volved by intramedullary lesions such as tumor, poliomyelitis, or most often motor neuron disease. Lesions of the basal meninges and the occipital bones (platybasia, invagination of occipital condyles, Paget's disease) may compress the nerve in its extramedullary course or in the hypoglossal canal. Isolated lesions of unknown cause can occur. Atrophy and fasciculation of the tongue develop weeks to months after interruption of the nerve.

MULTIPLE CRANIAL NERVE PALSIES

Several cranial nerves may be affected by the same disease process. In this situation, the main clinical problem is to determine whether the lesion lies within the brainstem or outside it. Lesions that lie on the surface of the brainstem are characterized by involvement of adjacent cranial nerves (often occurring in succession) and late and rather slight involvement of the long sensory and motor pathways and segmental structures lying within the brainstem. The opposite is true of primary lesions within the brainstem. The extramedullary lesion is more likely to cause bone erosion or enlargement of the foramens of exit of cranial nerves. The intramedullary lesion involving cranial nerves often produces a crossed sensory or motor paralysis (cranial nerve signs on one side of the body and tract signs on the opposite side).

Involvement of multiple cranial nerves outside the brainstem is frequently the result of diabetes or trauma, localized infections such as herpes zoster, infectious and noninfectious (especially carcinomatous) causes of meningitis (Chaps. 376 and 377), granulomatous diseases such as Wegener's granulomatosis, Behçet's disease, enlarging saccular aneurysms, or tumors. Among the tumors, nasopharyngeal cancers, lymphomas, neurofibromas, meningiomas, chordomas, cholesteatomas, carcinomas, and sarcomas have all been observed to involve a succession of lower cranial nerves. Owing to their anatomic relationships, the multiple cranial nerve palsies form a number of distinctive syndromes, listed in Table 371-2. Sarcoidosis is the cause of some cases of multiple cranial neuropathy, and chronic glandular tuberculosis the cause of a few others. Platybasia, basilar invagination of the skull, and the adult Chiari malformation are additional causes. A purely motor disorder without atrophy always raises the question of myasthenia gravis (Chap. 381). As noted above, Guillain-Barré syndrome commonly affects the facial nerves bilaterally. In the Fisher variant of the Guillain-Barré syndrome, oculomotor paresis occurs with ataxia and areflexia in the limbs (Chap. 380). Wernicke encephalopathy can cause a severe ophthalmoplegia combined with other brainstem signs.

The *cavernous sinus syndrome* (Fig. 371-4) is a distinctive and frequently life-threatening disorder. It often presents as orbital or facial pain; orbital swelling and chemosis due to occlusion of the ophthalmic veins; fever; oculomotor neuropathy affecting the third, fourth, and sixth cranial nerves; and trigeminal neuropathy affecting the ophthalmic (V_1) and occasionally the maxillary (V_2) divisions of the trigeminal nerve. Cavernous sinus thrombosis, often secondary to infection from orbital cellulitis (frequently *Staphylococcus aureus*), a cutaneous source on the face, or sinusitis (especially with mucormycosis in diabetic patients), is the most frequent cause; other etiologies include aneurysm of the carotid artery, a carotid-cavernous fistula (orbital bruit may be present), meningioma, nasopharyngeal carcinoma, other tumors, or an idiopathic granulomatous disorder (Tolosa-Hunt syndrome). The two cavernous sinuses directly communicate via intercavernous channels; thus, involvement on one side may extend to become bilateral. Early diagnosis is essential, especially when due to infection, and treatment depends on the underlying etiology. In infectious cases, prompt administration of broad-spectrum antibiotics, drainage of any abscess cavities, and identification of the offending organism are essential. Anticoagulant therapy may benefit cases of primary thrombosis. Repair or occlusion of the carotid artery may be required for treatment of fistulas or aneurysms. The Tolosa-Hunt syndrome generally responds to glucocorticoids. A dramatic improvement in pain is usually evident within a few days; oral prednisone (60 mg daily) is usually continued for several weeks and then gradually tapered.

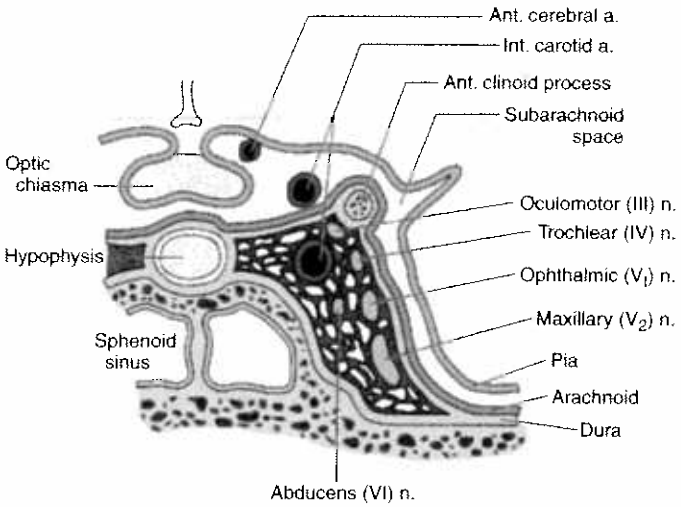

FIGURE 371-4 Anatomy of the cavernous sinus in coronal section, illustrating the location of the cranial nerves in relation to the vascular sinus, internal carotid artery (which loops anteriorly to the section), and surrounding structures.

An idiopathic form of multiple cranial nerve involvement on one or both sides of the face is occasionally seen. The syndrome consists of a subacute onset of boring facial pain, followed by paralysis of motor cranial nerves. The clinical features overlap those of the Tolosa-Hunt syndrome and appear to be due to idiopathic inflammation of the dura mater, which may be visualized by MRI. The syndrome is frequently responsive to glucocorticoids.

ACKNOWLEDGMENT

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372 Diseases of the Spinal Cord

Stephen L. Hauser, Allan H. Ropper

Diseases of the spinal cord are frequently devastating. They produce quadriplegia, paraplegia, and sensory deficits far beyond the damage they would inflict elsewhere in the nervous system because the spinal cord contains, in a small cross-sectional area, almost the entire motor output and sensory input of the trunk and limbs. Many spinal cord diseases are reversible if recognized and treated at an early stage (Table 372-1); thus, they are among the most critical of neurologic emergencies. The efficient use of diagnostic procedures, guided by knowledge of the anatomy and the clinical features of spinal cord diseases, is required for a successful outcome.

APPROACH TO THE PATIENT: Spinal Cord Disease

SPINAL CORD ANATOMY RELEVANT TO CLINICAL SIGNS The spinal cord is a thin, tubular extension of the central nervous system contained within the bony spinal canal. It originates at the medulla and continues caudally to the conus medullaris at the lumbar level; its fibrous extension, the filum terminale, terminates at the coccyx. The adult spinal cord is ~46 cm (18 in.) long, oval in shape, and enlarged in the cervical and lumbar regions, where neurons that innervate the upper and lower extremities, respectively, are located. The white matter tracts containing ascending sensory and descending motor pathways are located peripherally, whereas nerve cell bodies are clustered in an inner region shaped like a four-leaf clover that surrounds the central canal (anatomically an extension of the fourth ventricle). The membranes that cover the spinal cord—the pia, arachnoid, and dura—are continuous with those of the brain.

The spinal cord has 31 segments, each defined by an exiting ventral motor root and entering dorsal sensory root. During embryologic development, growth of the cord lags behind that of the vertebral column, and the mature spinal cord ends at approximately the first lumbar vertebral body. The lower spinal nerves take an increasingly downward course to exit via intervertebral foramina. The first seven pairs of cervical spinal nerves exit above the same-numbered vertebral bodies, whereas all the subsequent nerves exit below the same-numbered vertebral bodies because of the presence of eight cervical spinal cord segments but only seven cervical vertebrae. The relationship between spinal cord segments and the corresponding vertebral bodies is shown in Table 372-2. These relationships assume particular importance for localization of lesions that cause spinal cord compression. A T10 spinal cord sensory level, for example, indicates involvement of the cord adjacent to the seventh or eighth thoracic vertebral body (Figs. 25-2 and 25-3). In addition, at every level the main ascending and descending tracts are somatotopically organized with a laminated distribution that reflects the origin or destination of nerve fibers.

Determining the Level of the Lesion The presence of a horizontally defined level below which sensory, motor, and autonomic function is impaired is a hallmark of spinal cord disease. This *sensory level* is sought by asking the patient to identify a pinprick or cold stimulus (e.g., a dry tuning fork after immersion in cold water) applied to the proximal legs and lower trunk and sequentially moved up toward the neck on each side. The sensory level indicates damage to the spinothalamic tract one to two segments above the perceived level of a unilateral spinal cord lesion and at the level of a bilateral lesion. That is the result of the ascent of second-order sensory fibers, which originate in the dorsal horn, proceed to cross anterior to the central canal while ascending to join the opposite spinothalamic tract. Lesions that transect the descending corticospinal and other motor tracts cause paraplegia or quadriplegia, with the evolution over time of increased muscle tone, heightened deep tendon reflexes, and Babinski signs (the upper motor neuron syndrome). Such lesions also typically produce autonomic disturbances consisting of absent sweating below the implicated cord level and bladder, bowel, and sexual dysfunction.

The uppermost level of a spinal cord lesion can also be localized by attention to the *segmental signs* corresponding to disturbed motor or sensory innervation by an individual cord segment. A band of altered sensation (hyperalgesia or hyperpathia) at the upper end of the sensory disturbance, fasciculations or atrophy in muscles innervated by one or several segments, or a muted or absent deep tendon reflex may be noted at this level. These signs also occur with focal root or peripheral nerve disorders; thus, segmental signs are most useful when they occur together with signs of long tract damage. With severe and acute transverse lesions, the limbs initially may be flaccid rather than spastic. This state of "spinal shock" lasts for several days, rarely for weeks, and should not be mistaken for extensive damage to many segments of the cord or for an acute polyneuropathy.

The main features of transverse damage at each level of the spinal cord are summarized below.

Cervical Cord Upper cervical cord lesions produce quadriplegia and weakness of the diaphragm. Lesions at C4-C5 produce quadriplegia; at C5-C6, there is loss of power and reflexes in the biceps; at C7 weakness is found only in finger and wrist extensors and triceps; and at C8, finger and wrist flexion are impaired. Horner's syndrome (miosis, ptosis, and facial hypohidrosis) may accompany a cervical cord lesion at any level.

TABLE 372-1 TREATABLE SPINAL CORD DISORDERS

- Compressive
  - Epidural, intradural, or intramedullary neoplasm
  - Epidural abscess
  - Epidural hemorrhage
  - Cervical spondylosis
  - Herniated disc
  - Posttraumatic compression by fractured or displaced vertebra or hemorrhage
- Vascular
  - Arteriovenous malformation
  - Antiphospholipid syndrome and other hypercoagulable states
- Inflammatory
  - Multiple sclerosis
  - Neuromyelitis optica
  - Transverse myelitis
  - Sarcoidosis
  - Vasculitis
- Infectious
  - Viral: VZV, HSV-1 and -2, CMV, HIV, HTLV-I, others
  - Bacterial and mycobacterial: *Borrelia*, *Listeria*, syphilis, others
  - *Mycoplasma pneumoniae*
  - Parasitic: schistosomiasis, toxoplasmosis
- Developmental
  - Syringomyelia
  - Meningomyelocoele
  - Tethered cord syndrome
- Metabolic
  - Vitamin B_{12} deficiency (subacute combined degeneration)
  - Copper deficiency

Note: VZV, varicella-zoster virus; HSV, herpes simplex virus; CMV, cytomegalovirus; HTLV, human T cell lymphotropic virus.

TABLE 372-2 SPINAL CORD LEVELS RELATIVE TO THE VERTEBRAL BODIES

Spinal Cord Level	Corresponding Vertebral Body
Upper cervical	Same as cord level
Lower cervical	1 level higher
Upper thoracic	2 levels higher
Lower thoracic	2 to 3 levels higher
Lumbar	T10-T12
Sacral	T12-L1

Thoracic Cord Lesions here are localized by the sensory level on the trunk and by the site of midline back pain if it accompanies the syndrome. Useful markers for localization are the nipples (T4) and umbilicus (T10). Leg weakness and disturbances of bladder and bowel function accompany the paralysis. Lesions at T9-T10 paralyze the lower—but not the upper—abdominal muscles, resulting in upward movement of the umbilicus when the abdominal wall contracts (*Beevor's sign*).

