

Cauda equina compression often results in urine retention or incontinence due to loss of sphincter function.

Diagnosis

• CT, MRI, or CT myelography

CT, MRI, or CT myelography can identify the cause and precise level of the lesion. Electrodiagnostic studies may help identify the involved root. Because asymptomatic herniated disk is common, the clinician must carefully correlate symptoms with MRI abnormalities before invasive procedures are considered.

Treatment

• Conservative treatment initially

• Invasive procedures if neurologic deficits are progressive or severe

• Immediate surgical evaluation if spinal cord is compressed

Because a herniated disk desiccates over time, symptoms tend to abate regardless of treatment. Up to 95% of patients recover without surgery within 3 mo. Treatment should be conservative, unless neurologic deficits are progressive or severe. Heavy or vigorous physical activity is restricted, but ambulation and light activity (eg, lifting objects < 2.5 to 5 kg [≈ 5 to 10 lb] using correct techniques) are permitted as tolerated; prolonged bed rest (including traction) is contraindicated. Acetaminophen, NSAIDs, or other analgesics should be used as needed to relieve pain. Physical therapy and home exercises can improve posture and strengthen back muscles and thus reduce spinal movements that further irritate or compress the nerve root.

If lumbar radiculopathies result in persistent or worsening neurologic deficits, particularly objective deficits (weakness, reflex deficits), or in severe, intractable nerve root pain or sensory deficits, invasive procedures should be considered. Microscopic diskectomy and laminectomy with surgical removal of herniated material are usually the procedures of choice. Percutaneous approaches to remove bulging disk material are being evaluated. Dissolving herniated disk material with local injections of the enzyme chymopapain is not recommended. Lesions acutely compressing the spinal cord or cauda equina (eg, causing urine retention or incontinence) require immediate surgical evaluation (see p. 1810).

If cervical radiculopathies result in signs of spinal cord compression, surgical decompression is needed immediately; otherwise, it is done electively when nonsurgical treatments are ineffective.

Peripheral Neuropathy

Peripheral neuropathy is dysfunction of one or more peripheral nerves (the part of a spinal nerve distal to the root and plexus). It includes numerous syndromes characterized by varying

degrees of sensory disturbances, pain, muscle weakness and atrophy, diminished deep tendon reflexes, and vasomotor symptoms, alone or in any combination. Initial classification is based on history and physical examination. Electromyography and nerve conduction velocity studies help localize the lesion and determine whether the pathophysiology is primarily axonal (often metabolic) or demyelinating (often autoimmune). Treatment is aimed mainly at the cause.

Peripheral neuropathy may affect a single nerve (mononeuropathy), ≥ 2 discrete nerves in separate areas (multiple mononeuropathy), or many nerves simultaneously and often suggesting a diffuse process (polyneuropathy).

Mononeuropathies

Single and multiple mononeuropathies are characterized by sensory disturbances and weakness in the distribution of the affected nerve or nerves. Diagnosis is clinical but should be confirmed with electrodiagnostic tests. Treatment is directed at the cause, sometimes with splinting, NSAIDs, corticosteroid injections, and, for severe cases of nerve entrapment, surgery.

Trauma is the most common cause of acute mononeuropathy and may result as follows:

- Violent muscular activity or forcible over-extension of a joint may cause focal neuropathy, as may repeated small traumas (eg, tight gripping of small tools, excessive vibration from air hammers).

- Prolonged, uninterrupted pressure at bony prominences can cause pressure neuropathy, usually affecting superficial nerves (ulnar, radial, peroneal), particularly in thin people; such pressure may occur during sound sleep, intoxication, bicycle riding, or anesthesia.

- Compression of nerves in narrow passageways causes entrapment neuropathy (eg, in carpal tunnel syndrome).

- Nerve compression by a tumor, bony hyperostosis, a cast, crutches, or prolonged cramped postures (eg, during gardening) may cause compression paralysis.

Hemorrhage that compresses a nerve, exposure to cold or radiation, or direct tumor invasion may also cause neuropathy. Compression of a nerve may be transient (eg, caused by an activity) or fixed (eg, caused by a mass or anatomic abnormality).

Multiple mononeuropathy (mononeuritis multiplex) is usually secondary to connective tissue disorders (eg, polyarteritis nodosa, SLE, other types of vasculitis, Sjogren's syndrome, RA), sarcoidosis, metabolic disorders (eg, diabetes, amyloidosis), or infectious disorders (eg, Lyme disease, HIV infection, leprosy). However, diabetes usually causes sensorimotor distal polyneuropathy (see p. 1799).

Symptoms and Signs

Single and multiple mononeuropathies are characterized by pain, weakness, and paresthesias in the distribution of the affected nerve or nerves. Pure motor nerve involvement begins with painless weakness; pure sensory nerve involvement begins with sensory disturbances and no weakness. Multiple mononeuropathy is often asymmetric at its onset; nerves may be involved all at once or progressively. Extensive involvement of many nerves may simulate polyneuropathy.

Ulnar nerve palsy of the elbow is often caused by trauma to the nerve in the ulnar groove of the elbow by repeated leaning on the elbow or by asymmetric bone growth after a childhood fracture (tardy ulnar palsy). The ulnar nerve can also be compressed at the cubital tunnel. Compression at the level of the elbow can cause paresthesias and a sensory deficit in the 5th digit and medial half of the 4th digit; the thumb adductor, 5th digit abductor, and interosseus muscles are weak and may be atrophied. Severe chronic ulnar palsy causes a clawhand deformity. Sensory symptoms due to this syndrome are similar to those due to C8 root dysfunction secondary to cervical radiculopathy; however, radiculopathy normally affects the more proximal aspects of the C8 dermatome.

Carpal tunnel syndrome (see also p. 391) may be unilateral or bilateral. It results from compression of the median nerve in the volar aspect of the wrist between the transverse superficial carpal ligament and the flexor tendons of the forearm muscles. The compression causes paresthesias in the radial-palmar aspect of the hand and pain in the wrist and palm. Pain may be referred to the forearm and shoulder. Pain may be more severe at night. A sensory deficit in the palmar aspect of the first 3 fingers may follow, and the muscles that control thumb abduction and opposition may become weak and atrophied. Sensory symptoms due to this syndrome are similar to those due to C6 root dysfunction secondary to cervical radiculopathy.

Peroneal nerve palsy is usually caused by compression of the nerve against the lateral aspect of the fibular neck. It is most common among emaciated bedbound patients and thin people who habitually cross their legs. It causes footdrop (weakened dorsiflexion and eversion of the foot) and, occasionally, a sensory deficit in the anterolateral aspect of the lower leg and the dorsum of the foot or in the web space between the 1st and 2nd metatarsals.

Radial nerve palsy (Saturday night palsy) is caused by compression of the nerve against the humerus, as when the arm is draped over the back of a chair for a long time (eg, during intoxication or deep sleep). Typical symptoms include wristdrop (weakness of the wrist and finger extensors) and sensory loss in the dorsal aspect of the first dorsal interosseous muscle.

Diagnosis

• Clinical evaluation

• Electrodiagnostic testing if clinical diagnosis is inconclusive

Symptoms and examination findings may be nearly pathognomonic. Palpating muscles while they are contracting may detect weakness better than testing movement because during movement, other muscles may compensate for the weak one.

Electrodiagnostic tests are usually done to clarify the diagnosis, particularly when clinical findings are inconclusive for example:

• To distinguish sensory symptoms due to ulnar nerve palsy from C8 root dysfunction due to cervical radiculopathy

• To distinguish sensory symptoms due to carpal tunnel syndrome from C6 root dysfunction due to cervical radiculopathy

Electrodiagnostic tests also help localize the lesion, assess severity, and estimate prognosis.

Treatment

Underlying disorders are treated. Treatment of compression neuropathy depends on cause:

• Fixed compression (eg, by tumor) often must be relieved surgically.

• For transient compression, rest, heat, limited courses of NSAIDs in doses that reduce inflammation (eg, ibuprofen 800 mg tid), and avoidance or modification of the causative activity usually relieve symptoms.

• For carpal tunnel syndrome, corticosteroid injections are sometimes helpful.

Braces or splints are often used pending resolution to prevent contractures. Surgery should be considered when progression occurs despite conservative treatment.

Polyneuropathy

A polyneuropathy is a diffuse peripheral nerve disorder that is bilaterally symmetrical and thus

not confined to the distribution of a single nerve or a single limb. Electrodiagnostic tests should always be done to classify the nerve structures involved, distribution, and severity of the disorder and thus help identify the cause. Treatment is directed toward correcting the cause.

Some polyneuropathies (eg, due to lead toxicity, dapsone use, tick bite, porphyria, or Guillain-Barre syndrome) affect primarily motor fibers; others (eg, due to dorsal root ganglionitis of cancer, leprosy, AIDS, diabetes mellitus, or chronic pyridoxine intoxication) affect primarily sensory fibers. Some disorders (eg, Guillain-Barre syndrome, Lyme disease, diabetes, diphtheria) can also affect cranial nerves. Certain drugs and toxins can affect sensory or motor fibers or both (see Table 185-6).

Symptoms and Signs

Because pathophysiology and symptoms are related, polyneuropathies are often classified by area of dysfunction: myelin, vasa nervorum, or axon. They may be acquired or inherited (see p. 1790).

Myelin dysfunction: Myelin dysfunction polyneuropathies most often result from a parainfectious immune response triggered by an encapsulated bacterium (eg, *Campylobacter* sp), virus (eg, enteric or influenza viruses, HIV), or vaccine (eg, influenza vaccine). Presumably, antigens in these agents cross-react with antigens in the peripheral nervous system, causing an immune response (cellular, humoral, or both) that culminates in varying degrees of myelin dysfunction. In acute cases (eg, in Guillain-Barre syndrome—see p. 1788), rapidly progressive weakness and respiratory failure may develop. In chronic inflammatory demyelinating polyneuropathy (CIDP), symptoms may recur or progress over months and years.

Myelin dysfunction usually results in large-fiber sensory disturbances (paresthesias), significant muscle weakness greater than expected for degree of atrophy, and greatly diminished reflexes. Trunk musculature and cranial nerves may be involved. Demyelination typically occurs along the entire length of a nerve, causing proximal and distal symptoms. There may be side-to-side asymmetries, and the upper body may be affected before the lower body, or vice versa. Muscle bulk and tone are relatively preserved.