Lumbar Cord Lesions at the L2-L4 spinal cord levels paralyze flexion and adduction of the thigh, weaken leg extension at the knee, and abolish the patellar reflex. Lesions at L5-S1 paralyze only movements of the foot and ankle, flexion at the knee, and extension of the thigh, and abolish the ankle jerks (S1).

Sacral Cord/Conus Medullaris The conus medullaris is the tapered caudal termination of the spinal cord, comprising the lower sacral and single coccygeal segments. The conus syndrome is distinctive, consisting of bilateral saddle anesthesia (S3-S5), prominent bladder and bowel dysfunction (urinary retention and incontinence with lax anal tone), and impotence. The bulbocavernosus (S2-S4) and anal (S4-S5) reflexes are absent (Chap. 361). Muscle strength is largely preserved. By contrast, lesions of the cauda equina, the cluster of nerve roots derived from the lower cord, are characterized by low back and radicular pain, asymmetric leg weakness and sensory loss, variable areflexia in the lower extremities, and relative sparing of bowel and bladder function. Mass lesions in the lower spinal canal often produce a mixed clinical picture in which elements of both cauda equina and conus medullaris syndromes coexist. Cauda equina syndromes are also discussed in Chap. 16.

Special Patterns of Spinal Cord Disease The location of the major ascending and descending pathways of the spinal cord are shown in Fig. 372-1. Most fiber tracts—including the posterior columns and the spinocerebellar and pyramidal tracts—are situated on the side of the body they innervate. However, afferent fibers mediating pain and temperature sensation ascend in the spinothalamic tract contralateral to the side they supply. The anatomic configurations of these tracts produce characteristic syndromes that provide clues to the underlying disease process.

Brown-Sequard Hemicord Syndrome This consists of ipsilateral weakness (corticospinal tract) and loss of joint position and vibratory sense (posterior column), with contralateral loss of pain and temperature sense (spinothalamic tract) one or two levels below the lesion. Segmental signs, such as radicular pain, muscle atrophy, or loss of a deep tendon reflex, are unilateral. This classical pattern is rare, and partial forms are more commonly encountered.

Central Cord Syndrome The central cord syndrome results from damage to the gray matter nerve cells and crossing spinothalamic tracts near the central canal. In the cervical cord, the central cord syndrome produces arm weakness out of proportion to leg weakness and a "dissociated" sensory loss, signifying a loss of pain and temperature sense in a cape distribution over the shoulders, lower neck, and upper trunk in contrast to preservation of light touch, joint position, and vibration sense in these regions. Trauma, syringomyelia, tumors, and anterior spinal artery ischemia (including from aortic dissection) are the main causes.

Anterior Spinal Artery Syndrome Infarction of the cord is generally the result of occlusion or diminished flow in this artery. The result is extensive bilateral tissue destruction that spares the posterior columns. All spinal cord functions—motor, sensory, and autonomic—are lost below the level of the lesion, with the striking exception of retained vibration and position sensation.

Foramen Magnum Syndrome Lesions in this area interrupt decussating pyramidal tract fibers destined for the legs, which cross caudal to those of the arms, resulting in weakness of the legs (*crural paresis*). Compressive lesions near the foramen magnum may produce weakness of the ipsilateral shoulder and arm followed by weakness of the ipsilateral leg, then the contralateral leg, and finally the contralateral arm, an "around the clock" pattern that may begin in any of the four limbs. There is typically suboccipital pain spreading to the neck and shoulders.

Intramedullary and Extramedullary Syndromes It is useful to differentiate *intramedullary* processes, arising within the substance of the cord, from *extramedullary* ones that compress the spinal cord or its vascular supply. The differentiating features are only relative and serve as clinical guides. With extramedullary lesions, radicular pain is often prominent, and there is early sacral sensory loss (lateral spinothalamic tract) and spastic weakness in the legs (corticospinal tract) due to the superficial location of leg fibers in the corticospinal tract. Intramedullary lesions tend to produce poorly localized burning pain rather than radicular pain and spare sensation in the perine-

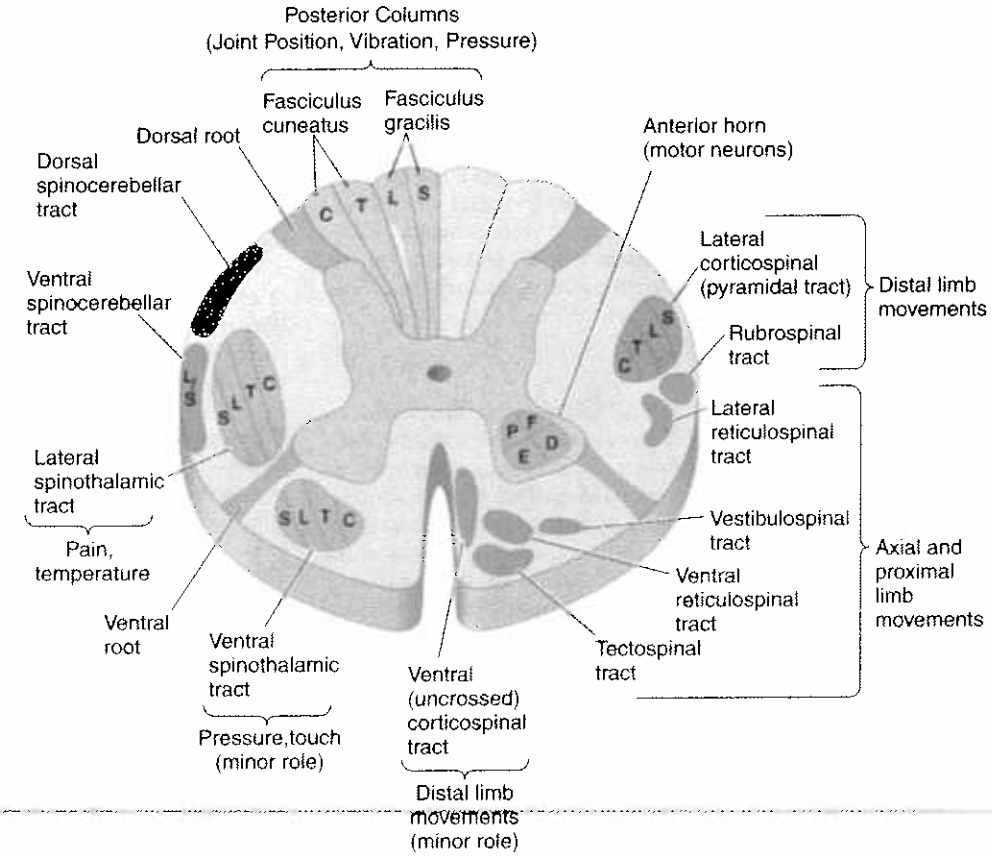

FIGURE 372-1 Transverse section through the spinal cord, composite representation, illustrating the principal ascending (***left***) and descending (***right***) pathways. The lateral and ventral spinothalamic tracts ascend contralateral to the side of the body that is innervated. C, cervical; T, thoracic; L, lumbar; S, sacral; P, proximal; D, distal; F, flexors; E, extensors.

al and sacral areas ("sacral sparing"), reflecting the laminated configuration of the spinothalamic tract with sacral fibers outermost; corticospinal tract signs appear later. Regarding extramedullary lesions, a further distinction is made between extradural and intradural masses, as the former are generally malignant and the latter benign (neurofibroma being a common cause). Consequently, a long duration of symptoms favors an intradural origin.

ACUTE AND SUBACUTE SPINAL CORD DISEASES

The initial symptoms of disease that evolve over days or weeks are focal neck or back pain, followed by various combinations of paresthesias, sensory loss, motor weakness, and sphincter disturbance evolving over hours to several days. There may be only mild sensory symptoms or a devastating functional transection of the cord. Partial lesions selectively involve the posterior columns or anterior spinothalamic tracts or are limited to one side of the cord. Paresthesias or numbness typically begins in the feet and ascends symmetrically or asymmetrically. These symptoms initially simulate Guillain-Barré syndrome, but involvement of the trunk with a sharply demarcated spinal cord level indicates the myelopathic nature of the process. In severe and abrupt cases, areflexia reflecting spinal shock may be present, but hyperreflexia supervenes over days or weeks; persistent areflexic paralysis with a sensory level indicates necrosis over multiple segments of the spinal cord.

APPROACH TO THE PATIENT: Compressive and Noncompressive Myelopathy

DISTINGUISHING COMPRESSIVE FROM NONCOMPRESSIVE MYELOPATHY The first priority is to exclude a treatable compression of the cord by a mass. The common causes are tumor, epidural abscess or hematoma, herniated disc, or vertebral pathology. Epidural compression due to malignancy or abscess often causes warning signs of neck or back pain, bladder disturbances, and sensory symptoms that precede the development of paralysis. Spinal subluxation, hemorrhage, and noncompressive etiologies such as infarction are more likely to produce myelopathy without antecedent symptoms. MRI with gadolinium infusion, centered on the clinically suspected level, is the initial diagnostic procedure; in some cases it is appropriate to image the entire spine (cervical through sacral regions) to search for additional clinically silent lesions. Once compressive lesions have been excluded, noncompressive causes of acute myelopathy that are intrinsic to the cord are considered, primarily vascular, inflammatory, and infectious etiologies.

COMPRESSIVE MYELOPATHIES

Neoplastic Spinal Cord Compression In adults, most neoplasms are epidural in origin, resulting from metastases to the adjacent spinal bones. The propensity of solid tumors to metastasize to the vertebral column probably reflects the high proportion of bone marrow located in the axial skeleton. Almost any malignant tumor can metastasize to the spinal column, with breast, lung, prostate, kidney, lymphoma, and plasma cell dyscrasia being particularly frequent. The thoracic cord is most commonly involved; exceptions are metastases from prostate and ovarian cancer, which occur disproportionately in the sacral and lumbar vertebrae, probably resulting from spread through Batson's plexus, a network of veins along the anterior epidural space. Retroperitoneal neoplasms (especially lymphomas or sarcomas) enter the spinal canal through the intervertebral foramina; they produce radicular pain and other signs of root involvement prior to cord compression.

Pain is usually the initial symptom; it may be aching and localized or sharp and radiating in quality. This spinal ache typically worsens with movement, coughing, or sneezing and characteristically awakens patients at night. A recent onset of persistent back pain, particularly if in the thoracic spine (which is uncommonly involved by spondylosis), should prompt consideration of vertebral metastasis. Rarely, pain is mild or absent. Plain radiographs of the spine and radionuclide bone scans have only a limited role in diagnosis because they do not identify 15–20% of metastatic vertebral lesions and fail to detect paravertebral masses that reach the epidural space through the intervertebral foramina. MRI provides excellent anatomic resolution of the extent of spinal tumors (Fig. 372-2) and is able to distinguish between malignant lesions and other masses—epidural abscess, tuberculoma, or epidural hemorrhage, among others—that present in a similar fashion. Vertebral metastases are usually hypointense relative to a normal bone marrow signal on T1-weighted MRI scans; after the administration of gadolinium, contrast enhancement may deceptively "normalize" the appearance of the tumor by increasing its intensity to that of normal bone marrow. Infections of the spinal column (osteomyelitis and related disorders) are distinctive in that, unlike tumor, they may cross the disk space to involve the adjacent vertebral body.

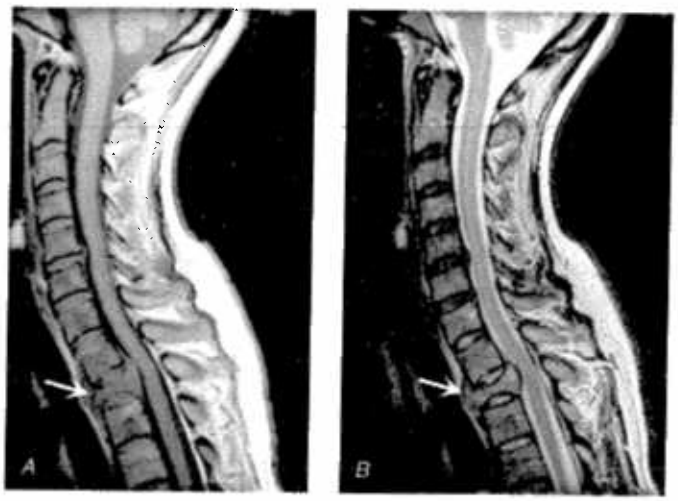

FIGURE 372-2 Epidural spinal cord compression due to breast carcinoma. Sagittal T1-weighted (***A***) and T2-weighted (***B***) MRI scans through the cervicothoracic junction reveal an infiltrated and collapsed second thoracic vertebral body with posterior displacement and compression of the upper thoracic spinal cord. The low-intensity bone marrow signal in *A* signifies replacement by tumor.

If spinal cord compression is suspected, imaging should be obtained promptly. If there are radicular symptoms but no evidence of myelopathy, it is usually safe, if necessary, to defer imaging for 24–48 h. With back or neck pain only, imaging studies may be obtained within a few days. Up to 40% of patients who present with cord compression at one level are found to have asymptomatic epidural disease elsewhere; thus, the length of the spine should be imaged when epidural malignancy is in question.

℞ NEOPLASTIC SPINAL CORD COMPRESSION

Management of cord compression includes glucocorticoids to reduce cord edema, local radiotherapy (initiated as early as possible) to the symptomatic lesion, and specific therapy for the underlying tumor type. Glucocorticoids (dexamethasone, up to 40 mg daily) can be administered before the imaging study if the clinical suspicion is strong and continued at a lower dose until radiotherapy (generally 3000 cGy administered in 15 daily fractions) is completed. Radiotherapy appears to be as effective as surgery, even for most classically radioresistant metastases. Biopsy of the epidural mass is unnecessary in patients with known preexisting cancer but is indicated if a history of underlying cancer is lacking. Surgery, either decompression by laminectomy or vertebral body resection, should be considered when signs of cord compression worsen despite radiotherapy, when the maximum tolerated dose of radiotherapy has been delivered previously to the site, or when a vertebral compression fracture or spinal instability contributes to cord compression. A good response to radiotherapy can be expected in individuals who are ambulatory at presentation; new weakness is prevented, and some recovery of motor function occurs in approximately half of treated patients. Fixed motor deficits (paraplegia or quadriplegia), once estab-

FIGURE 372-3 MRI of a thoracic meningioma. Coronal T1-weighted post-contrast image through the thoracic spinal cord demonstrates intense and uniform enhancement of a well-circumscribed extramedullary mass (*arrows*) which displaces the spinal cord to the left.

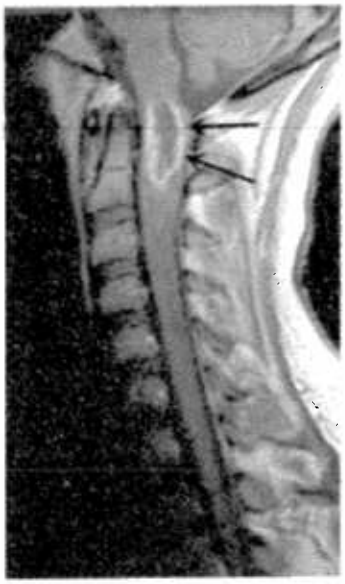

FIGURE 372-4 MRI of an intramedullary astrocytoma. Sagittal T1-weighted post-contrast image through the cervical spine demonstrates expansion of the upper cervical spine by a mass lesion emanating from within the spinal cord at the cervicomedullary junction. Irregular peripheral enhancement occurs within the mass (*arrows*).

lished for >12 h, do not usually improve, and beyond 48 h the prognosis for substantial motor recovery is poor.

In contrast to tumors of the epidural space, most intradural mass lesions are slow-growing and benign. Meningiomas and neurofibromas account for most of these, with occasional cases caused by chordoma, lipoma, dermoid, or sarcoma. Meningiomas (Fig. 372-3) are often located posterior to the thoracic cord or near the foramen magnum, although they can arise from the meninges anywhere along the spinal canal. Neurofibromas are benign tumors of the nerve sheath that typically arise near the posterior root; when multiple, neurofibromatosis is the likely etiology. Symptoms usually begin with radicular sensory symptoms followed by an asymmetric, progressive spinal cord syndrome. Therapy is by surgical resection.

Primary intramedullary tumors of the spinal cord are uncommon. They present as central cord or hemicord syndromes, often in the cervical region; there may be poorly localized burning pain in the extremities and sparing of sacral sensation. In adults, these lesions are ependymomas, hemangioblastomas, or low-grade astrocytomas (Fig. 372-4). Complete resection of an intramedullary ependymoma is often possible with microsurgical techniques. Debulking of an intramedullary astrocytoma can also be helpful, as these are often slowly growing lesions; the value of adjunctive radiotherapy and chemotherapy is uncertain. Secondary (metastatic) intramedullary tumors are also common, especially in patients with advanced metastatic disease (Chap. 374).

Spinal Epidural Abscess Spinal epidural abscess presents as a clinical triad of midline dorsal pain, fever, and progressive limb weakness. Prompt recognition of this distinctive process will in most cases prevent permanent sequelae. Aching pain is almost always present, either over the spine or in a radicular pattern. The duration of pain prior to presentation is generally ≤2 weeks but may on occasion be several months or longer. Fever is usual, accompanied by elevated white blood cell count and sedimentation rate. As the abscess expands, further spinal cord damage results from venous congestion and thrombosis. Once weakness and other signs of myelopathy appear, progression may be rapid. A more chronic sterile granulomatous form of abscess is also known, usually after treatment of an acute epidural infection.

Risk factors include an impaired immune status (diabetes mellitus, renal failure, alcoholism, malignancy), intravenous drug abuse, and infections of the skin or other tissues. Two-thirds of epidural infections result from hematogenous spread of bacteria from the skin (furunculosis), soft tissue (pharyngeal or dental abscesses), or deep viscera (bacterial endocarditis). The remainder arise from direct extension of a local infection to the subdural space; examples of local predisposing conditions are vertebral osteomyelitis, decubitus ulcers, lumbar puncture, epidural anesthesia, or spinal surgery. Most cases are due to *Staphylococcus aureus*; gram-negative bacilli, *Streptococcus*, anaerobes, and fungi can also cause epidural abscesses. Tuberculosis from an adjacent vertebral source, Pott's disease, remains an important cause in the underdeveloped world.

MRI scans (Fig. 372-5) localize the abscess and exclude other causes of myelopathy. Lumbar puncture is only required if encephalopathy or other clinical signs raise the question of associated meningitis, a feature that is found in <25% of cases. The level of the puncture should be planned to minimize the risk of meningitis due to passage of the needle through infected tissue or herniation due to decompression below an area of obstruction to the flow of cerebrospinal fluid (CSF). A high cervical tap is often the safest approach. CSF abnormalities in subdural abscess consist of pleocytosis with a preponderance of polymorphonuclear cells, an elevated protein level, and a reduced glucose

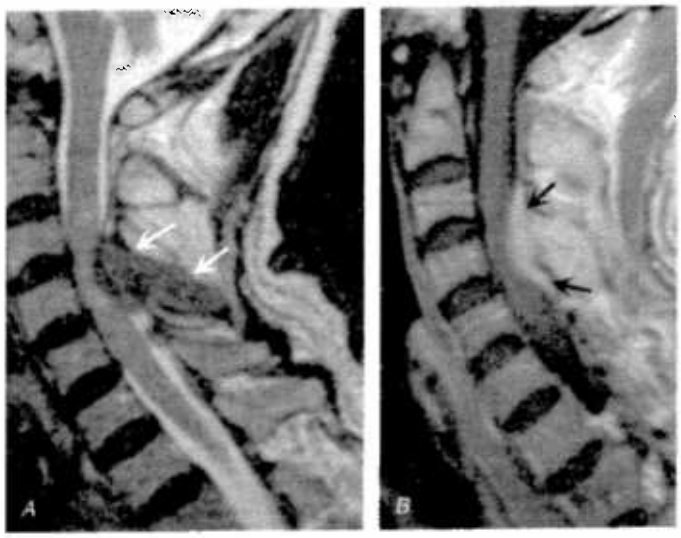

FIGURE 372-5 MRI of a spinal epidural abscess due to tuberculosis. ***A.*** Sagittal T2-weighted free spin-echo MR sequence. A hypointense mass replaces the posterior elements of C3 and extends epidurally to compress the spinal cord (*arrows*). ***B.*** Sagittal T1-weighted image after contrast administration reveals a diffuse enhancement of the epidural process (*arrows*) with extension into the epidural space.

level, but the responsible organism is not cultured unless there is associated meningitis. Blood cultures are positive in <25% of cases.

Rx SPINAL EPIDURAL ABSCESS

Treatment is by decompressive laminectomy with debridement combined with long-term antibiotic treatment. Surgical evacuation prevents development of paralysis and may improve or reverse paralysis in evolution, but it is unlikely to improve deficits of more than several days duration. Antibiotics should be started empirically before surgery and then modified on the basis of culture results; medication is continued for at least 4 weeks. If surgery is contraindicated or if there is a fixed paraplegia or quadriplegia that is unlikely to improve following surgery, long-term administration of systemic and oral antibiotics can be used; in such cases, the choice of antibiotics may be guided by results of blood cultures. However, paralysis may develop or progress during antibiotic therapy; thus, initial surgical management remains the treatment of choice unless the abscess is limited in size and causes few or no neurologic signs.

Spinal Epidural Hematoma Hemorrhage into the epidural (or subdural) space causes acute focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder. Therapeutic anticoagulation, trauma, tumor, or blood dyscrasia are predisposing conditions. Rare cases complicate lumbar puncture or epidural anesthesia, sometimes in association with use of low-molecular-weight heparin. MRI and CT confirm the clinical suspicion and can delineate the extent of the bleeding. Treatment consists of prompt reversal of any underlying clotting disorder and surgical decompression. Surgery may be followed by substantial recovery, especially in patients with some preservation of motor function preoperatively. Because of the risk of hemorrhage, lumbar puncture should be avoided whenever possible in patients with severe thrombocytopenia or other coagulopathies.

Hematomyelia Hemorrhage into the substance of the spinal cord is a rare result of trauma, intraparenchymal vascular malformation (see below), vasculitis due to polyarteritis nodosa or systemic lupus erythematosus (SLE), bleeding disorders, or a spinal cord neoplasm. Hematomyelia presents as an acute painful transverse myelopathy. With large lesions, extension into the subarachnoid space may occur, resulting in subarachnoid hemorrhage (Chap. 269). Diagnosis is by MRI or CT. Therapy is supportive, and surgical intervention is generally not useful. An exception is hematomyelia due to an underlying vascular malformation, for which selective spinal angiography may be indicated, followed by surgery to evacuate the clot and remove the underlying vascular lesion.

NONCOMPRESSIVE MYELOPATHIES

The most frequent causes of noncompressive acute transverse myelopathy (ATM) are spinal cord infarction; systemic inflammatory disorders, including SLE and sarcoidosis; demyelinating diseases, including multiple sclerosis (MS) and neuromyelitis optica; postinfectious or idiopathic transverse myelitis, which is presumed to be an immune condition related to acute disseminated encephalomyelitis (Chap. 375); and infectious (primarily viral) causes. After spinal cord compression is excluded, the evaluation generally requires a lumbar puncture and a search for underlying systemic disease (Table 372-3).

Spinal Cord Infarction The cord is supplied by three arteries that course vertically over its surface: a single anterior spinal artery and paired posterior spinal arteries. In addition to the vertebral arteries, the anterior spinal artery is fed by radicular vessels that arise at C6, at an upper thoracic level, and, most consistently, at T11-L2 (artery of Adamkiewicz). At each segment, paired penetrating vessels branch from the anterior spinal artery to supply the anterior two-thirds of the spinal cord; the posterior spinal arteries, which often become less distinct below the midthoracic level, supply the posterior columns.