Vasa nervorum compromise: Chronic arteriosclerotic ischemia, vasculitis, and hypercoagulable states can compromise the vascular supply to nerves.

[**Table 185-6.** Toxic Causes of Neuropathies]

Usually, small-fiber sensory and motor dysfunction occurs first. Patients typically have painful, often burning sensory disturbances. Abnormalities tend to be asymmetric early in the disorder and rarely affect the proximal one third of the limb or trunk muscles. Cranial nerve involvement is rare, except in diabetes, which commonly affects the 3rd cranial (oculomotor) nerve. Later, if nerve lesions coalesce, symptoms and signs may appear symmetric. Dysautonomia and skin changes (eg, atrophic, shiny skin) sometimes occur. Muscle weakness tends to be proportional to atrophy, and reflexes are rarely lost completely.

Axonopathy: Axonopathies tend to be distal; they may be symmetric or asymmetric.

Symmetric axonopathies result most often from toxic-metabolic disorders. Common causes include the following:

- Diabetes mellitus
- Chronic renal insufficiency
- Adverse effects of chemotherapy drugs (eg, vinca alkaloids)

Axonopathy may result from nutritional deficiencies (most commonly, of thiamin or vitamin B_6, B_{12}, or E) or from excess intake of vitamin B_6 or alcohol. Less common metabolic causes include hypothyroidism, porphyria, sarcoidosis, and amyloidosis. Other causes include certain infections (eg, Lyme disease), drugs (eg, nitrous oxide), and exposure to certain chemicals (eg, Agent Orange, *n*-hexane) or heavy

metals (eg, lead, arsenic, mercury). In a paraneoplastic syndrome associated with small-cell lung cancer, loss of dorsal root ganglia and their sensory axons results in subacute sensory neuropathy.

Primary axon dysfunction may begin with symptoms of large- or small-fiber dysfunction or both. Usually, the resulting neuropathy has a distal symmetric, stocking-glove distribution; it evenly affects the lower extremities before the upper extremities and progresses symmetrically from distal to proximal areas.

Asymmetric axonopathy can result from parainfectious or vascular disorders.

Diagnosis

• Electrodiagnostic testing

• Laboratory tests, determined by suspected type of neuropathy

Polyneuropathy is suspected in patients with diffuse or multifocal sensory deficits, weakness without hyperreflexia, or both. Clinical findings, particularly tempo of onset, aid in diagnosis and identification of the cause, as in the following:

• Asymmetric neuropathies suggest a disorder affecting the myelin sheath or vasa nervorum.

• Symmetric, distal neuropathies suggest toxic or metabolic causes.

• Slowly progressive, chronic neuropathies tend to be inherited or due to long-term toxic exposure or metabolic disorders.

• Acute neuropathies suggest an autoimmune response, vasculitis, or a postinfectious cause.

• Rash, skin ulcers, and Raynaud's syndrome in patients with an asymmetric axonal neuropathy suggest a hypercoagulable state or parainfectious or autoimmune vasculitis.

• Weight loss, fever, lymphadenopathy, and mass lesions may suggest a tumor or paraneoplastic syndrome.

Electrodiagnostic tests: Regardless of clinical findings, electromyography (EMG) and nerve conduction velocity studies are necessary to classify type of neuropathy. At a minimum, EMG of both lower extremities should be done to assess for asymmetry and full extent of axon loss. Because EMG and nerve conduction studies assess primarily large myelinated fibers in distal limb segments, EMG may be normal in patients with proximal myelin dysfunction (eg, early in Guillain-Barre syndrome) and in patients with primarily small-fiber dysfunction. In such cases, quantitative sensory or autonomic testing or both may be done depending on the presenting symptoms.

Laboratory tests: Baseline laboratory tests for all patients include CBC, electrolytes, renal function tests, rapid plasma reagin test, and measurement of fasting plasma glucose, HbA_{1C}, vitamin B_{12}, folate, and thyroid-stimulating hormone. Some clinicians include serum protein electrophoresis. The need for other tests is determined by polyneuropathy subtype. When EMG and clinical differentiation are inconclusive, tests for all subtypes may be necessary.

For acute myelin dysfunction neuropathies, the approach is the same as that for Guillain-Barre syndrome (see p. 1788); forced vital capacity is measured to check for incipient respiratory failure. In acute or chronic myelin dysfunction, tests for infectious disorders and immune dysfunction, including tests for hepatitis and HIV and serum protein electrophoresis, are done. A lumbar puncture should also be done; myelin dysfunction due to an autoimmune response often causes albuminocytologic dissociation: increased CSF protein (> 45 mg%) but normal WBC count (≤ 5/μL).

For vasa nervorum compromise or asymmetric axonal polyneuropathies, tests for hypercoagulable states and parainfectious or autoimmune vasculitis, particularly if suggested by clinical findings, should be done; the minimum is ESR, serum protein electrophoresis, and measurement of rheumatoid factor, antinuclear

antibodies, and serum CK. CK may be elevated when rapid onset of disease results in muscle injury. Coagulation studies (eg, protein C, protein S, antithrombin III, anticardiolipin antibody, and homocysteine levels) should be done only if personal or family history suggests a hypercoagulable state. Tests for sarcoidosis, hepatitis C, or Wegener's granulomatosis should be done only if symptoms and signs suggest one of these disorders. If no cause is identified, nerve and muscle biopsy should be done. An affected sural nerve is usually biopsied. A muscle adjacent to the biopsied sural nerve or a quadriceps, biceps brachii, or deltoid muscle may be biopsied. The muscle should be one with moderate weakness that has not been tested by EMG using a needle. An abnormality is more often detected when the contralateral muscle has EMG abnormalities, particularly when the neuropathy is somewhat symmetric. Nerve biopsies are useful in symmetric and asymmetric polyneuropathies but are particularly useful in asymmetric axonopathies.

If initial tests do not identify the cause of distal symmetric axonopathies, a 24-h urine collection is tested for heavy metals, and urine protein electrophoresis is done. If chronic heavy metal poisoning is suspected, testing of hairs from the pubis or axillary region may help.

Whether tests for other causes are needed depends on history and physical examination findings.

Treatment

• Treatment directed at the cause

• Supportive care

Treatment focuses on correcting the causes when possible; a causative drug or toxin can be eliminated, or a dietary deficiency corrected. Although these actions may halt progression and lessen symptoms, recovery is slow and may be incomplete. If the cause cannot be corrected, treatment focuses on minimizing disability and pain. Physical and occupational therapists can recommend useful assistive devices. Amitriptyline, gabapentin, mexiletine, and topical lidocaine may relieve neuropathic pain (eg, diabetic burning feet).

For myelin dysfunction polyneuropathies, immune system-modifying treatments are usually used:

• Plasmapheresis or IV immune globulin for acute myelin dysfunction

• Corticosteroids or antimetabolite drugs for chronic myelin dysfunction

Plexus Disorders

Disorders of the brachial or lumbosacral plexus cause a painful mixed sensorimotor disorder of the corresponding limb.

Because several nerve roots intertwine within the plexus (see Fig. 185-1), the symptom pattern does not fit the distribution of individual roots or nerves. Disorders of the rostral brachial plexus affect the shoulders, those of the caudal brachial plexus affect the hands, and those of the lumbosacral plexus affect the legs.

Plexus disorders (plexopathies) are usually due to physical compression or injury. In infants, traction during birth may cause plexopathy. In adults, the cause is usually trauma (typically, for the brachial plexus, a fall that forces the head away from the shoulder) or invasion by metastatic cancer (typically, breast or lung cancer for the brachial plexus and intestinal or GU tumors for the lumbosacral plexus). In patients receiving anticoagulants, a hematoma may compress the lumbosacral plexus. Neurofibromatosis (see p. 2903) occasionally involves a plexus. Other causes include postradiation fibrosis (eg, after radiation therapy for breast cancer) and diabetes.

Acute brachial neuritis (neuralgic amyotrophy, Parsonage-Turner syndrome) occurs primarily in men and typically in young adults, although it can occur at any age. Cause is unknown, but viral or immunologic inflammatory processes are suspected.

Symptoms and Signs

Manifestations include extremity pain and motor or sensory deficits that do not correspond to an isolated nerve root or peripheral nerve.

For acute brachial neuritis, symptoms include severe supraclavicular pain, weakness, and diminished reflexes, with minor sensory abnormalities in the distribution of the brachial plexus. Usually, weakness develops and reflexes decrease as pain resolves. Severe weakness develops within 3 to 10 days, then typically regresses over the next few months. The most commonly affected muscles are the serratus anterior (causing winging of the scapula), other muscles innervated by the upper trunk, and muscles innervated by the anterior interosseus nerve (in the forearm—patients may not be able to make an O with the thumb and index finger).

Diagnosis

• Electromyography and somatosensory evoked potentials

• Sometimes MRI

Diagnosis is suggested by clinical findings. Electromyography and somatosensory evoked potentials should be done to clarify the anatomic distribution (including possible nerve root involvement). MRI of the appropriate plexus and adjacent spine is indicated for all nontraumatic plexopathies that are not a typical case of brachial neuritis.

Treatment

• Treatment directed at the cause

Corticosteroids, although commonly prescribed, have no proven benefit. Surgery may be indicated for injuries, hematomas, and benign or metastatic tumors. Metastases should also be treated with radiation therapy, chemotherapy, or both. Glycemic control can benefit patients with diabetic plexopathy.

[Fig. 185-1. Plexuses.]

Spinal Muscular Atrophies

Spinal muscular atrophies include several types of hereditary disorders characterized by skeletal muscle wasting due to progressive degeneration of anterior horn cells in the spinal cord and of motor nuclei in the brain stem. Manifestations may begin in infancy or childhood. They vary by the specific type and may include hypotonia; hyporeflexia; difficulty sucking, swallowing, and breathing; unmet developmental milestones; and, in more severe types, very early death. Diagnosis is by genetic testing. Treatment is supportive.