Spinal cord ischemia can occur at any level; however, the presence of the artery of Adamkiewicz creates a watershed of marginal blood flow in the upper thoracic segments. With systemic hypotension, cord infarction occurs at the level of greatest ischemic risk, usually T3-T4, and also at boundary zones between the anterior and posterior spinal artery territories. The latter may result in a rapidly progressive syndrome over hours of weakness and spasticity with little sensory change.

Acute infarction in the territory of the *anterior spinal artery* produces paraplegia or quadriplegia, dissociated sensory loss affecting pain and temperature sense but sparing vibration and position sense, and loss of sphincter control ("anterior cord syndrome"). Onset may be sudden and dramatic but more typically is progressive over minutes or a few hours, quite unlike stroke in the cerebral hemispheres. Sharp midline or radiating back pain localized to the area of ischemia is frequent. Areflexia due to spinal shock is often present initially; with time, hyperreflexia and spasticity appear. Less common is infarction in the territory of the *posterior spinal arteries*, resulting in loss of posterior column function.

Spinal cord infarction results from aortic atherosclerosis, dissecting aortic aneurysm (manifest as chest or back pain with diminished pulses in legs), vertebral artery occlusion or dissection in the neck, or profound hypotension from any cause. Cardiogenic emboli, vasculitis related to collagen vascular disease [particularly SLE and the antiphospholipid antibody syndrome (see below)], and surgical interruption of aortic aneurysms are other causative conditions. Occasional cases develop from *embolism of nucleus pulposus* material into spinal vessels, usually from local spine trauma. In a substantial number of cases no cause can be found, and thromboembolism in arterial feeders is suspected. The MRI may fail to demonstrate limited infarctions of the cord, especially in the first day, but as often it is abnormal at the affected level.

In cord infarction due to presumed thromboembolism, acute anticoagulation is probably not indicated, with the exception of the unusual transient ischemic attack or incomplete infarction with a stuttering or progressive course. The antiphospholipid antibody syndrome is treated with anticoagulation. Drainage of spinal fluid has reportedly been successful in some cases of cord infarction but has not been studied systematically.

Inflammatory and Immune Myelopathies (Myelitis) This broad category includes MS and postinfectious myelitis, both of which are demyelinating in nature (see below), as well as connective tissue disease. In approximately one-quarter of cases of myelitis, no underlying cause can be identified. Some will later manifest additional symptoms of a systemic immune-mediated disease such as SLE or, more often, MS. *Recurrent episodes of myelitis* are usually due to an immune-mediated

TABLE 372-3 EVALUATION OF ACUTE TRANSVERSE MYELOPATHY

1. MRI of spinal cord with and without contrast (exclude compressive causes).
2. CSF studies: Cell count, protein, glucose, IgG index/synthesis rate, oligoclonal bands, VDRL; Gram's stain, acid-fast bacilli, and India ink stains; PCR for VZV, HSV-2, HSV-1, EBV, CMV, HHV-6, enteroviruses, HIV; antibody for HTLV-I, *B. burgdorferi*, *M. pneumoniae*, and *Chlamydia pneumoniae*; viral, bacterial, mycobacterial, and fungal cultures.
3. Blood studies for infection: HIV; RPR; IgG and IgM enterovirus antibody; IgM mumps, measles, rubella, group B arbovirus, *Brucella melitensis*, *Chlamydia psittaci*, *Bartonella henselae*, schistosomal antibody; cultures for *B. melitensis*. Also consider nasal/pharyngeal/anal cultures for enteroviruses; stool O&P for *Schistosoma* ova.
4. Immune-mediated disorders: ESR; ANA; ENA; dsDNA; rheumatoid factor; anti-SSA; anti-SSB, complement levels; antiphospholipid and anticardiolipin antibodies; p-ANCA; antimicrosomal and antithyroglobulin antibodies; if Sjögren syndrome suspected, Schirmer test, salivary gland scintography, and salivary/lacrimal gland biopsy.
5. Sarcoidosis: Serum angiotensin-converting enzyme; serum Ca; 24 hour urine Ca; chest x-ray; chest CT; total body gallium scan; lymph node biopsy.
6. Demyelinating disease: Brain MRI scan, evoked potentials, CSF oligoclonal bands, neuromyelitis optica antibody (aquaporin-4).
7. Vascular causes: CT myelogram; spinal angiogram.

Note: VDRL, Venereal Disease Research Laboratory; PCR, polymerase chain reaction; VZV, varicella-zoster virus; HHV, human herpes virus; RPR, rapid plasma reagin (test); O&P, ova and parasites; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; ENA, epithelial neutrophil-activating peptide.

disease such as a demyelinating disease, SLE, or sarcoid; or to infection with herpes simplex virus (HSV) type 2 (below).

SYSTEMIC INFLAMMATORY DISORDERS Myelitis occurs in a small number of patients with SLE (Chap. 313), many cases of which are associated with antiphospholipid antibodies. The CSF is usually normal or shows a mild lymphocytic pleocytosis; oligoclonal bands are a variable finding. Responses to glucocorticoids and/or cyclophosphamide have been reported, but there is no systematic evidence of their benefit. Other immune-mediated myelitides include cases associated with Sjögren's syndrome (Chap. 317), mixed connective tissue disease (Chap. 316), Behçet's syndrome (Chap. 320), and vasculitis with perinuclear antineutrophilic cytoplasmic (p-ANCA) antibodies (Chap. 319).

Another important consideration in this group is sarcoid myelopathy (Chap. 322), in which an edematous swelling of the spinal cord may mimic tumor; there is almost always gadolinium enhancement of the lesion and of the adjacent surface of the cord. The CSF profile consists of variable lymphocytic pleocytosis; oligoclonal bands are present in one-third of cases. The diagnosis is particularly difficult when systemic manifestations of sarcoid are minor or absent (nearly 50% of cases) or when other classic neurologic manifestations of the disease—such as cranial neuropathy, hypothalamic involvement, or meningeal enhancement visualized by MRI—are lacking. A slit-lamp examination of the eye to search for uveitis, chest x-ray and CT to assess pulmonary involvement and mediastinal lymphadenopathy, serum angiotensin-converting enzyme (ACE; positive in only one-quarter of cases), serum calcium, and a gallium scan may assist in the diagnosis. The usefulness of spinal fluid ACE is uncertain. Initial treatment is with oral glucocorticoids; immunosuppressant drugs are used for resistant cases.

DEMYELINATING MYELOPATHIES Multiple sclerosis (Chap. 375) may present with myelitis, particularly in individuals of Asian or African ancestry. In Caucasians, MS rarely causes a complete transverse myelopathy (i.e., acute bilateral signs), but it is among the most common causes of a partial syndrome. Neuromyelitis optica (NMO) is a demyelinating syndrome consisting of a severe myelopathy associated with optic neuritis; the optic neuritis is often bilateral and may precede or follow myelitis by weeks or months (Chap. 375). A specific serum antibody test is available. NMO is also associated with SLE and antiphospholipid antibodies (see above) as well as with other connective tissue diseases.

MRI findings in MS-associated myelitis typically consist of mild swelling and edema of the cord and diffuse or multifocal areas of abnormal signal on T2-weighted sequences. Contrast enhancement, indicating disruption in the blood-brain barrier associated with inflammation, is present in many acute cases. A brain MRI is most helpful in gauging the likelihood that a case of myelitis represents an initial attack of MS. A normal scan indicates that the risk of evolution to MS is low, ~10–15% over 5 years; in contrast, the finding of multiple periventricular T2-bright lesions indicates a much higher risk, >50% over 5 years and >90% by 14 years. The CSF may be normal, but more often there is a mild pleocytosis, occasionally up to several hundred mononuclear cells per microliter, with normal or mildly elevated CSF protein levels; oligoclonal bands are variable, but when bands are present, a diagnosis of MS is more likely. These bands are generally absent in neuromyelitis optica.

There are no adequate trials of therapy for MS-associated transverse myelitis. Intravenous methylprednisolone (500 mg qd for 3 days) followed by oral prednisone (1 mg/kg per day for several weeks, then gradual taper) has been used as initial treatment. A course of plasma exchange is indicated for severe cases if glucocorticoids are ineffective. Preliminary data suggest that treatment with anti-CD20 (anti-B cell) monoclonal antibody may protect against relapses in patients with NMO.

POSTINFECTIOUS MYELITIS Many cases of myelitis, termed *postinfectious* or *postvaccinal*, follow an infection or vaccination. Numerous organisms have been implicated, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), mycoplasma, influenza, measles, varicella, rubeola, and mumps. As in the related disorder acute disseminated encephalomyelitis (Chap. 375), postinfectious myelitis often begins as the patient appears to be recovering from an acute febrile infection, or in the subsequent days or weeks, but an infectious agent cannot be isolated from the nervous system or spinal fluid. The presumption is that the myelitis represents an autoimmune disorder triggered by infection and is not due to direct infection of the spinal cord. Treatment is usually with glucocorticoids or, in fulminant cases, plasma exchange. There are no trials by which to adequately judge these therapies.

ACUTE INFECTIOUS MYELITIS Many viruses have been associated with an acute myelitis that is infectious in nature rather than postinfectious. Nonetheless, the two processes are often difficult to distinguish. Herpes zoster is the best characterized viral myelitis, but HSV types 1 and 2, EBV, CMV, and rabies virus are other well-described causes. HSV-2 (and less commonly HSV-1) produces a distinctive syndrome of recurrent sacral myelitis in association with outbreaks of genital herpes mimicking MS. Poliomyelitis is the prototypic viral myelitis, but it is more or less restricted to the gray matter of the cord. Chronic viral myelitic infections, such as that due to HIV, are discussed below.

Bacterial and mycobacterial myelitis (most are essentially abscesses) are far less common than viral causes. Almost any pathogenic species may be responsible, including *Listeria monocytogenes*, *Borrelia burgdorferi* (Lyme disease), and *Treponema pallidum* (syphilis). *Mycoplasma pneumoniae* may be a cause of myelitis, but its status is uncertain since many cases are more properly classified as postinfectious.

Schistosomiasis (Chap. 212) is an important cause of parasitic myelitis in endemic areas. The process is intensely inflammatory and granulomatous, caused by a local response to tissue-digesting enzymes from the ova of the parasite. Toxoplasmosis (Chap. 207) can occasionally cause a focal myelopathy, and this diagnosis should be considered, particularly in patients with AIDS.

In cases of suspected viral myelitis, it may be appropriate to begin specific therapy pending laboratory confirmation. Herpes zoster, HSV, and EBV myelitis are treated with intravenous acyclovir (10 mg/kg q8h) or oral valacyclovir (2 gm tid) for 10–14 days; CMV with ganciclovir (5 mg/kg IV bid) plus foscarnet (60 mg/kg IV tid), or cidofovir (5 mg/kg per week for 2 weeks).

CHRONIC MYELOPATHIES

SPONDYLITIC MYELOPATHY

Spondylitic myelopathy is one of the most common causes of gait difficulty in the elderly. Neck and shoulder pain with stiffness are early symptoms; impingement of bone and soft tissue overgrowth on nerve roots results in radicular arm pain, most often in a C5 or C6 distribution. Compression of the cervical cord, which occurs in fewer than one-third of cases, produces a slowly progressive spastic paraparesis, at times asymmetric and often accompanied by paresthesias in the feet and hands. Vibratory sense is diminished in the legs, there is a Romberg sign, and occasionally there is a sensory level for vibration on the upper thorax. In some cases, coughing or straining produces leg weakness or radiating arm or shoulder pain. Dermatomal sensory loss in the arms, atrophy of intrinsic hand muscles, increased deep-tendon reflexes in the legs, and extensor plantar responses are common. Urinary urgency or incontinence occurs in advanced cases, but there are many alternative causes of these problems in older individuals. A tendon reflex in the arms is often diminished at some level; the biceps is most often affected (C5-C6). In individual cases, radicular, myelopathic, or combined signs may predominate. The diagnosis should be considered in cases of progressive cervical myelopathy, paresthesias of the feet and hands, or wasting of the hands.

Diagnosis is made by MRI or myelography. Extrinsic cord compression and deformation is appreciated on axial MRI views, and T2-weighted sequences may reveal areas of high signal intensity within the cord adjacent to the site of compression. A cervical collar may be helpful in milder cases, but definitive therapy consists of surgical decom-

pression. Posterior laminectomy or an anterior approach with resection of the protruded disc and bony material may be required. Cervical spondylosis and related degenerative diseases of the spine are discussed in Chap. 16.