Spinal muscular atrophies usually result from autosomal recessive mutations of a single gene locus on the short arm of chromosome 5, causing a homozygous deletion. They may involve the CNS and thus are not purely peripheral nervous system disorders. There are 4 main types.

Type I spinal muscular atrophy (Werdnig-Hoffmann disease) is present in utero and becomes symptomatic by about age 6 mo. Affected infants have hypotonia (often notable at birth), hyporeflexia, tongue fasciculations, and pronounced difficulty sucking, swallowing, and eventually breathing. Death, usually due to respiratory failure, occurs within the first yr in 95% and by age 4 yr in all.

In **type II (intermediate) spinal muscular atrophy,** symptoms usually manifest between age 3 and 15 mo; < 25% of affected children learn to sit, and none walk or crawl. Children have flaccid muscle weakness and fasciculations, which may be hard to see in young children. Deep tendon reflexes are absent. Dysphagia may be present. The disorder is often fatal in early life, frequently resulting from respiratory complications. However, progression can stop spontaneously, leaving children with

permanent, nonprogressive weakness and a high risk of severe scoliosis and its complications.

Type III spinal muscular atrophy (Wohlfart-Kugelberg-Welander disease) usually manifests between age 15 mo and 19 yr. Findings are similar to those of type I, but progression is slower and life expectancy is longer; some patients have a normal life span. Some familial cases are secondary to specific enzyme defects (eg, hexosaminidase deficiency). Symmetric weakness and wasting progress from proximal to distal areas and are most evident in the legs, beginning in the quadriceps and hip flexors. Later, arms are affected. Life expectancy depends on whether respiratory complications develop.

Type IV spinal muscular atrophy can be recessive, dominant, or X-linked, with adult onset (age 30 to 60 yr) and slow progression of primarily proximal muscle weakness and wasting. Differentiating this disorder from amyotrophic lateral sclerosis that involves predominantly lower motor neurons may be difficult.

Diagnosis

• Electrodiagnostic testing

• Genetic testing

The diagnosis should be suspected in patients with unexplained muscle wasting and flaccid weakness, particularly in infants and children.

Electromyography (EMG) and nerve conduction velocity studies should be done; muscles innervated by cranial nerves should be included. Conduction is normal, but affected muscles, which are often clinically unaffected, are denervated.

Definitive diagnosis is by genetic testing, which detects the causative mutation in about 95% of patients. Muscle biopsy is done occasionally. Serum enzymes (eg, CK, aldolase) may be slightly increased. Amniocentesis, done if family history is positive, is often diagnostic.

Treatment

• Supportive care

There is no specific treatment. Physical therapy, braces, and special appliances can benefit patients with static or slowly progressive disease by preventing scoliosis and contractures. Adaptive devices available through physical and occupational therapists may improve children's independence and self-care by enabling them to feed themselves, write, or use a computer.

Thoracic Outlet Compression Syndromes

Thoracic outlet compression syndromes are a group of poorly defined disorders characterized by pain and paresthesias in a hand, the neck, a shoulder, or an arm. They appear to involve compression of the brachial plexus (and perhaps the subclavian vessels) as these structures traverse the thoracic outlet. Diagnostic techniques have not been established. Treatment includes physical therapy, analgesics, and, in severe cases, surgery.

Pathogenesis is often unknown but sometimes involves compression of the lower trunk of the brachial plexus (and perhaps the subclavian vessels) as these structures traverse the thoracic outlet below the scalene muscles and over the 1st rib, before they enter the axilla, but this involvement is unclear. Compression may be caused by a cervical rib, an abnormal 1st thoracic rib, abnormal insertion or position of the scalene muscles, or a malunited clavicle fracture. Thoracic outlet syndromes are more common among women and usually develop between age 35 and 55.

Symptoms and Signs

Pain and paresthesias usually begin in the neck or shoulder and extend to the medial aspect of the arm

and hand and sometimes to the adjacent anterior chest wall. Many patients have mild to moderate sensory impairment in the C8 to T1 distribution on the painful side; a few have prominent vascular-autonomic changes in the hand (eg, cyanosis, swelling). In even fewer, the entire affected hand is weak.

Rare complications include Raynaud's syndrome and distal gangrene.

Diagnosis

• Clinical evaluation

• Sometimes electrodiagnostic tests, MRI, or both

Diagnosis is suggested by distribution of symptoms. Various maneuvers are alleged to demonstrate compression of vascular structures (eg, by extending the brachial plexus), but sensitivity and specificity are not established. Auscultating bruits at the clavicle or apex of the axilla or finding a cervical rib by x-ray can aid in diagnosis. Although angiography may detect kinking or partial obstruction of axillary arteries or veins, neither finding is incontrovertible evidence of disease. Other testing is controversial, but evaluation as for brachial plexopathy (eg, electrodiagnostic tests, MRI—see p. 1802) may be reasonable.

Treatment

• Physical therapy and analgesia

• In severe cases, surgery

Most patients without objective neurologic deficits respond to physical therapy, NSAIDs, and low-dose tricyclic antidepressants.

If cervical ribs or subclavian artery compression is identified, an experienced specialist should decide whether surgery is necessary. With few exceptions, surgery should be reserved for patients who have significant or progressive neurovascular deficits and who do not respond to conservative treatment.

Chapter 186. Spinal Cord Disorders

Introduction

Spinal cord disorders can cause permanent severe neurologic disability. For some patients, such disability can be avoided or minimized if evaluation and treatment are rapid. Spinal cord disorders usually result from conditions extrinsic to the cord—eg, compression due to spinal stenosis, herniated disk, tumor, abscess, or hematoma. Less commonly, disorders are intrinsic to the cord. Intrinsic insults include infarction, hemorrhage, transverse myelitis, arteriovenous malformation, HIV infection, poliovirus infection (see p. 1426), syphilis (which can cause tabes dorsalis—see p. 1478), trauma (see p. 3227), vitamin B_{12} deficiency (which causes subacute combined degeneration—see p. 38), decompression sickness (see p. 3287), lightning injury (which can cause keraunoparalysis—see p. 3250), radiation therapy (which can cause myelopathy), syrinx, or spinal cord tumor (see p. 1821). Spinal nerve roots outside of the spinal cord may also be damaged (see p. 1795).

Anatomy

The spinal cord extends caudally from the medulla at the foramen magnum and terminates at the upper lumbar vertebrae, where it forms the conus medullaris. In the lumbosacral region, nerve roots from lower cord segments descend within the spinal column in a nearly vertical sheaf, forming the cauda equina.

The white matter at the cord's periphery contains ascending and descending tracts of myelinated sensory and motor nerve fibers. The central H-shaped gray matter is composed of cell bodies and nonmyelinated fibers (see Fig. 186-1). The anterior (ventral) horns of the "H" contain lower motor neurons, which receive impulses from the motor cortex via the descending corticospinal tracts and, at the local level, from internuncial neurons and afferent fibers from muscle spindles. The axons of the lower motor neurons are the efferent fibers of the spinal nerves. The posterior (dorsal)

[**Fig. 186-1.** Spinal nerve.]

horns contain sensory fibers that originate in cell bodies in the dorsal root ganglia. The gray matter also contains many internuncial neurons that carry motor, sensory, or reflex impulses from dorsal to ventral nerve roots, from one side of the cord to the other, or from one level of the cord to another. The spinothalamic tract transmits pain and temperature sensation contralaterally in the spinal cord; most other tracts transmit information ipsilaterally. The cord is divided into functional segments (levels) corresponding approximately to the attachments of the 31 pairs of spinal nerve roots.

Symptoms and Signs

Neurologic dysfunction due to spinal cord disorders occurs at the involved spinal cord segment (see Table 186-1) and at all segments below it. The exception is the central cord syndrome (see Table 186-2), which may spare segments below.

Spinal cord disorders cause various patterns of deficits depending on which nerve tracts within the cord or which spinal roots outside the cord are damaged. Disorders affecting spinal nerves, but not directly affecting the cord, cause sensory or motor abnormalities or both only in the areas supplied by the affected spinal nerves.

Spinal cord dysfunction causes paresis, loss of sensation, reflex changes, and autonomic dysfunction (eg, bowel, bladder, and erectile dysfunction; loss of sweating). Dysfunction may be partial (incomplete). Autonomic and reflex abnormalities are usually

[**Table 186-1.** Effects of Spinal Cord Dysfunction by Segmental Level]

[**Table 186-2.** Spinal Cord Syndromes]

the most objective signs of cord dysfunction; sensory abnormalities are the least objective.

Corticospinal tract lesions cause upper motor neuron dysfunction. Acute, severe lesions (eg, infarction, traumatic lesions) cause spinal shock with flaccid paresis (decreased muscle tone, hyporeflexia, and no extensor plantar responses). After days or weeks, upper motor neuron dysfunction evolves into spastic paresis (increased muscle tone, hyperreflexia, and clonus). Extensor plantar responses and autonomic dysfunction are present. Flaccid paresis that lasts more than a few weeks suggests lower motor neuron dysfunction (eg, due to Guillain-Barre syndrome).

Specific cord syndromes include transverse sensorimotor myelopathy, Brown-Sequard syndrome, central cord syndrome, anterior cord syndrome, and conus medullaris syndrome (see Table 186-2).

Cauda equina syndrome, which involves damage to nerve roots at the caudal end of the cord, is not a spinal cord syndrome. However, it mimics conus medullaris syndrome, causing distal leg paresis and sensory loss in and around the perineum and anus (saddle anesthesia), as well as bladder, bowel, and pudendal dysfunction (eg, urinary retention, urinary frequency, urinary or fecal incontinence, erectile dysfunction, loss of rectal tone, abnormal bulbocavernosus and anal wink reflexes).

Diagnosis

• MRI

Neurologic deficits at segmental levels suggest a spinal cord disorder. Similar deficits, especially if unilateral, may result from nerve root or peripheral nerve disorders, which can usually be differentiated clinically. Level and pattern of spinal cord dysfunction help determine presence and location of a spinal cord lesion but not always type of lesion.

MRI is the most accurate imaging test for spinal cord disorders; MRI shows spinal cord parenchyma, soft-tissue lesions (eg, abscesses, hematomas, tumors, abnormalities involving intervertebral disks), and bone lesions (eg, erosion, severe hypertrophic changes, collapse, fracture, subluxation, tumors). Myelography with a radiopaque dye followed by CT is used less often. It is not as accurate as MRI and is more invasive but may be more readily available. Plain x-rays may help detect bone lesions.

Acute Transverse Myelitis

Acute transverse myelitis is acute inflammation of gray and white matter in one or more adjacent spinal cord segments, usually thoracic. Causes include multiple sclerosis, infections, autoimmune or postinfectious inflammation, vasculitis, and certain drugs. Symptoms include bilateral motor, sensory, and sphincter deficits below the level of the lesion. Diagnosis is usually by MRI, CSF analysis, and blood tests. IV corticosteroids and plasma exchange may be helpful early. Otherwise, treatment is supportive measures and correction of any causes.

Acute transverse myelitis is most commonly due to multiple sclerosis but can occur with vasculitis, mycoplasmal infections, Lyme disease, syphilis, TB, or viral meningoencephalitis or in patients taking amphetamines, IV heroin, or antiparasitic or antifungal drugs. Transverse myelitis occurs with optic neuritis in a variant of multiple sclerosis called neuromyelitis optica (Devic disease—see p. 1783). The mechanism of transverse myelitis is often unknown, but some cases follow viral infection or vaccination, suggesting an autoimmune reaction. Inflammation tends to involve the spinal cord diffusely at one or more levels, affecting all spinal cord functions.

Symptoms and Signs

Pain in the neck, back, or head may occur. A bandlike tightness around the chest or abdomen, weakness, tingling, numbness of the feet and legs, and difficulty voiding develop over hours to a few days. Deficits may progress over several more days to a complete transverse sensorimotor myelopathy, causing paraplegia, loss of sensation below the lesion, urinary retention, and fecal incontinence. Occasionally, position and vibration sensation are spared, at least initially. The syndrome occasionally recurs in patients with multiple sclerosis, SLE, or antiphospholipid syndrome.

Diagnosis

• MRI and CSF analysis

• Other tests to identify treatable causes

Diagnosis is suggested by transverse sensorimotor myelopathy with segmental deficits. Guillain-Barre syndrome (see p. 1788) can be distinguished because it does not localize to a specific spinal segment. Diagnosis requires MRI and CSF analysis. MRI typically shows cord swelling and helps exclude other treatable causes of spinal cord dysfunction (eg, spinal cord compression). CSF usually contains monocytes, protein content is slightly increased, and IgG index is elevated (normal, ≤ 0.85). A new and specific antibody marker for neuromyelitis optica (NMO-IgG), which distinguishes neuromyelitis optica from multiple sclerosis, has been recently described.

Tests for treatable causes should include chest x-ray; PPD; serologic tests for mycoplasma, Lyme disease, and HIV; vitamin B_{12} and folate levels; ESR; antinuclear antibodies; and CSF and blood Venereal Disease Research Laboratory (VDRL) tests. History may suggest a drug as a cause. Brain MRI is done; multiple sclerosis develops in 50% of patients who have multiple periventricular T2 bright lesions and in 5% who do not have them.

Prognosis

Generally, the more rapid the progression is, the worse the prognosis. Pain suggests more intense inflammation. About one third of patients recover, one third retain some weakness and urinary urgency, and one third are bedbound and incontinent. Multiple sclerosis eventually develops in about 10 to 20% of the patients in whom the cause is initially unknown.

Treatment

• Treatment of the cause

• Sometimes corticosteroids

Treatment is directed at the cause or associated disorder but is otherwise supportive. In idiopathic cases, high-dose corticosteroids are often given and sometimes followed by plasma exchange because the cause may be autoimmune. Efficacy of such a regimen is uncertain.

Arteriovenous Malformations

Arteriovenous malformations (AVMs) in or around the spinal cord can cause cord compression, ischemia, parenchymal hemorrhage, subarachnoid hemorrhage, or a combination. Symptoms may include gradually progressive, ascending, or waxing and waning segmental neurologic deficits; radicular pain; and sudden back pain with sudden segmental neurologic deficits. Diagnosis is by MRI. Treatment is with surgery or stereotactic radiosurgery and may include angiographic embolization.

AVMs are the most common spinal vascular malformations. Most are thoracolumbar, posterior, and outside the cord (extramedullary). The rest are cervical or upper thoracic and often inside the cord (intramedullary). AVMs may be small and localized or may affect up to half the cord. They may compress or even replace normal spinal cord parenchyma, or they may rupture, causing focal or generalized hemorrhage.

Symptoms and Signs

A cutaneous angioma sometimes overlies a spinal AVM. AVMs commonly compress nerve roots, causing pain that radiates down the distribution of a nerve root (radicular pain), or compress the spinal cord, causing segmental neurologic deficits that gradually progress or that wax and wane. Combined lower and

upper motor neuron deficits are common. AVMs may rupture into the spinal cord parenchyma, causing sudden, severe back pain and sudden segmental neurologic deficits. Rarely, high cervical AVMs rupture into the subarachnoid space, causing sudden and severe headache, nuchal rigidity, and impaired consciousness (see p. 1654).

Diagnosis

• Imaging

Spinal cord AVMs may be detected incidentally during imaging. AVMs are suspected clinically in patients with unexplained segmental neurologic deficits or subarachnoid hemorrhage, particularly those who have sudden, severe back pain or cutaneous midline angiomas. Diagnosis is by MRI, magnetic resonance angiography, selective arteriography, or, occasionally, myelography plus CT.

Treatment

Surgery is indicated if spinal cord function is threatened, but expertise in specialized microtechniques is required. Stereotactic radiosurgery is helpful if the AVM is small and located in a surgically inaccessible location. Angiographic embolization occludes feeder arteries and often precedes surgical removal or stereotactic radiosurgery.

Cervical Spondylosis and Spondylotic Cervical Myelopathy

Cervical spondylosis is osteoarthritis of the cervical spine causing stenosis of the canal and sometimes cervical myelopathy due to encroachment of bony osteoarthritic growths (osteophytes) on the lower cervical spinal cord, sometimes with involvement of lower cervical nerve roots (radiculomyelopathy).

Cervical spondylosis due to osteoarthritis is common. Occasionally, particularly when the spinal canal is congenitally narrow (< 10 mm), osteoarthritis leads to stenosis of the canal and bony impingement on the cord, causing compression and myelopathy (functional disturbance of the spinal cord). Hypertrophy of the ligamentum flavum can aggravate this effect. Osteophytes in the neural foramina, most commonly between C5 and C6 or C6 and C7, can cause radiculopathy (a nerve root disorder—see also p. 1795). Manifestations vary according to the neural structures involved but commonly include pain.

Symptoms and Signs

Cord compression commonly causes gradual spastic paresis, paresthesias, or both in the hands and feet and may cause hyperreflexia. Neurologic deficits may be asymmetric, nonsegmental, and aggravated by cough or Valsalva maneuvers. After trauma, people with cervical spondylosis may develop central cord syndrome. Eventually, muscle atrophy and flaccid paresis may develop in the upper extremities at the level of the lesion, with spasticity below the level of the lesion.

Nerve root compression commonly causes early radicular pain; later there may be weakness, hyporeflexia, and muscle atrophy.

Diagnosis

• MRI or CT

Cervical spondylosis is suspected when characteristic neurologic deficits occur in patients who are elderly, have osteoarthritis, or have radicular pain at the C5 or C6 levels. Diagnosis is by MRI or CT.

Treatment

• For radiculopathy only, NSAIDs and a soft cervical collar

• For cord involvement or refractory radiculopathy, cervical laminectomy

For patients with cord involvement, cervical laminectomy is usually needed; a posterior approach can relieve the compression but leaves anterior compressive osteophytes and may result in spinal instability and kyphosis. Thus, an anterior approach with spinal fusion is generally preferred. Patients with only radiculopathy may try nonsurgical treatment with NSAIDs and a soft cervical collar; if this approach is ineffective, surgical decompression may be required.

Hereditary Spastic Paraparesis

Hereditary spastic paraparesis is a group of rare hereditary disorders characterized by progressive, spinal, nonsegmental, spastic leg paresis, sometimes with intellectual disability, seizures, and other extraspinal deficits.

The genetic basis of hereditary spastic paraparesis varies and, for many forms, is unknown. In all forms, the descending corticospinal tracts and, to a lesser extent, the dorsal columns and spinocerebellar tracts degenerate, sometimes with loss of anterior horn cells. Onset can be at any age, from the first year of life to old age, depending on the specific genetic form.

Symptoms and Signs

Symptoms and signs include spastic leg paresis, with progressive gait difficulty, hyperreflexia, clonus, and extensor plantar responses. Sensation and sphincter function are usually spared. The arms may also be affected. Deficits are not localized to a spinal cord segment. In some forms, patients also have extraspinal neurologic deficits (eg, spinocerebellar and ocular symptoms, extrapyramidal symptoms, optic atrophy, retinal degeneration, intellectual disability, dementia, polyneuropathy).

Diagnosis

• Clinical evaluation

Hereditary spastic paraparesis is suggested by a family history and any signs of spastic paraparesis. Diagnosis is by exclusion of other causes and sometimes by genetic testing.

Treatment

• Drugs to relieve spasticity

Treatment for all forms is symptomatic. Baclofen 10 mg po bid, increased as needed up to 40 mg po bid, is given for spasticity. Alternatives include diazepam, clonazepam, dantrolene, botulinum toxin (botulinum toxin type A or botulinum toxin type B), and tizanidine.

Spinal Cord Infarction

(Ischemic Myelopathy)

Spinal cord infarction usually results from ischemia originating in an extravertebral artery. Symptoms include sudden and severe back pain, bilateral flaccid limb weakness, and loss of sensation, particularly pain and temperature. Diagnosis is by MRI. Treatment is generally supportive.

The primary vascular supply for the posterior third of the spinal cord is the posterior spinal arteries; for the anterior two thirds, it is the anterior spinal arteries. Each of the anterior spinal arteries has only a few feeder arteries in the upper cervical region and one large feeder (the artery of Adamkiewicz) in the lower thoracic region. The feeder arteries originate in the aorta.