VASCULAR MALFORMATIONS OF THE CORD AND DURA

Although uncommon, vascular malformations of the cord and overlying dura are treatable causes of progressive myelopathy. True arteriovenous malformations (AVMs) are located posteriorly along the surface of the cord or within the dura, where they are more properly classified as fistulas. Most are at or below the midthoracic level. The typical presentation is a middle-aged man with a progressive myelopathy that worsens slowly or intermittently and may have periods of apparent remission resembling MS. Acute deterioration due to hemorrhage into the spinal cord or subarachnoid space may also occur but is rare. A saltatory progression is most common and is the result of local ischemia and edema from venous congestion. Most patients have incomplete sensory, motor, and bladder disturbances. The motor disorder may predominate and produce a mixture of upper and restricted lower motor neuron signs, simulating amyotrophic lateral sclerosis (ALS). Pain over the dorsal spine, dysesthesias, or radicular pain may be present. Other symptoms suggestive of AVM include intermittent claudication, symptoms that change with posture, exertion such as singing, menses, or fever. A rare AVM process presents as a progressive thoracic myelopathy with paraparesis developing over weeks or several months, characterized pathologically by abnormally thick, hyalinized vessels within the cord (Foix-Alajouanine syndrome).

Spinal bruits are infrequent but should be sought at rest and after exercise in suspected cases. High-resolution MRI with contrast administration detects many but not all AVMs (Fig. 372-6). A small number not detected by MRI may be visualized by CT myelography as enlarged vessels along the surface of the cord. Definitive diagnosis requires selective spinal angiography, which defines the feeding vessels and the extent of the malformation. Endovascular embolization of the major feeding vessels may stabilize a progressive neurologic deficit or allow for gradual recovery.

RETROVIRUS-ASSOCIATED MYELOPATHIES

The myelopathy associated with the human T cell lymphotropic virus type I (HTLV-I), formerly called tropical spastic paraparesis, is a slowly progressive spastic syndrome with variable sensory and bladder disturbance (Chap. 181). Approximately half of patients have mild back or leg pain. The neurologic signs may be asymmetric, often lacking a well-defined sensory level; the only sign in the arms may be hyperreflexia after several years of illness. The onset is insidious, and the illness is slowly progressive at a variable rate; most patients are unable to walk within 10 years of onset. This presentation may resemble primary progressive MS or a thoracic AVM. Diagnosis is made by demonstration of HTLV-I–specific antibody in serum by enzyme-linked immunosorbent assay (ELISA), confirmed by radioimmunoprecipitation or western blot analysis. There is no effective treatment, but symptomatic therapy for spasticity and bladder symptoms may be helpful.

A progressive myelopathy may also result from HIV infection (Chap. 182). It is characterized by vacuolar degeneration of the posterior and lateral tracts, resembling subacute combined degeneration (see below).

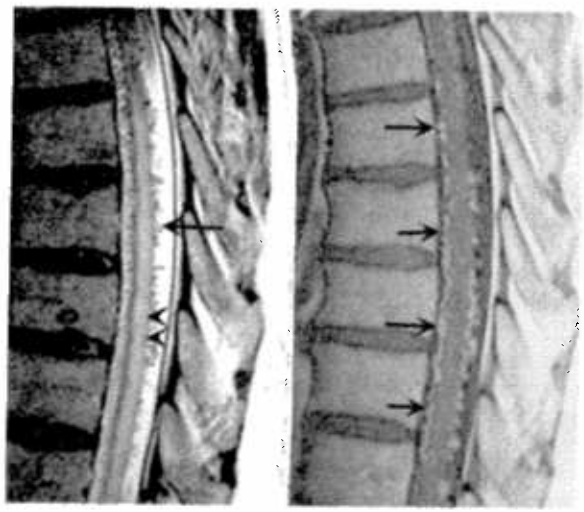

FIGURE 372-6 Arteriovenous malformation. Sagittal MR scans of the thoracic spinal cord: T2 fast spin-echo technique (***left***) and T1 post-contrast image (***right***). On the T2-weighted image (*left*), abnormally high signal intensity is noted in the central aspect of the spinal cord (*arrowheads*). Numerous punctate flow voids indent the dorsal and ventral spinal cord (*arrow*). These represent the abnormally dilated venous plexus supplied by a dural arteriovenous fistula. After contrast administration (*right*), multiple, serpentine, enhancing veins (*arrows*) on the ventral and dorsal aspect of the thoracic spinal cord are visualized, diagnostic of arteriovenous malformation. This patient was a 54-year-old man with a 4-year history of progressive paraparesis.

SYRINGOMYELIA

Syringomyelia is a developmental cavitary expansion of the cervical cord that is prone to enlarge and produce progressive myelopathy. Symptoms begin insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years. Many young patients acquire a cervical-thoracic scoliosis. More than half of all cases are associated with Chiari type I malformations in which the cerebellar tonsils protrude through the foramen magnum and into the cervical spinal canal. The pathophysiology of syrinx expansion is controversial, but some interference with the normal flow of CSF seems likely, perhaps by the Chiari malformation. Acquired cavitations of the cord in areas of necrosis are also termed *syrinx cavities*; these follow trauma, myelitis, necrotic spinal cord tumors, and chronic arachnoiditis due to tuberculosis and other etiologies.

The classic presentation is a central cord syndrome consisting of a dissociated sensory loss and areflexic weakness in the upper limbs. The sensory deficit is recognizable by loss of pain and temperature sensation with sparing of touch and vibration in a distribution that is "suspended" over the nape of the neck, shoulders, and upper arms (cape distribution) or in the hands. Most cases begin asymmetrically with unilateral sensory loss in the hands that leads to injuries and burns that are not appreciated by the patient. Muscle wasting in the lower neck, shoulders, arms, and hands with asymmetric or absent reflexes in the arms reflects expansion of the cavity into the gray matter of the cord. As the cavity enlarges and further compresses the long tracts, spasticity and weakness of the legs, bladder and bowel dysfunction, and a Horner's syndrome appear. Some patients develop facial numbness and sensory loss from damage to the descending tract of the trigeminal nerve (C2 level or above). In cases with Chiari malformations, cough-induced headache and neck, arm, or facial pain are reported. Extension of the syrinx into the medulla, syringobulbia, causes palatal or vocal cord paralysis, dysarthria, horizontal or vertical nystagmus, episodic dizziness, and tongue weakness.

MRI scans accurately identify developmental and acquired syrinx cavities and their associated spinal cord enlargement (Fig. 372-7). MRI scans of the brain and the entire spinal cord should be obtained to delineate the full longitudinal extent of the syrinx, assess posterior fossa structures for the Chiari malformation, and determine whether hydrocephalus is present.

Rx SYRINGOMYELIA

Treatment of syringomyelia is generally unsatisfactory. The Chiari tonsillar herniation is usually decompressed, generally by suboccipital craniectomy, upper cervical laminectomy, and placement of a dural graft. Obstruction of fourth ventricular outflow is reestablished by this procedure. If the syrinx cavity is large, some surgeons recommend direct decompression or drainage by one of a number of methods, but the added benefit of this procedure is uncertain, and morbidity is common. With Chiari malformations, shunting of hydrocephalus should generally precede any attempt to correct the syrinx. Surgery may stabilize the neurologic deficit, and some patients improve.

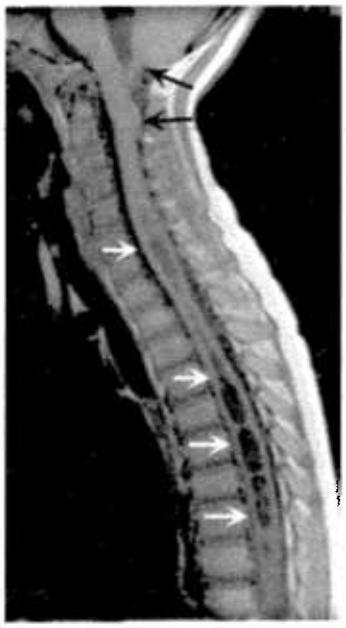

FIGURE 372-7 MRI of syringomyelia associated with a Chiari malformation. Sagittal T1-weighted image through the cervical and upper thoracic spine demonstrates descent of the cerebellar tonsils and vermis below the level of the foramen magnum (*black arrows*). Within the substance of the cervical and thoracic spinal cord, a CSF collection dilates the central canal (*white arrows*).

Syringomyelia secondary to trauma or infection is treated with a decompression and drainage procedure in which a small shunt is inserted between the syrinx cavity and the subarachnoid space; alternatively, the cavity can be fenestrated. Cases due to intramedullary spinal cord tumor are generally managed by resection of the tumor.

CHRONIC MYELOPATHY OF MULTIPLE SCLEROSIS

A chronic progressive myelopathy is the most frequent cause of disability in both primary progressive and secondary progressive forms of MS. Involvement is typically bilateral but asymmetric and produces motor, sensory, and bladder/bowel disturbances. Fixed motor disability appears to result from extensive loss of axons in the corticospinal tracts; thus, the symptoms are not simply due to demyelination. Diagnosis is facilitated by identification of earlier attacks such as optic neuritis. MRI, CSF, and evoked response testing are confirmatory. Therapy with interferon β, glatiramer acetate, or natalizumab is indicated for patients with progressive myelopathy who also have coexisting MS relapses. These therapies are sometimes also offered to patients without relapses, despite the lack of evidence supporting their value in this setting. MS is discussed in Chap. 375.

SUBACUTE COMBINED DEGENERATION (VITAMIN B_{12} DEFICIENCY)

This treatable myelopathy presents with subacute paresthesias in the hands and feet, loss of vibration and position sensation, and a progressive spastic and ataxic weakness. Loss of reflexes due to an associated peripheral neuropathy in a patient who also has Babinski signs, is an important diagnostic clue. Optic atrophy and irritability or other mental changes may be prominent in advanced cases and are rarely the presenting symptoms. The myelopathy of subacute combined degeneration tends to be diffuse rather than focal; signs are generally symmetric and reflect predominant involvement of the posterior and lateral tracts, including Romberg's sign. The diagnosis is confirmed by the finding of macrocytic red blood cells, a low serum B_{12} concentration, elevated serum levels of homocysteine and methylmalonic acid, and in uncertain cases a positive Schilling test (Chap. 288). Treatment is by replacement therapy, beginning with 1000 μg of intramuscular vitamin B_{12} repeated at regular intervals or by subsequent oral treatment.

HYPOCUPRIC MYELOPATHY

This recently described myelopathy is virtually identical to subacute combined degeneration (described above) and probably explains many cases previously described with normal serum levels of B_{12}. Low levels of serum copper are found and often there is also a low level of serum ceruloplasmin. Some cases follow gastrointestinal procedures that result in impaired copper absorption, but many others are idiopathic. Improvement or at least stabilization may be expected with reconstitution of copper stores by oral supplementation. The pathophysiology and pathology are not known.

TABES DORSALIS

The classic syndromes of tabes dorsalis and meningovascular syphilis of the spinal cord are now less frequent than in the past but must be considered in the differential diagnosis of spinal cord disorders. The characteristic symptoms of tabes are fleeting and repetitive lancinating pains, primarily in the legs or less often in the back, thorax, abdomen, arms, and face. Ataxia of the legs and gait due to loss of position sense occurs in half of patients. Paresthesias, bladder disturbances, and acute abdominal pain with vomiting (visceral crisis) occur in 15–30% of patients. The cardinal signs of tabes are loss of reflexes in the legs; impaired position and vibratory sense; Romberg's sign; and, in almost all cases, bilateral Argyll Robertson pupils, which fail to constrict to light but accommodate. Diabetic polyradiculopathy may simulate tabes.

FAMILIAL SPASTIC PARAPLEGIA

Many cases of slowly progressive myelopathy are genetic in origin (Chap. 369). More than 20 different causative loci have been identified, including autosomal dominant, autosomal recessive, and X-linked forms. Most patients present with almost imperceptibly progressive spasticity and weakness in the legs, usually but not always symmetrical. Sensory symptoms and signs are absent or mild, but sphincter disturbances may be present. In some families additional neurologic signs are prominent, including nystagmus, ataxia, or optic atrophy. The onset may be as early as the first year of life or as late as middle adulthood. Only symptomatic therapies for the spasticity are currently available.