Because collateral circulation for the anterior spinal artery is sparse in places, certain cord segments (eg, those around the 2nd to 4th thoracic segments) are especially vulnerable to ischemia. Injury to an extravertebral feeder artery or the aorta (eg, due to atherosclerosis, dissection, or clamping during

surgery) causes infarction more commonly than do intrinsic disorders of spinal arteries. Thrombosis is an uncommon cause, and polyarteritis nodosa is a rare cause.

Symptoms and Signs

Sudden pain in the back with tightness radiating circumferentially is followed by segmental bilateral flaccid weakness and sensory loss. Pain and temperature sensation are disproportionately impaired. The anterior spinal artery is typically affected, resulting in the anterior cord syndrome (see Table 186-2). Position and vibration sensation, conducted by the posterior columns, and often light touch are relatively spared. If the infarct is small and affects primarily tissue farthest away from an occluded artery (toward the center of the cord), central cord syndrome is also possible. Neurologic deficits may partially resolve after the first few days.

Diagnosis

• MRI

Infarction is suspected when severe back pain and characteristic deficits develop suddenly. Diagnosis is by MRI. Acute transverse myelitis, spinal cord compression, and demyelinating disorders may cause similar findings but are usually more gradual and are excluded by MRI and by CSF analysis.

Treatment

• Supportive care

Occasionally, the cause of infarction (eg, aortic dissection, polyarteritis nodosa) can be treated, but often the only possible treatment is supportive.

Spinal Cord Compression

(See also p. 3230 for treatment of spinal trauma.)

Various lesions can compress the spinal cord, causing segmental sensory, motor, reflex, and sphincter deficits. Diagnosis is by MRI. Treatment is directed at relieving compression.

Compression is caused far more commonly by lesions outside the spinal cord (extramedullary) than by lesions within it (intramedullary). Compression may be acute, subacute, or chronic.

Acute compression develops within minutes to hours. It is often due to trauma (eg, vertebral crush fracture with displacement of fracture fragments, disk herniation, metastatic tumor, severe bone or ligamentous injury causing hematoma, vertebral subluxation or dislocation). It is occasionally due to abscess and rarely due to spontaneous epidural hematoma. Acute compression may follow subacute and chronic compression, especially if the cause is abscess or tumor.

Subacute compression develops over days to weeks. It is usually caused by a metastatic extramedullary tumor, a subdural or an epidural abscess or hematoma, or a cervical or, rarely, thoracic herniated disk.

Chronic compression develops over months to years. It is commonly caused by bony protrusions into the cervical, thoracic, or lumbar spinal canal (eg, due to osteophytes or spondylosis, especially when the spinal canal is narrow, as occurs in spinal stenosis—see p. 384). Compression can be aggravated by a herniated disk and hypertrophy of the ligamentum flavum. Less common causes include arteriovenous malformations and slow-growing extramedullary tumors.

Atlantoaxial subluxation (see p. 385) and other craniocervical junction abnormalities (see p. 1757) may cause acute, subacute, or chronic spinal cord compression.

Lesions that compress the spinal cord may also compress nerve roots or, rarely, occlude the spinal cord's blood supply, causing infarction.

Symptoms and Signs

Acute or advanced spinal cord compression causes segmental deficits, paraparesis or quadriparesis, hyperreflexia, extensor plantar responses, loss of sphincter tone (with bowel and bladder dysfunction), and sensory deficits. Subacute or chronic compression may begin with local back pain, often radiating down the distribution of a nerve root (radicular pain), and sometimes hyperreflexia and loss of sensation. Sensory loss may begin in the sacral segments. Complete loss of function may follow suddenly and unpredictably, possibly resulting from secondary spinal cord infarction. Spinal percussion tenderness is prominent if the cause is metastatic carcinoma, abscess, or hematoma.

Intramedullary lesions tend to cause poorly localized burning pain rather than radicular pain and to spare sensation in sacral dermatomes. These lesions usually result in spastic paresis.

Diagnosis

• MRI or CT myelography

Spinal cord compression is suggested by spinal or radicular pain with reflex, motor, or sensory deficits, particularly at a segmental level. MRI is done immediately if available. If MRI is unavailable, CT myelography is done; a small amount of iohexol (a nonionic, low osmolar radiopaque dye) is introduced via a lumbar puncture and allowed to run cranially to check for complete CSF block. If a block is detected, a radiopaque dye is introduced via a cervical puncture to determine the rostral extension of the block. If traumatic bone abnormalities (eg, fracture, dislocation, subluxation) that require immediate spinal immobilization are suspected, plain spinal x-rays can be done. However, CT detects bone abnormalities better.

Treatment

• Relief of compression

Treatment is directed at relieving pressure on the cord. Incomplete or very recent complete loss of function may be reversible, but complete loss of function rarely is; thus, *for acute compression, diagnosis and treatment must occur immediately.*

If compression is due to a tumor, IV dexamethasone 100 mg is given immediately, followed by 25 mg q 6 h and immediate surgery or radiation therapy. Surgery is indicated in the following cases:

• Neurologic deficits worsen despite nonsurgical treatment.

• A biopsy is needed.

• The spine is unstable.

• Tumors recur after radiation therapy.

• An abscess or a compressive subdural or epidural hematoma is suspected.

Spinal Epidural Abscess

A spinal epidural abscess is an accumulation of pus in the epidural space that can mechanically compress the spinal cord.

Spinal epidural abscesses usually occur in the thoracic or lumbar regions. An underlying infection is often present; it may be remote (eg, endocarditis, furuncle, dental abscess) or contiguous (eg, vertebral osteomyelitis, pressure ulcer, retroperitoneal abscess). In about one third of cases, the cause cannot be

determined. The most common causative organism is *Staphylococcus aureus*, followed by *Escherichia coli* and mixed anaerobes. Occasionally, the cause is a tuberculous abscess of the thoracic spine (Pott's disease). Rarely, a similar abscess occurs in the subdural space.

Symptoms and Signs

Symptoms begin with local or radicular back pain and percussion tenderness, which become severe. Fever is common. Spinal cord compression may develop; compression of lumbar spinal roots may cause cauda equina syndrome, with neurologic deficits resembling those of conus medullaris syndrome (eg, leg paresis, saddle anesthesia, bladder and bowel dysfunction). Deficits progress over hours to days.

Diagnosis

• MRI

The diagnosis is suggested by characteristic neurologic deficits and by back pain worsened by recumbency, particularly in patients who have a fever or have had a recent infection. Diagnosis is by MRI; myelography followed by CT can be used if MRI is not available. Samples from blood and infectious areas are cultured. Lumbar puncture is contraindicated because it may trigger cord herniation if the abscess causes complete obstruction of CSF. Plain x-rays are not routinely indicated but may show osteomyelitis in about one third of patients.

Treatment

• Antibiotics

• If abscess causes neurologic compromise, immediate drainage

Antibiotics with or without parenteral needle aspiration may be sufficient; however, abscesses causing neurologic compromise (eg, paresis, bowel or bladder dysfunction) are surgically drained immediately. Pus is gramstained and cultured. Pending culture results, antibiotics to cover staphylococcus and anaerobes are given as for brain abscess (see p. 1726). If the abscess developed after a neurosurgical procedure, an aminoglycoside is added to cover gram-negative bacteria.

Spinal Subdural or Epidural Hematoma

A spinal subdural or epidural hematoma is an accumulation of blood in the subdural or epidural space that can mechanically compress the spinal cord.

Spinal subdural or epidural hematoma (usually thoracic or lumbar) is rare but may result from back trauma, anticoagulant or thrombolytic therapy, or, in patients with bleeding diatheses, lumbar puncture.

Symptoms and Signs

Symptoms begin with local or radicular back pain and percussion tenderness; they are often severe. Spinal cord compression may develop; compression of lumbar spinal roots may cause cauda equina syndrome and lower extremity paresis. Deficits progress over minutes to hours.

Diagnosis

• MRI

Hematoma is suspected in patients with acute, nontraumatic spinal cord compression or sudden, unexplained lower extremity paresis, particularly if a possible cause (eg, trauma, bleeding diathesis) is present. Diagnosis is by MRI or, if MRI is not immediately available, by CT myelography.

Treatment

• Drainage

Treatment is immediate surgical drainage. Patients taking coumarin anticoagulants are given phytonadione (vitamin K_1) 2.5 to 10 mg sc and fresh frozen plasma as needed to normalize INR. Patients with thrombocytopenia are given platelets (see p. 1039).

Syrinx

A syrinx is a fluid-filled cavity within the spinal cord (syringomyelia) or brain stem (syringobulbia). Predisposing factors include craniocervical junction abnormalities, spinal cord trauma, and spinal cord tumors. Symptoms include flaccid weakness of the hands and arms and deficits in pain and temperature sensation in a capelike distribution over the back and neck; light touch and position and vibration sensation are not affected. Diagnosis is by MRI. Treatment includes correction of the cause and surgical procedures to drain the syrinx or otherwise open CSF flow.

Syrinxes usually result from lesions that partially obstruct CSF flow. At least one half of syrinxes occur in patients with congenital abnormalities of the craniocervical junction (eg, herniation of cerebellar tissue into the spinal canal, called Chiari malformation), brain (eg, encephalocele—see p. 2994), or spinal cord (eg, myelomeningocele—see p. 2995). For unknown reasons, these congenital abnormalities often expand during the teen or young adult years. A syrinx can also develop in patients who have a spinal cord tumor, scarring due to previous spinal trauma, or no known predisposing factors. About 30% of people with a spinal cord tumor eventually develop a syrinx.

Syringomyelia is a paramedian, usually irregular, longitudinal cavity. It commonly begins in the cervical area but may extend downward along the entire length of the spinal cord. Syringobulbia, which is rare, usually occurs as a slitlike gap within the lower brain stem and may disrupt or compress the lower cranial nerves or ascending sensory or descending motor pathways.

Symptoms and Signs

Symptoms usually begin insidiously between adolescence and age 45. Syringomyelia develops in the center of the spinal cord, causing a central cord syndrome (see Table 186-2). Pain and temperature sensory deficits occur early but may not be recognized for years. The first abnormality recognized may be a painless burn or cut. Syringomyelia typically causes weakness, atrophy, and often fasciculations and hyporeflexia of the hands and arms; a deficit in pain and temperature sensation in a capelike distribution over the shoulders, arms, and back is characteristic. Light touch and position and vibration sensation are not affected. Later, spastic leg weakness develops. Deficits may be asymmetric.

Syringobulbia may cause vertigo, nystagmus, unilateral or bilateral loss of facial sensation, lingual atrophy and weakness, dysarthria, dysphagia, hoarseness, and sometimes peripheral sensory or motor deficits due to medullary compression.

Diagnosis

• MRI of spinal cord and brain with gadolinium

A syrinx is suggested by an unexplained central cord syndrome or other characteristic neurologic deficits, particularly pain and temperature sensory deficits in a capelike distribution. MRI of the entire spinal cord and brain is done. Gadolinium enhancement is useful for detecting any associated tumor.

Treatment

• Sometimes surgical decompression

Underlying problems (eg, craniocervical junction abnormalities, postoperative scarring, spinal tumors) are corrected when possible. Surgical decompression of the foramen magnum and upper cervical cord is the only useful treatment, but surgery usually cannot reverse severe neurologic deterioration.

Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy

Tropical spastic paraparesis/HTLV-1-associated myelopathy is a slowly progressive viral immunemediated disorder of the spinal cord caused by the human T-lymphotropic virus 1 (HTLV-1). It causes spastic weakness of both legs. Diagnosis is by serologic and PCR tests of serum and CSF. Treatment includes supportive care and possibly immunosuppressive therapies.

The HTLV-1 retrovirus is transmitted via sexual contact, IV drug use, exposure to infected blood, or from mother to child, via breastfeeding. It is most common among prostitutes, IV drug users, hemodialysis patients, and people from endemic areas such as equatorial regions, southern Japan, and parts of South America. HTLV-2 may cause a similar disorder.

The virus resides in T cells in blood and CSF. CD4+ memory T cells, CD8+ cytotoxic T cells, and macrophages infiltrate the perivascular areas and parenchyma of the spinal cord; astrocytosis occurs. For several years after onset of neurologic symptoms, inflammation of spinal gray and white matter progresses, causing preferential degeneration of the lateral and posterior columns. Myelin and axons in the anterior columns are also lost.

Symptoms and Signs

Spastic weakness develops gradually in both legs, with extensor plantar responses and bilateral symmetric loss of position and vibratory sensation in the feet. Achilles tendon reflexes are often absent. Urinary incontinence and urgency are common. Symptoms usually progress over several years.

Diagnosis

• Serologic and PCR tests of serum and CSF

The disorder is suggested by typical neurologic deficits that are otherwise unexplained, particularly in patients with risk factors. Serum and CSF serologic tests, PCR tests, and spinal cord MRI are indicated. If CSF-to-serum ratio of HTLV-1 antibodies is > 1 or if PCR detects HTLV-1 antigen in CSF, the diagnosis is very likely. Protein and Ig levels in CSF may also be elevated, often with oligoclonal bands; lymphocytic pleocytosis occurs in up to 50% of patients. Spinal cord lesions often appear hyperintense on T2-weighted MRI.

Treatment

• Immunomodulatory or immunosuppressive therapies

No treatment has proved effective, but interferon alfa, IV immune globulin, and oral methylprednisolone may have some benefit. Treatment of spasticity is symptomatic (eg, with baclofen or tizanidine).

Chapter 187. Intracranial and Spinal Tumors

Introduction

Intracranial tumors may involve the brain or other structures (eg, cranial nerves, meninges). The tumors usually develop during early or middle adulthood but may develop at any age; they are becoming more common among the elderly. Brain tumors are found in about 2% of routine autopsies.

Some tumors are benign, but because the cranial vault allows no room for expansion, even these tumors can be serious.

Classification

Some primary intracranial tumors (eg, gliomas, medulloblastomas, ependymomas) originate in brain parenchyma; others (eg, meningiomas, acoustic neuromas, other schwannomas) originate in extraneural structures. Extracranial tumors may metastasize to any intracranial structure or to the skull. In the brain, metastases are about 10 times more common than primary tumors.

Type of tumor varies somewhat by site (see Table 187-1) and patient age (see Table 187-2).

Pathophysiology

Neurologic dysfunction may result from the following:

• Invasion and destruction of brain tissue by the tumor

• Direct compression of adjacent tissue by the tumor

• Increased intracranial pressure (because the tumor occupies space within the skull)

• Bleeding within or outside the tumor

• Cerebral edema

• Obstruction of dural venous sinuses (especially by bone or extradural metastatic tumors)

• Obstruction of CSF drainage (occurring early with 3rd-ventricle or posterior fossa tumors)

• Obstruction of CSF absorption (eg, when leukemia or carcinoma involves the meninges)

• Obstruction of arterial flow

• Rarely, paraneoplastic syndromes (see p. 1054)

A malignant tumor can develop new internal blood vessels, which can bleed or become occluded, resulting in necrosis and neurologic dysfunction that mimics stroke.

Benign tumors grow slowly. They may become quite large before causing symptoms, partly because often there is no cerebral edema. Malignant tumors grow rapidly but rarely spread beyond the CNS. Death results from local tumor growth and thus can result from benign as well as malignant tumors. Therefore, distinguishing between benign and malignant

[**Table 187-1.** Common Localizing Manifestations of Brain Tumors]

is prognostically less important for brain tumors than for other tumors.

Symptoms and Signs

Many symptoms result from increased intracranial pressure:

- Headache
- Deterioration in mental status
- Focal brain dysfunction

Headache is the most common symptom. Headache may be most intense when patients awake from deep non-REM sleep (usually several hours after falling asleep) because hypoventilation, which increases cerebral blood flow and thus intracranial pressure, is usually maximal during non-REM sleep. Headache is also progressive and may be worsened by recumbency or the Valsalva maneuver. When intracranial pressure is very high, the headache may be accompanied by vomiting, sometimes with little nausea preceding it. Papilledema develops in about 25% of patients with a brain tumor but may be absent even when intracranial pressure is increased. In infants and very young children, increased intracranial pressure may enlarge the head. If intracranial pressure increases sufficiently, brain herniation occurs (see
Fig. 174-1 on p. 1657).

Deterioration in mental status is the 2nd most common symptom. Manifestations include drowsiness, lethargy, personality changes, disordered conduct, and impaired cognition, particularly with malignant brain tumors. Generalized seizures may occur, more often with primary than metastatic brain

[**Table 187-2.** Common Tumors]

tumors. Impaired consciousness (see p. 1656) can result from herniation, brain stem dysfunction, or diffuse bilateral cortical dysfunction. Airway reflexes may be impaired.

Some symptoms result from focal brain dysfunction. Focal neurologic deficits, endocrine dysfunction, or focal seizures (sometimes with secondary generalization) may develop depending on the tumor's location (see Table 187-1). Focal deficits often suggest the tumor's location. However, sometimes focal deficits do not correspond to the tumor's location. Such deficits, called false localizing signs, include the following:

- Unilateral or bilateral lateral rectus palsy (with paresis of eye abduction) due to increased intracranial pressure compressing the 6th cranial nerve
- Ipsilateral hemiplegia due to compression of the contralateral cerebral peduncle against the tentorium (Kernohan's notch)
- Ipsilateral visual field defect due to ischemia in the contralateral occipital lobe

Some tumors cause meningeal inflammation, resulting in subacute or chronic meningitis (see p. 1734).

Diagnosis

- T1-weighted MRI with gadolinium or CT with contrast

Early-stage brain tumors are often misdiagnosed. A brain tumor should be considered in patients with any of the following:

- Progressive focal or global deficits of brain function
- New seizures
- Persistent, unexplained, recent-onset headaches, particularly if worsened by sleep

• Evidence of increased intracranial pressure (eg, papilledema, unexplained vomiting)

• Pituitary or hypothalamic endocrinopathy

Similar findings can result from other intracranial masses (eg, abscess, aneurysm, arteriovenous malformation, intracerebral hemorrhage, subdural hematoma, granuloma, parasitic cysts such as neurocysticercosis) or ischemic stroke.

A complete neurologic examination, neuroimaging, and chest x-rays (for a source of metastases) should be done. T1-weighted MRI with gadolinium is the study of choice. CT with contrast agent is an alternative. MRI usually detects low-grade astrocytomas and oligodendrogliomas earlier than CT and shows brain structures near bone (eg, the posterior fossa) more clearly. If whole-brain imaging does not show sufficient detail in the target area (eg, sella turcica, cerebellopontine angle, optic nerve), closely spaced images or other special views of the area are obtained. If neuroimaging is normal but increased intracranial pressure is suspected, idiopathic intracranial hypertension (see p. 1720) should be considered and lumbar puncture done.

Radiographic clues to the type of tumor, mainly location (see Table 187-1) and pattern of enhancement on MRI, may be inconclusive; brain biopsy, sometimes excisional biopsy, may be required. Specialized tests (eg, molecular and genetic tumor markers in blood and CSF) can help in some cases; eg, in patients with AIDS, Epstein-Barr virus titers in CSF typically increase as CNS lymphoma develops.

Treatment

• Airway protection

• Dexamethasone for increased intracranial pressure

• Mannitol for herniation

• Definitive therapy with excision, radiation therapy, chemotherapy, or a combination

Patients in a coma or with impaired airway reflexes require endotracheal intubation. Brain herniation due to tumors is treated with mannitol 25 to 100 g infused IV, a corticosteroid (eg, dexamethasone 16 mg IV, followed by 4 mg po or IV q 6 h), and endotracheal intubation. Mass lesions should be surgically decompressed as soon as possible.

Increased intracranial pressure due to tumors but without herniation is treated with corticosteroids (eg, dexamethasone as for herniation above or prednisone 30 to 40 mg po bid).

Treatment of the brain tumor depends on pathology and location (for acoustic neuroma, see p. 441). Surgical excision should be used for diagnosis (excisional biopsy) and symptom relief. It may cure benign tumors. For tumors infiltrating the brain parenchyma, treatment is multimodal. Radiation therapy is required, and chemotherapy appears to benefit some patients.

Treatment of metastatic tumors includes radiation therapy and sometimes stereotactic radiosurgery. For patients with a solitary metastasis, surgical excision of the tumor before radiation therapy improves outcome.