ADRENOMYELONEUROPATHY

This X-linked disorder is a variant of adrenoleukodystrophy. Affected males usually have a history of adrenal insufficiency beginning in childhood and then develop a progressive spastic (or ataxic) paraparesis beginning in early adulthood; some patients also have a mild peripheral neuropathy. Female heterozygotes may develop a slower, insidiously progressive spastic myelopathy beginning later in adulthood and without adrenal insufficiency. Diagnosis is usually made by demonstration of elevated levels of very long chain fatty acids in plasma and in cultured fibroblasts. The responsible gene encodes ADLP, a peroxisomal membrane transporter that is a member of the ATP-binding cassette (ABC) family. Steroid replacement is indicated if hypoadrenalism is present, and bone marrow transplantation and nutritional supplements have been attempted for this condition without clear evidence of efficacy.

OTHER CHRONIC MYELOPATHIES

Primary lateral sclerosis (Chap. 369) is a degenerative disorder characterized by progressive spasticity with weakness, eventually accompanied by dysarthria and dysphonia; bladder symptoms occur in approximately half of patients. Sensory function is spared. The disorder resembles ALS and is considered a variant of the motor neuron degenerations, but without the characteristic lower motor neuron disturbance. Some cases may represent familial spastic paraplegia, particularly autosomal recessive or X-linked varieties in which a family history may be absent.

There are a number of rare toxic causes of spastic myelopathy, including lathyrism due to ingestion of chick peas containing the excitotoxin β-*N*-oxalylaminoalanine (BOAA), seen primarily in the developing world, and nitrous oxide inhalation producing a myelopathy identical to subacute combined degeneration. SLE (Chap. 313), Sjögren's syndrome (Chap. 317), and sarcoidosis (Chap. 322) may each cause a myelopathy without overt evidence of systemic disease. Cancer-related causes of chronic myelopathy, besides the common neoplastic compressive myelopathy discussed earlier, include a rare paraneoplastic myelopathy (Chap. 97) or radiation injury (Chap. 374). It is notable that metastases to the cord are probably more common than

TABLE 372-4 EXPECTED NEUROLOGIC FUNCTION FOLLOWING COMPLETE CORD LESIONS

Level	Self-Care	Transfers	Maximum Mobility
High quadriplegia (C1-C4)	Dependent on others; requires respiratory support	Dependent on others	Motorized wheelchair
Low quadriplegia (C5-C8)	Partially independent with adaptive equipment	May be dependent or independent	May use manual wheelchair, drive an automobile with adaptive equipment
Paraplegia (below T1)	Independent	Independent	Ambulates short distances with aids

Source: Adapted from JF Ditunno, CS Formal: Chronic spinal cord injury. N Engl J Med 330:550, 1994, with permission.

either of these. In obscure cases, a cause can often be identified through periodic reassessment.

REHABILITATION OF SPINAL CORD DISORDERS

The prospects for recovery from an acute destructive spinal cord lesion fade after ~6 months. There are currently no effective means to promote repair of injured spinal cord tissue; promising experimental approaches include the use of factors that influence reinnervation by axons of the corticospinal tract, nerve and neural sheath graft bridges, and the local introduction of stem cells. The disability associated with irreversible spinal cord damage is determined primarily by the level of the lesion and by whether the disturbance in function is complete or incomplete (Table 372-4). Even a complete high cervical cord lesion may be compatible with a productive life. The primary goals are development of a rehabilitation plan framed by realistic expectations and attention to the neurologic, medical, and psychological complications that commonly arise.

Many of the usual symptoms associated with medical illnesses, especially somatic and visceral pain, may be lacking because of the destruction of afferent pain pathways. Unexplained fever, worsening of spasticity, or deterioration in neurologic function should prompt a search for infection, thrombophlebitis, or an intraabdominal pathology. The loss of normal thermoregulation and inability to maintain normal body temperature can produce recurrent fever (*quadriplegic fever*), although most episodes of fever are due to infection of the urinary tract, lung, skin, or bone.

Bladder dysfunction generally results from loss of supraspinal innervation of the detrusor muscle of the bladder wall and the sphincter musculature. Detrusor spasticity is treated with anticholinergic drugs (oxybutinin, 2.5–5 mg qid) or tricyclic antidepressants with anticholinergic properties (imipramine, 25–200 mg/d). Failure of the sphincter muscle to relax during bladder emptying (urinary dyssynergia) may be managed with the α-adrenergic blocking agent terazosin hydrochloride (1–2 mg tid or qid), with intermittent catheterization, or, if that is not feasible, by use of a condom catheter in men or a permanent indwelling catheter. Surgical options include the creation of an artificial bladder by isolating a segment of intestine that can be catheterized intermittently (enterocystoplasty) or can drain continuously to an external appliance (urinary conduit). Bladder areflexia due to acute spinal shock or conus lesions is best treated by catheterization. Bowel regimens and disimpaction are necessary in most patients to ensure at least biweekly evacuation and avoid colonic distention or obstruction.

Patients with acute cord injury are at risk for venous thrombosis and pulmonary embolism. During the first 2 weeks, use of calf-compression devices and anticoagulation with heparin (5000 U subcutaneously every 12 h) or warfarin (INR, 2–3) are recommended. In cases of persistent paralysis, anticoagulation should probably be continued for 3 months.

Prophylaxis against decubitus ulcers should involve frequent changes in position in a chair or bed, the use of special mattresses, and cushioning of areas where pressure sores often develop, such as the sacral prominence and heels. Early treatment of ulcers with careful cleansing, surgical or enzyme debridement of necrotic tissue, and appropriate dressing and drainage may prevent infection of adjacent soft tissue or bone.

Spasticity is aided by stretching exercises to maintain mobility of joints. Drug treatment is effective but may result in reduced function, as some patients depend upon spasticity as an aid to stand, transfer, or walk. Baclofen (15–240 mg/d in divided doses) is effective; it acts by facilitating GABA-mediated inhibition of motor reflex arcs. Diazepam acts by a similar mechanism and is useful for leg spasms that interrupt sleep (2–4 mg at bedtime). Tizanidine (2–8 mg tid), an α_2 adrenergic agonist that increases presynaptic inhibition of motor neurons, is another option. For nonambulatory patients, the direct muscle inhibitor dantrolene (25–100 mg qid) may be used, but it is potentially hepatotoxic. In refractory cases, intrathecal baclofen administered via an implanted pump, botulinum toxin injections, or dorsal rhizotomy may be required to control spasticity.

A paroxysmal autonomic hyperreflexia may occur following lesions above the major splanchnic sympathetic outflow at T6. Headache, flushing, and diaphoresis above the level of the lesion, as well as hypertension with bradycardia or tachycardia, are the major symptoms. The trigger is typically a noxious stimulus—for example, bladder or bowel distention, a urinary tract infection, or a decubitus ulcer—below the level of the cord lesion. Treatment consists of removal of offending stimuli; ganglionic blocking agents (mecamylamine, 2.5–5 mg) or other short-acting antihypertensive drugs are useful in some patients.

Attention to these details allows longevity and a productive life for patients with complete transverse myelopathies.

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373 Concussion and Other Head Injuries

Allan H. Ropper

Almost 10 million head injuries occur annually in the United States, about 20% of which are serious enough to cause brain damage. Among men <35 years, accidents, usually motor vehicle collisions, are the chief cause of death, and >70% of these involve head injury. Furthermore, minor head injuries are so common that almost all physicians will be called upon to provide immediate care or to see patients who are suffering from various sequelae.

Medical personnel caring for head injury patients should be aware that (1) spinal injury often accompanies head injury and care must be taken to prevent compression of the spinal cord due to instability of the spinal column; (2) intoxication is an important accompaniment of

traumatic brain injury and, when appropriate, testing should be carried out for drugs and alcohol; and (3) accompanying systemic injuries, including rupture of abdominal organs, may produce vascular collapse or respiratory compromise requiring immediate attention.

TYPES OF HEAD INJURIES

CONCUSSION

This classically refers to an immediate but transient loss of consciousness that is associated with a short period of amnesia. Some patients do not lose consciousness after a minor head injury and instead may appear dazed, confused or report feeling "star struck." The mechanics of concussion involve a blunt forward impact that creates sudden deceleration of the head and an anterior-posterior movement of the brain within the skull. Severe concussion may precipitate a brief convulsion or autonomic signs such as facial pallor, bradycardia, faintness with mild hypotension, or sluggish pupillary reaction, but most patients are soon neurologically normal. The loss of consciousness in concussion is believed to be a transient electrophysiologic dysfunction of the reticular activating system in the upper midbrain caused by rotation of the cerebral hemispheres on the relatively fixed brainstem (Chap. 268).

Gross and light-microscopic changes in the brain are usually absent following concussion, but biochemical and ultrastructural changes, such as mitochondrial ATP depletion and local disruption of the blood-brain barrier, suggest that transient abnormalities occur. CT and MRI scans are usually normal; however, a small number of patients will be found to have an intracranial hemorrhage or brain contusion.

A brief period of both retrograde and anterograde amnesia is typical of concussion and disappears rapidly in alert patients. The memory loss spans the moments before impact but with severe injuries loss of memory may encompass the previous days or weeks (rarely months). The extent of retrograde amnesia roughly correlates with the severity of injury. Memory is regained in an orderly way from the most distant to recent memories, with islands of amnesia occasionally remaining. The mechanism of amnesia is not known. Hysterical posttraumatic amnesia is not uncommon after head injury and should be suspected when inexplicable abnormalities of behavior occur, such as recounting events that cannot be recalled on later testing, a bizarre affect, forgetting one's own name, or a persistent anterograde deficit that is excessive in comparison with the degree of injury. A further discussion of amnesia is provided in Chap. 27.

A single, uncomplicated concussion only infrequently produces permanent neurobehavioral changes in patients who are free of preexisting psychiatric problems and substance abuse. Nonetheless, residual minor problems in memory and concentration may have an anatomic correlate in microscopic cerebral lesions (see below).

CONTUSION, BRAIN HEMORRHAGE, AND AXONAL SHEARING LESIONS

A surface bruise of the brain, or *contusion*, consists of varying degrees of petechial hemorrhage, edema, and tissue destruction. Contusions and deeper hemorrhages result from mechanical forces that displace and compress the hemispheres forcefully and by deceleration of the brain against the inner skull, either under a point of impact (coup lesion) or, as the brain swings back, in the antipolar area (contrecoup lesion). Trauma sufficient to cause prolonged unconsciousness usually produces some degree of contusion. Blunt deceleration impact, as from an automobile dashboard or from falling forward while drunk, causes contusions on the orbital surfaces of the frontal lobes and the anterior and basal portions of the temporal lobes. With lateral forces, as from impact on an automobile door frame, the contusions are situated on the lateral convexity of the hemisphere. The clinical signs are determined by the location and size of the contusion; often, there are no focal neurologic abnormalities. A hemiparesis or gaze preference is fairly typical of moderately sized contusions. Large bilateral contusions produce coma with extensor posturing, while those limited to the frontal lobes cause a taciturn state. Contusions in the temporal lobe may cause delirium or an aggressive, combative syndrome.

Contusions are easily visible on CT and MRI scans, appearing as inhomogeneous hyperdensities on CT and as hyperintensities on MRI;

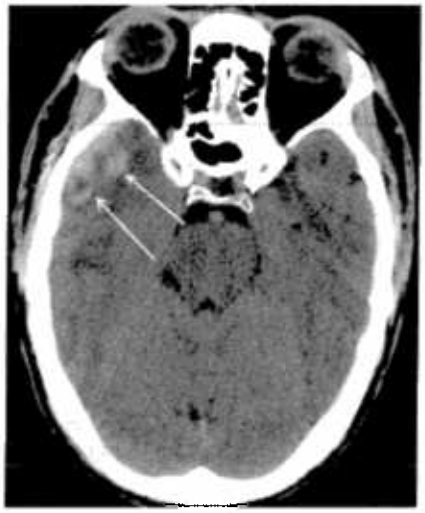

FIGURE 373-1 Traumatic cerebral contusion. Noncontrast CT scan demonstrating a hyperdense hemorrhagic region in the anterior temporal lobe.

the signal changes reflect small scattered areas of cortical and subcortical blood and localized brain edema (Fig. 373-1); there is usually some subarachnoid bleeding detected by scans or lumbar puncture. Blood in the cerebrospinal fluid (CSF) resulting from trauma may provoke a mild inflammatory reaction. Over a few days, contusions acquire a surrounding contrast enhancement and edema that may be mistaken for tumor or abscess. Glial and macrophage reactions result in scarred, hemosiderin-stained depressions on the cortex (*plaques jaunes*) that are the main source of posttraumatic epilepsy.