End-of-life issues: If brain tumors are expected to soon be fatal, end-of-life issues should be considered (see p. 3480).

Radiation Therapy and Neurotoxicity

Radiation therapy may be directed diffusely to the whole head for diffuse or multicentric tumors or locally for well-demarcated tumors. Localized brain radiation therapy may be conformal, targeting the tumor with the aim of sparing normal brain tissue, or stereotactic, involving brachytherapy, a gamma knife, or a linear

accelerator. In brachytherapy, radioactive stable iodine ($^{125}I_3$) or iridium-192 ($^{192}Ir_4$) is implanted in or near the tumor. Gliomas are treated with conformal radiation therapy; a gamma knife or linear accelerator is useful for metastases. Giving radiation daily tends to maximize efficacy and minimize neurotoxicity damage to normal CNS tissue (see p. 3255).

Degree of neurotoxicity depends on

• Cumulative radiation dose

• Individual dose size

• Duration of therapy

• Volume of tissue irradiated

• Individual susceptibility

Because susceptibility varies, prediction of radiation neurotoxicity is imprecise. Symptoms can develop in the first few days (acute) or months of treatment (early-delayed) or several months to years after treatment (late-delayed). Rarely, radiation causes gliomas, meningiomas, or peripheral nerve sheath tumors years after therapy.

Acute radiation neurotoxicity: Typically, acute neurotoxicity involves headache, nausea, vomiting, somnolence, and sometimes worsening focal neurologic signs in children and adults. It is particularly likely if intracranial pressure is high. Using corticosteroids to lower intracranial pressure can prevent or treat acute toxicity. Acute toxicity lessens with subsequent treatments.

Early-delayed neurotoxicity: In children or adults, early-delayed neurotoxicity can cause encephalopathy, which must be distinguished by MRI or CT from worsening or recurrent brain tumor. It occurs in children who have received prophylactic whole-brain radiation therapy for leukemia; they develop somnolence, which lessens spontaneously over several days to weeks, possibly more rapidly if corticosteroids are used.

After radiation therapy to the neck or upper thorax, early-delayed neurotoxicity can result in a myelopathy, characterized by Lhermitte's sign (an electric shock-like sensation radiating down the back and into the legs when the neck is flexed). The myelopathy resolves spontaneously.

Late-delayed neurotoxicity: After diffuse brain radiation therapy, many children and adults develop late-delayed neurotoxicity if they survive long enough. The most common cause in children is diffuse therapy given to prevent leukemia or to treat medulloblastoma. After diffuse therapy, the main symptom is progressive dementia; adults also develop an unsteady gait. MRI or CT shows cerebral atrophy.

After localized therapy, neurotoxicity more often involves focal neurologic deficits. MRI or CT shows a mass that may be enhanced by contrast agent and that may be difficult to distinguish from recurrence of the primary tumor. Excisional biopsy of the mass is diagnostic and often ameliorates symptoms.

Late-delayed myelopathy can develop after radiation therapy for extraspinal tumors (eg, due to Hodgkin lymphoma). It is characterized by progressive paresis and sensory loss, often as a Brown-Sequard syndrome (ipsilateral paresis and proprioceptive sensory loss, with contralateral loss of pain and temperature sensation). Most patients eventually become paraplegic.

Gliomas

Gliomas are primary tumors that originate in brain parenchyma. Symptoms and diagnosis are similar to those of other brain tumors. Treatment involves surgical excision, radiation therapy, and, for some tumors, chemotherapy. Excision rarely cures.

Gliomas include astrocytomas, oligodendrogliomas, medulloblastomas, and ependymomas. Many gliomas infiltrate brain tissue diffusely and irregularly.

Astrocytomas are the most common gliomas. They are classified, in ascending order of malignancy, as

• Grade 1 or 2: Low-grade astrocytomas

• Grade 3: Anaplastic astrocytomas

• Grade 4: Glioblastomas, including glioblastoma multiforme, the most malignant

Low-grade or anaplastic astrocytomas tend to develop in younger patients and can evolve into glioblastomas (secondary glioblastomas). Glioblastomas contain chromosomally heterogeneous cells. They can develop de novo (primary glioblastomas), usually in middle-aged or elderly people. Primary and secondary glioblastomas have distinct genetic characteristics, which can change as the tumors evolve. Some astrocytomas contain oligodendroglioma cells; patients with these tumors (called oligoastrocytomas) have a better prognosis than those with pure astrocytomas.

Oligodendrogliomas are among the most benign gliomas. They affect mainly the cerebral cortex, particularly the frontal lobes. Some oligodendrogliomas are characterized by deletion of the p arm of chromosome 1(1p deletion), deletion of the q arm of chromosome 19 (19q deletion), or both. These deletions predict longer survival and better response to radiation therapy and chemotherapy. Anaplastic oligodendrogliomas are a more malignant form of oligodendrogliomas and are managed accordingly.

Medulloblastomas and **ependymomas** usually develop near the 4th ventricle. Medulloblastomas develop mainly in children and young adults. Ependymomas, which are uncommon, develop mainly in children. Both types of tumors predispose to obstructive hydrocephalus.

Symptoms and signs vary by location (see Table 187-1). Diagnosis is the same as that of other brain tumors.

Treatment

• Surgical excision

• Radiation therapy

• Chemotherapy for some types

Anaplastic astrocytomas and glioblastomas: Treatment involves surgery, radiation therapy, and chemotherapy to reduce tumor mass. Excising as much tumor as possible is safe, prolongs survival, and improves neurologic function.

After surgery, patients receive a full tumor dose of radiation therapy (60 Gy over 6 wk); ideally, conformal radiation therapy, which targets the tumor and spares normal brain tissue, is used.

For glioblastomas, chemotherapy with temozolomide is now routinely given with radiation therapy. The dose is 75/mg/m^2/day (including weekend days when radiation is skipped) for 42 days, then 150 mg/m^2 po once/day for 5 days/mo during the next month, followed by 200 mg/m^2 po once/day for 5 days/mo in subsequent months for a total of 6 to 12 mo. During treatment with temozolomide, trimethoprim/sulfamethoxazole 800 mg/160 mg is given 3 times/wk to prevent *Pneumocystis jirovecii* pneumonia.

Patients receiving chemotherapy require a CBC at varying intervals. Implantation of chemotherapy wafers during surgical resection may be appropriate for some patients.

Investigational therapies (eg, stereotactic radiosurgery, new chemotherapeutic drugs, gene or immune

therapy, radiation therapy plus temozolomide) should also be considered.

After conventional multimodal treatment, the survival rate for patients with anaplastic astrocytomas or glioblastomas is about 50% at 1 yr, 25% at 2 yr, and 10 to 15% at 5 yr. Prognosis is better in the following cases:

• Patients are < 45 yr

• Histology is anaplastic astrocytoma (rather than glioblastoma multiforme)

• Initial excision improves neurologic function and leaves minimal or no residual tumor

Low-grade astrocytomas: These tumors are excised if possible, followed by radiation therapy. When radiation therapy should begin is controversial. Early treatment may maximize efficacy but may cause brain damage earlier.

With treatment, 5-yr survival rate is about 40 to 50%.

Oligodendrogliomas: Treatment involves excision and radiation therapy, similar to low-grade astrocytomas. Chemotherapy is sometimes also used.

With treatment, 5-yr survival rate is about 50 to 60%.

Medulloblastomas: Treatment involves whole-brain radiation therapy using about 35 Gy, a posterior fossa boost using 15 Gy, and spinal cord radiation therapy using about 35 Gy. Chemotherapy may be given as adjunctive therapy and for recurrences. Several drugs are effective for certain patients; these drugs include nitrosoureas, procarbazine, vincristine alone or in combination, intrathecal methotrexate, combination chemotherapy (eg, mechlorethamine, vincristine [Oncovin], procarbazine, plus prednisone [MOPP]), cisplatin, and carboplatin. However, no regimen is consistently effective.

With treatment, survival rates are at least 50% at 5 yr and about 40% at 10 yr.

Ependymomas: Usually, surgery to excise the tumor and open CSF pathways is done, followed by radiation therapy. For histologically benign ependymomas, radiation therapy is directed at the tumor; for more malignant tumors with residual tumor after surgery, whole-brain radiation therapy is used. For tumors with evidence of dissemination, radiation therapy is directed at the whole brain and spinal cord.

How much of the tumor can be excised may predict survival best. With treatment, overall 5-yr survival rate is about 50%; however, for patients with no residual tumor, the 5-yr survival rate is > 70%.

Meningiomas

Meningiomas are benign tumors of the meninges that can compress adjacent brain tissue. Symptoms depend on the tumor's location. Diagnosis is by MRI with contrast agent. Treatment may include excision, stereotactic radiosurgery, and sometimes radiation therapy.

Meningiomas, particularly those < 2 cm in diameter, are among the most common intracranial tumors. Meningiomas are the only brain tumor more common among women. These tumors tend to occur between ages 40 and 60 but can occur during childhood. These benign tumors can develop wherever there is dura, most commonly over the convexities near the venous sinuses, along the base of the skull, in the posterior fossa, and rarely within ventricles. Multiple meningiomas may develop. Meningiomas compress but do not invade brain parenchyma. They can invade and distort adjacent bone. There are many histologic types; all follow a similar clinical course, and some become malignant.

Symptoms and Signs

Symptoms depend on which part of the brain is compressed and thus on the tumor's location (see Table 187-3). Midline tumors in the elderly can cause dementia with few other focal neurologic findings.

Diagnosis

• MRI

Diagnosis is similar to that of other brain tumors, usually by MRI with a paramagnetic contrast agent. Bone abnormalities (eg, brain atrophy, hyperostosis around the cerebral convexities, changes in the tuberculum sellae) may be seen incidentally on CT or plain x-rays.

Treatment

• For symptomatic or enlarging meningiomas, excision or radiation therapy

For asymptomatic small meningiomas, particularly in older adults, monitoring with serial neuroimaging is sufficient.

Symptomatic or enlarging meningiomas should be excised if possible. If they are large, encroach on blood vessels (usually surrounding

[Table 187-3. Symptoms of Meningiomas by Site]

veins), or are close to critical brain areas (eg, brain stem), surgery may cause more damage than the tumor and is thus deferred.