Torsion or shearing forces within the brain cause hemorrhages of the basal ganglia and other deep regions. Large hemorrhages after minor trauma suggest that there is a bleeding diathesis or cerebrovascular amyloidosis. For unexplained reasons, deep cerebral hemorrhages may not develop until several days after injury. Sudden neurologic deterioration in a comatose patient or a sudden rise in intracranial pressure (ICP) should therefore prompt investigation with a CT scan.

Another type of deep white matter lesion consists of widespread acute disruption, or shearing, of axons at the time of impact. Most characteristic are small areas of tissue injury in the corpus callosum and dorsolateral pons. The presence of widespread axonal damage in both hemispheres, a state called *diffuse axonal injury*, is proposed to explain persistent coma and the vegetative state after closed head injury (Chap. 268), but small ischemic-hemorrhagic lesions in the midbrain and thalamus are as often the cause of this clinical state. Only severe shearing lesions that contain blood are visualized by CT, usually in the corpus callosum and centrum semiovale (Fig. 373-2); however, special imaging sequences of the MRI can demonstrate such lesions throughout the white matter.

SKULL FRACTURES

A blow to the skull causes fracture if the elastic tolerance of the bone is exceeded. Intracranial lesions accompany roughly two-thirds of skull fractures, and the presence of a skull fracture increases manyfold the chances of an underlying subdural or epidural hematoma. Consequently, fractures are primarily markers of the site and severity of injury. They also provide potential pathways for entry of bacteria (meningitis) or air (pneumocephalus) to the CSF and for leakage of CSF out through the dura.

Most fractures are linear and extend from the point of impact toward the base of the skull. Basilar skull fractures are often extensions of adjacent linear fractures over the convexity of the skull but may occur independently owing to stresses on the floor of the middle cranial fossa or occiput. Basilar fractures are usually parallel to the petrous bone or along the sphenoid bone and directed toward the sella turcica and ethmoidal groove. Although most basilar fractures are uncomplicated, they can cause CSF leakage, pneumocephalus, and cavernous-

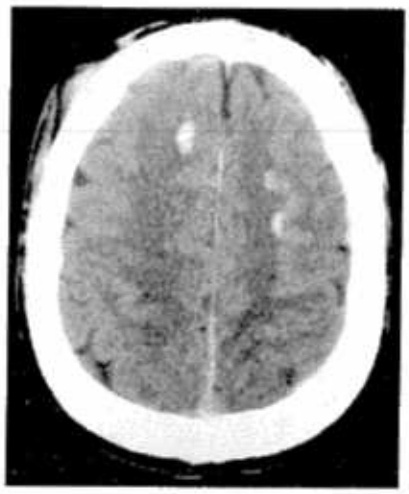

FIGURE 373-2 Multiple small areas of hemorrhage and tissue disruption in the white matter of the frontal lobes on noncontrast CT scan. These appear to reflect an extreme type of the diffuse axonal shearing lesions that occur with closed head injury.

carotid fistulas. Hemotympanum (blood behind the tympanic membrane), delayed ecchymosis over the mastoid process (Battle sign), or periorbital ecchymosis ("raccoon sign") are associated signs. Because routine x-ray examination may fail to disclose basilar fractures, they should be suspected if these clinical signs are present.

CSF may leak through the cribriform plate or the adjacent sinus and allow a watery discharge from the nose (CSF rhinorrhea). Persistent rhinorrhea and recurrent meningitis are indications for surgical repair of torn dura underlying the fracture. The site of the leak is often difficult to determine, but useful diagnostic tests include the instillation of water-soluble contrast into the CSF followed by CT with the patient in various positions, or injection of radionuclide compounds or fluorescein into the CSF and the insertion of absorptive nasal pledgets. The site of an intermittent leak is rarely delineated, and many resolve spontaneously.

Sellar fractures, even those associated with serious neuroendocrine dysfunction, may be radiologically occult or are evident by an air-fluid level in the sphenoid sinus. Fractures of the dorsum sella cause sixth or seventh nerve palsies or optic nerve damage.

Petrous bone fractures, especially those oriented along the long axis of the bone, may be associated with facial palsy, disruption of ear ossicles, and CSF otorrhea. Transverse petrous fractures are less common; they almost always damage the cochlea or labyrinths and often the facial nerve as well. External bleeding from the ear is usually from local abrasion of the external canal but can also result from petrous fracture.

Fractures of the frontal bone are usually depressed, involving the frontal and paranasal sinuses and the orbits; permanent anosmia results if the olfactory filaments in the cribriform plate are disrupted. Depressed skull fractures are typically compound, but they are often asymptomatic because the impact energy is dissipated in breaking the bone; however, a few have underlying brain contusions. Debridement and exploration of compound fractures are required in order to avoid infection; simple fractures do not require surgery.

CRANIAL NERVE INJURIES

The cranial nerves most often injured with head trauma are the olfactory, optic, oculomotor, and trochlear; the first and second branches of the trigeminal nerve; and the facial and auditory nerves. Anosmia and an apparent loss of taste (actually a loss of perception of aromatic flavors, with elementary taste perception retained) occur in ~10% of persons with serious head injuries, particularly after falls on the back of the head. This is the result of displacement of the brain and shearing of the olfactory nerve filaments and may occur in the absence of a fracture. At least partial recovery of olfactory and gustatory function is the rule, but if bilateral anosmia persists for several months, the prognosis is poor. Partial optic nerve injuries from closed trauma result in blurring of vision, central or paracentral scotomas, or sector defects. Direct orbital injury may cause short-lived blurred vision for close objects due to reversible iridoplegia. Diplopia limited to downward gaze and corrected when the head is tilted away from the side of the affected eye indicates trochlear nerve damage. It occurs frequently as an isolated problem after minor head injury or may develop after a delay of several days without pathophysiologic explanation. Direct facial nerve injury caused by a basilar fracture is present immediately in up to 3% of severe injuries; it may also be delayed 5–7 days. Fractures through the petrous bone, particularly the less common transverse type, are liable to produce facial palsy. Delayed palsy, the mechanism of which is unknown, has a good prognosis. Injury to the eighth cranial nerve from a fracture of the petrous bone causes loss of hearing, vertigo, and nystagmus immediately after injury. Deafness from eighth nerve injury must be distinguished from that due to rupture of the eardrum, blood in the middle ear, or disruption of the ossicles from fracture through the middle ear. Dizziness and high-tone hearing loss occur with direct cochlear concussion.

SEIZURES

Convulsions are surprisingly uncommon immediately after a head injury, but a brief period of tonic extensor posturing or a few clonic movements of the limbs just after the moment of impact can occur. However, the cortical scars that evolve from contusions are highly epileptogenic and may later manifest as seizures, even after many years (Chap. 363). The severity of injury roughly determines the risk of future seizures. It has been estimated that 17% of individuals with brain contusion, subdural hematoma, or prolonged loss of consciousness will develop a seizure disorder and that this risk extends for an indefinite period of time, whereas the risk is ≤2% after mild injury. The majority of convulsions in the latter group occurs within 5 years of injury but may be delayed for decades. Penetrating injuries have a much higher rate of subsequent epilepsy.

SUBDURAL AND EPIDURAL HEMATOMAS

Hemorrhages beneath the dura (subdural) or between the dura and skull (epidural) each have characteristic clinical and radiologic features. They are associated with underlying contusions and other injuries, often making it difficult to determine the relative contribution of each component to the clinical state. The mass effect and raised ICP caused by these hematomas may be life threatening, making it imperative to identify them rapidly by CT or MRI scan and to remove them when appropriate.

Acute Subdural Hematoma (Fig. 373-3) Up to one-third of patients have a lucid interval lasting minutes to hours before coma supervenes, but most are drowsy or comatose from the moment of injury. Direct cranial trauma may be minor and is not required for acute subdural hemorrhage to occur, especially in the elderly and those taking anticoagulant medications. Acceleration forces alone, as from whiplash, are sometimes sufficient to produce subdural hemorrhage. A unilateral headache and slightly enlarged pupil on the same side are frequently but not invariably present. Stupor or coma, hemiparesis, and unilateral pupillary enlargement are signs of larger hematomas. In an acutely deteriorating patient, burr (drainage) holes or an emergency craniotomy are required. Small subdural hematomas may be asymptomatic and usually do not require evacuation.

A subacutely evolving syndrome due to subdural hematoma occurs days or weeks after injury with drowsiness, headache, confusion, or mild hemiparesis; it usually arises in alcoholics and in the elderly, often after only minor trauma.

On imaging studies subdural hematomas appear as crescentic collections over the convexity of one or both hemispheres, most commonly in the frontotemporal region, and less often in the inferior middle fossa or over the occipital poles (Fig. 373-3). Interhemispheric, posterior fossa, or bilateral convexity hematomas are less frequent and are difficult to diagnose clinically, although drowsiness and the signs

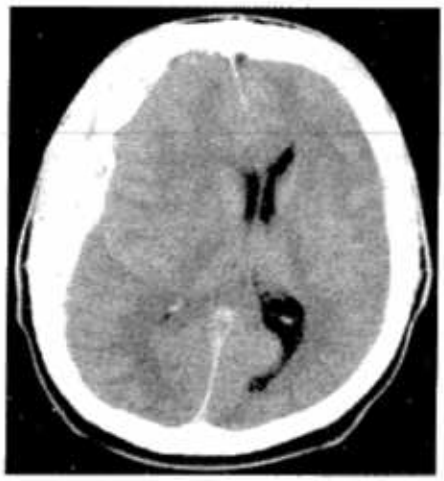

FIGURE 373-3 Acute subdural hematoma. Noncontrast CT scan reveals a hyperdense clot which has an irregular border with the brain and causes more horizontal displacement (mass effect) than might be expected from its thickness. The disproportionate mass effect is the result of the large rostral-caudal extent of these hematomas. Compare to Fig. 373-4.

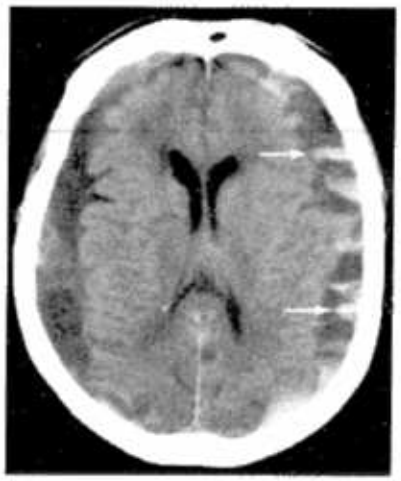

FIGURE 373-5 CT scan of chronic bilateral subdural hematomas of different ages. The collections began as acute hematomas and have become hypodense in comparison to the adjacent brain after a period during which they were isodense and difficult to appreciate. Some areas of resolving blood are contained on the more recently formed collection on the left (*arrows*).

expected for damage in each region can usually be detected. The bleeding that causes larger hematomas is primarily venous in origin, although additional arterial bleeding sites are sometimes found at operation and a few large hematomas have a purely arterial origin.

Epidural Hematoma (Fig. 373-4) These evolve more rapidly than subdural hematomas and are correspondingly more treacherous. They occur in up to 10% of cases of severe head injury but are associated with underlying cortical damage less often than are subdural hematomas. Most patients are unconscious when first seen. A "lucid interval" of several minutes to hours before coma supervenes is most characteristic of epidural hemorrhage, but it is still uncommon, and epidural hemorrhage is by no means the only cause of this temporal sequence. Rapid surgical evacuation and ligation or cautery of the damaged vessel that is the source of bleeding, usually the middle meningeal artery that has been lacerated by an overlying skull fracture, is indicated.