Stereotactic radiosurgery is used for surgically inaccessible meningiomas and electively for other meningiomas. It is also used when tumor tissue remains after surgical excision or when patients are elderly.

If stereotactic radiosurgery is impossible or if a meningioma recurs, radiation therapy may be useful.

Pineal Region Tumors

Most pineal region tumors are germ cell tumors.

Common primary pineal region tumors include germ cell tumors: germinomas (most common), choriocarcinomas, yolk-sac tumors, and teratomas. Less common primary pineal tumors include pineocytomas and the rare malignant pineoblastomas.

Pineal region tumors tend to occur during childhood but can occur at any age.

These tumors may increase intracranial pressure by compressing the aqueduct of Sylvius. They may also cause paresis of upward gaze, ptosis, and loss of pupillary light and accommodation reflexes by compressing the pretectum rostral to the superior colliculi (Parinaud's syndrome). These tumors may cause precocious puberty, especially in boys, probably because the hypothalamus is compressed.

CSF β-human chorionic gonadotropin or α-fetoprotein may be elevated, depending on the tumor type. Elevated levels suggest the diagnosis; levels may be measured to monitor response to treatment.

Prognosis and treatment depend on tumor histology. Radiation therapy, chemotherapy, radiosurgery, and surgery are used alone or in combination. Germinomas are very sensitive to radiation therapy and are often cured.

Pituitary Tumors

Most pituitary tumors are adenomas. Symptoms include headache and endocrinopathies; endocrinopathies result when the tumor produces hormones or destroys hormone-producing tissue. Diagnosis is by MRI. Treatment includes correction of any endocrinopathy and surgery, radiation therapy, or dopaminergic agonists.

Most tumors of the pituitary and suprasellar region are pituitary adenomas. Rarely, pituitary tumors are carcinomas. Meningiomas, craniopharyngiomas, metastases, and dermoid cysts may also develop in the region of the sella turcica.

Adenomas may be secretory or nonsecretory. Secretory adenomas produce pituitary hormones; many secretory adenomas are < 10 mm in size (microadenomas). Secretory adenomas can be classified by histologic staining characteristics (eg, acidophilic, basophilic, chromophobe [nonstaining]). The hormone produced often correlates with these characteristics; eg, acidophilic adenomas overproduce growth hormone, and basophilic adenomas overproduce ACTH. The hormone most commonly overproduced is prolactin.

Any tumor that grows out of the pituitary can compress optic nerve tracts, including the chiasm. Tumors may also compress or destroy pituitary or hypothalamic tissue, impairing hormone production or secretion.

Symptoms and Signs

Headache may result from an enlarging pituitary adenoma, even when intracranial pressure is not increased. Visual manifestations such as bitemporal hemianopia, unilateral optic atrophy, and contralateral hemianopia may develop if a tumor compresses optic nerve tracts (see Fig. 69-1 on p. 620).

Many patients present with an endocrinopathy due to hormone deficiency or excess:

- Diabetes insipidus if less vasopressin is released because the hypothalamus is compressed
- Amenorrhea and galactorrhea in women and, less commonly, erectile dysfunction and gynecomastia in men if prolactin is overproduced
- Gigantism before puberty or acromegaly after puberty if growth hormone is overproduced
- Cushing's syndrome if ACTH is overproduced

Rarely, hemorrhage into a pituitary tumor causes pituitary apoplexy, with sudden headache, ophthalmoplegia, and visual loss.

Diagnosis

- MRI with 1-mm slices

Pituitary tumors are suspected in patients with unexplained headaches, characteristic visual abnormalities, or endocrinopathies. Neuroimaging with 1-mm thick slices is done. MRI is usually much more sensitive than CT, particularly for microadenomas.

Treatment

Endocrinopathies are treated.

Pituitary tumors that produce ACTH, growth hormone, or thyroid-stimulating hormone are surgically excised, usually using a transsphenoidal approach. Sometimes, particularly for surgically inaccessible or multifocal tumors, radiation therapy is required.

Adenomas that produce prolactin are treated with dopaminergic agonists (eg, bromocriptine, pergolide, cabergoline), which lower blood levels and often shrink the tumor. Surgery and radiation therapy are usually unnecessary.

Primary Brain Lymphomas

Primary brain lymphomas originate in neural tissue and are usually B-cell tumors. Diagnosis requires neuroimaging and sometimes CSF analysis (including Epstein-Barr titers) or brain biopsy. Treatment includes corticosteroids, chemotherapy, and radiation therapy.

Incidence of primary brain lymphomas is increasing, particularly among immunocompromised patients and the elderly. Lymphomas tend to infiltrate the brain diffusely, often as multicentric masses adjacent to the ventricles, but may occur as solitary brain masses. Lymphomas may also occur in the meninges, uvea, or vitreous humor. Most are B-cell tumors, often immunoblastic. The Epstein-Barr virus may contribute to development of lymphomas in immunocompromised patients. Most patients do not develop subsequent systemic lymphoma.

Diagnosis

• MRI

• Sometimes CSF analysis or biopsy

MRI can suggest the diagnosis. MRI may be unable to distinguish cerebral toxoplasmosis, which is common among patients with AIDS, from lymphoma.

If there are meningeal signs, CSF is examined; it may contain lymphoma cells. In immunocompromised patients, Epstein-Barr virus DNA may be detected in CSF. If CSF does not contain lymphoma cells or Epstein-Barr virus DNA, guided-needle or open biopsy is required. Because lymphoma is initially highly sensitive to corticosteroids, giving these drugs just before biopsy may cause the lesion to disappear, resulting in a false-negative biopsy.

Treatment

• Corticosteroids

• Chemotherapy

• Radiation therapy

Most primary brain lymphomas are difficult to cure because they infiltrate the brain diffusely. Usually, corticosteroids result in rapid improvement initially. Many chemotherapy regimens, particularly those containing methotrexate (delivered as high-dose IV infusions), are effective; with methotrexate, median survival may approach 4 yr. Methotrexate can also be delivered intrathecally, usually via an sc intraventricular device (Ommaya reservoir). The drug is sometimes infused into the carotid artery after general anesthesia is induced and 25% mannitol is given IV to open the bloodbrain barrier.

Chemotherapy regimens may be followed by radiation therapy, usually after 12 to 16 wk but sometimes delayed until the tumor recurs. The delay helps reduce radiation toxicity.

Spinal Cord Tumors

Spinal cord tumors may develop within the spinal cord parenchyma, directly destroying tissue, or outside the cord parenchyma, often compressing the cord or nerve roots. Symptoms include progressive back pain and neurologic deficits referable to the spinal cord or spinal nerve roots. Diagnosis is by MRI. Treatment may include corticosteroids, surgical excision, and radiation therapy.

Spinal cord tumors may be intramedullary (within the cord parenchyma) or extramedullary (outside the parenchyma).

Intramedullary tumors: The most common are gliomas (eg, ependymomas, low-grade astrocytomas). Intramedullary tumors infiltrate and destroy cord parenchyma; they may extend over multiple spinal cord segments or result in a syrinx (see p. 1812).

Extramedullary tumors: These tumors may be intradural or extradural. Most intradural tumors are benign, usually meningiomas and neurofibromas, which are the most common primary spinal tumors. Most extradural tumors are metastatic, usually from carcinomas of the lungs, breasts, prostate, kidneys, or thyroid or from lymphoma (eg, Hodgkin lymphoma, lymphosarcoma, reticulum cell sarcoma).

Intradural and extradural tumors cause neurologic damage by compressing the spinal cord or nerve roots. Most extradural tumors invade and destroy bone before compressing the cord.

Symptoms and Signs

Pain is an early symptom, especially for extradural tumors. It is progressive, unrelated to activity, and worsened by recumbency. Pain may occur in the back, radiate along the sensory distribution of a particular dermatome (radicular pain), or both. Usually, neurologic deficits referable to the spinal cord eventually develop. Common examples are spastic weakness, incontinence, and dysfunction of some or all of the sensory tracts at a particular segment of the spinal cord and below. Deficits are usually bilateral.

Many patients with extramedullary tumors present with pain, but some present with sensory deficits of the distal lower extremities, segmental neurologic deficits, symptoms of spinal cord compression, or a combination. Symptoms of spinal cord compression can worsen rapidly and result in paraplegia and loss of bowel and bladder control. Symptoms of nerve root compression are also common; they include pain and paresthesias followed by sensory loss, muscular weakness, and, if compression is chronic, muscle wasting, which occurs along the distribution of the affected roots.

Diagnosis

• MRI

Patients with segmental neurologic deficits or suspected spinal cord compression require emergency diagnosis and treatment.

The following suggest spinal tumors:

• Progressive, unexplained, or nocturnal back or radicular pain

• Segmental neurologic deficits

• Unexplained neurologic deficits referable to the spinal cord or nerve roots

• Unexplained back pain in patients with primary tumors of the lungs, breasts, prostate, kidneys, or thyroid or with lymphoma

Diagnosis is by MRI of the affected area of the spinal cord. CT with myelography is an alternative but is less accurate.

If MRI does not show a spinal cord tumor, clinicians consider other spinal masses (eg, abscesses, arteriovenous malformations—see p. 1808) and paravertebral tumors. Spinal x-rays, taken for other reasons, may show bone destruction, widening of the vertebral pedicles, or distortion of paraspinal tissues, especially if the tumor is metastatic.

Treatment

• Corticosteroids

• Excision, radiation therapy, or both

For patients with neurologic deficits, corticosteroids (eg, dexamethasone 50 mg IV, then 10 mg po qid) are begun immediately to reduce spinal cord edema and preserve function. Tumors compressing the spinal

cord are treated as soon as possible.

Some well-localized primary spinal cord tumors can be excised surgically. Deficits resolve in about half of these patients. If tumors cannot be surgically excised, radiation therapy is used, with or without surgical decompression. Compressive metastatic extradural tumors are usually surgically excised from the vertebral body, then treated with radiation therapy. Noncompressive metastatic extradural tumors may be treated with radiation therapy alone but may require excision if radiation therapy is ineffective.