Chronic Subdural Hematoma A history of trauma may or may not be elicited in relation to chronic subdural hematoma. The causative injury may have been trivial and forgotten; 20–30% of patients recall no head injury, particularly the elderly and those with clotting disorders. Headache is common but not invariable. Additional features may include slowed thinking, vague change in personality, seizure, or a mild hemiparesis. The headache may fluctuate in severity, sometimes with changes in head position. Bilateral chronic subdural hematomas produce perplexing clinical syndromes. Focal signs such as hemiparesis may be lacking, and the initial clinical impression may be of a stroke, brain tumor, drug intoxication, depression, or a dementing illness because drowsiness, inattentiveness, and incoherence of thought are more prominent than focal signs such as hemiparesis. Patients with undetected bilateral subdural hematomas have a low tolerance for surgery, anesthesia, and drugs that depress the nervous system, remaining drowsy or confused for long periods. Chronic hematomas rarely cause brief episodes of hemiparesis or aphasia that are indistinguishable from transient ischemic attacks; on occasion a chronic collection can expand over a period of days or weeks and clinically resemble a brain tumor.

Skull x-rays are usually normal except for a shift of the calcified pineal body to one side or an occasional unexpected fracture. In long-standing cases an irregular calcification of membranes that surround the hematoma may be appreciated. CT without contrast infusion shows a low-density mass over the convexity of the hemisphere (Fig. 373-5), but between 2 and 6 weeks after the initial bleeding the hemorrhage becomes isodense compared to adjacent brain and is then inapparent. Many subdural hematomas that are a week or more in age contain areas of blood adjacent to intermixed serous fluid. Bilateral chronic hematomas may fail to be detected because of the absence of lateral tissue shifts; this circumstance is suggested by a "hypernormal" CT scan with fullness of the cortical sulci and small ventricles in an older patient. The infusion of contrast material demonstrates enhancement of the vascular fibrous capsule surrounding the collection. MRI reliably identifies subacute and chronic hematomas.

Clinical observation coupled with serial imaging is a reasonable approach to patients with few symptoms and small chronic subdural collections. Treatment with glucocorticoids alone is sufficient for some hematomas, but surgical evacuation is more often successful. The fibrous membranes that grow from the dura and encapsulate the collection require removal to prevent recurrent fluid accumulation. Small hematomas are resorbed, leaving only the organizing membranes. On imaging studies very chronic subdural hematomas may be difficult to distinguish from hygromas, which are collections of CSF from a rent in the arachnoid membrane. As noted, cortical damage underlying a chronic hematoma may serve as the origin of seizures.

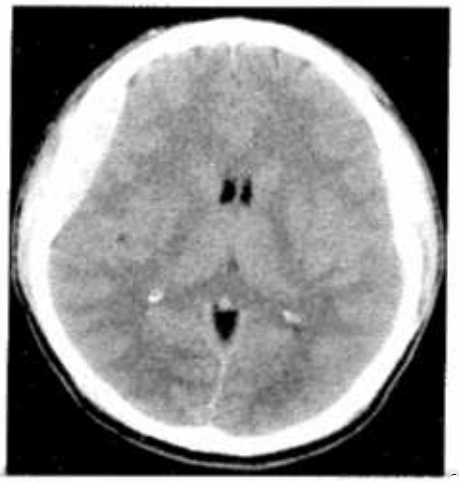

FIGURE 373-4 Acute epidural hematoma. The tightly attached dura is stripped from the inner table of the skull, producing a characteristic lenticular-shaped hemorrhage on noncontrast CT scan. Epidural hematomas are usually caused by tearing of the middle meningeal artery following fracture of the temporal bone.

MINOR INJURY

The patient who is fully alert and attentive minutes after head injury but who has one or more symptoms of headache, dizziness, faintness, nausea, a single episode of emesis, difficulty with concentration, or slight blurring of vision has a good prognosis with little risk of subsequent deterioration. Such patients have usually sustained a concussion and are expected to have a brief amnestic period. Children are particularly prone to drowsiness, vomiting, and irritability, which are sometimes delayed for several hours after apparently minor injuries. Vasovagal syncope that follows injury may cause undue concern. Constant generalized or frontal headache is common in the following days. It may be migrainous (throbbing and hemicranial) in nature or aching and bilateral. After several hours of observation, patients with minor injury may be accompanied home and observed for a day by a family member or friend; written instructions to return if symptoms worsen should be provided.

Persistent severe headache and repeated vomiting in the context of normal alertness and no focal neurologic signs are usually benign, but radiologic studies should be obtained and a period of observation in the hospital is justified. The decision to perform imaging tests depends largely on clinical signs that indicate the impact was severe (e.g., prolonged concussion, periorbital or mastoid hematoma, repeated vomiting, palpable skull fracture), on the seriousness of other bodily injuries, and on the degree of surveillance that can be anticipated after discharge. Two prospective studies have suggested that older age, two or more episodes of vomiting, >30 min of retrograde or persistent anterograde amnesia, seizure, and concurrent drug or alcohol intoxication are sensitive (but not specific) indicators of intracranial hemorrhage that justify CT scanning. It is appropriate to be more liberal in obtaining CT scans in children since a small number, even without loss of consciousness, will display intracranial lesions.

Concussion in Sports In the current absence of adequate data, a common sense approach has been taken to returning an athlete who has suffered a concussion to physical activities. It is generally advisable to avoid contact sports for several days at least, and for weeks after a severe concussion or after more than one minor concussion or if there are protracted neurologic symptoms (Table 373-1). These guidelines are designed to avoid cognitive decline and an extremely rare complication of recurrent head injury, termed the *second impact syndrome*, in which cerebral swelling follows a minor head injury. There is some evidence that repeated concussions in football and soccer players are associated with mild but cumulative cognitive deficits, but this topic is controversial.

TABLE 373-1 GUIDELINES FOR MANAGEMENT OF CONCUSSION IN SPORTS

Severity of Concussion
Grade 1: Transient confusion, no loss of consciousness (LOC), all symptoms resolve within 15 min.
Grade 2: Transient confusion, no LOC, but concussive symptoms or mental status abnormalities persist longer than 15 min.
Grade 3: Any LOC, either brief (seconds) or prolonged (minutes).
On-site Evaluation
1. Mental status testing a. Orientation—time, place, person, circumstances of injury b. Concentration—digits backward, months of year in reverse order c. Memory—names of teams, details of contest, recent events, recall of three words and objects at 0 and 5 min 2. Finger-to-nose with eyes open and closed 3. Pupillary symmetry and reaction 4. Romberg and tandem gait 5. Provocative testing—40-yard sprint, 5 push ups, 5 sit ups, 5 knee bends (development of dizziness, headaches, or other symptoms is abnormal)
Management Guidelines
Grade 1: Remove from contest. Examine immediately and at 5 min intervals. May return to contest if exam clears within 15 min. A second grade 1 concussion eliminates player for 1 week, with return contingent upon normal neurologic assessment at rest and with exertion.
Grade 2: Remove from contest, cannot return for at least 1 week. Examine at frequent intervals on sideline. Formal neurologic exam the next day. If headache or other symptoms persist for 1 week or longer, CT or MRI scan is indicated. After 1 full asymptomatic week, repeat neurologic assessment at rest and with exercise before cleared to resume play. A second grade 2 concussion eliminates player for at least 2 weeks following complete resolution of symptoms at rest or with exertion. If imaging shows abnormality, player is removed from play for the season.
Grade 3: Transport by ambulance to emergency department if still unconscious or worrisome signs are present; cervical spine stabilization may be indicated. Neurologic exam and, when indicated, CT or MRI scan will guide subsequent management. Hospital admission indicated when signs of pathology are present or if mental status remains abnormal. If findings are normal at the time of the initial medical evaluation, the athlete may be sent home, but daily exams as an outpatient are indicated. A brief (LOC for seconds) grade 3 concussion eliminates player for 1 week, and a prolonged (LOC for minutes) grade 3 concussion for 2 weeks, following complete resolution of symptoms. A second grade 3 concussion should eliminate player from sports for at least 1 month following resolution of symptoms. Any abnormality on CT or MRI scans should result in termination of the season for the athlete, and return to play at any future time should be discouraged.

Source: Modified from Quality Standards Subcommittee of the American Academy of Neurology: *The American Academy of Neurology Practice Handbook.* The American Academy of Neurology, St. Paul, MN, 1997.

INJURY OF INTERMEDIATE SEVERITY

Patients who have persistent confusion, behavioral changes, subnormal alertness, extreme dizziness, or focal neurologic signs such as hemiparesis should be admitted to the hospital and soon thereafter have a CT scan. Usually a cerebral contusion or hematoma is found. The common clinical syndromes in this group include (1) delirium with a disinclination to be examined or moved, expletive speech, and resistance if disturbed (anterior temporal lobe contusions); (2) a quiet, disinterested, slowed mental state (abulia) with dull facial expression alternating with irascibility (inferior frontal and frontopolar contusions); (3) a focal deficit such as aphasia or mild hemiparesis (due to subdural hematoma or convexity contusion, or, less often but frequently missed, carotid artery dissection); (4) confusion and inattention, poor performance on simple mental tasks, and fluctuating or slightly erroneous orientation (associated with several types of injuries, including those described above as well as medial frontal contusions and interhemispheric subdural hematoma); (5) repetitive vomiting, nystagmus, drowsiness, and unsteadiness (usually from labyrinthine concussion, but occasionally due to a posterior fossa subdural hematoma or vertebral artery dissection); and (6) diabetes insipidus (damage to the median eminence or pituitary stalk). *Injuries of this degree are often complicated by drug or alcohol intoxication, and clinically inapparent cervical spine injury may be present.*

Most patients in this category, after appropriate surgical removal of hematomas, improve over several days or weeks. During the first week the state of alertness, memory, and other cognitive functions often fluctuates, and irascibility or agitation is common. Behavioral changes are worse at night, as with many other encephalopathies, and may be treated with small doses of antipsychotic medications. Subtle abnormalities of attention, intellect, spontaneity, and memory tend to return to normal weeks or months after the injury, sometimes surprisingly abruptly. Persistent problems in cognition are discussed below.

SEVERE INJURY

Patients who are comatose from the onset require immediate neurologic attention and resuscitation. After intubation, with care taken to immobilize the cervical spine, the depth of coma, pupillary size and reactivity, limb movements, and Babinski responses are assessed. As soon as vital functions permit and cervical spine x-rays and a CT scan have been obtained, the patient should be transported to a critical care unit where systemic complications that follow severe brain injury can be treated. Hypoxia should be reversed and normal saline used as the preferred resuscitation fluid. The finding of an epidural or subdural hematoma or large intracerebral hemorrhage is an indication for

TABLE 373-2 GLASGOW COMA SCALE FOR HEAD INJURY

Eye opening (E)		Verbal response (V)	
Spontaneous	4	Oriented	5
To loud voice	3	Confused, disoriented	4
To pain	2	Inappropriate words	3
Nil	1	Incomprehensible sounds	2
Best motor response (M)		Nil	1
Obeys	6		
Localizes	5		
Withdraws (flexion)	4		
Abnormal flexion posturing	3		
Extension posturing	2		
Nil	1		

Note: Coma score = E + M + V. Patients scoring 3 or 4 have an 85% chance of dying or remaining vegetative, while scores >11 indicate only a 5–10% likelihood of death or vegetative state and 85% chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of recovery.

prompt surgery and intracranial decompression in an otherwise salvageable patient. The use of prophylactic anticonvulsants has been recommended by some neurosurgeons but there is little supportive data. Management of raised ICP, a frequent feature of severe head injury, is discussed in Chap. 269.

GRADING AND PROGNOSIS

In severe head injury, the clinical features of eye opening, motor responses of the limbs, and verbal output have been found to be generally predictive of outcome. These three features are summarized in the Glasgow Coma Scale; a score between 3 and 15 is assigned based on responses (Table 373-2). Over 85% of patients with aggregate scores of <5 die within 24 h. However, a number of patients with slightly higher scores and a poor initial prognosis, including a few without pupillary light responses, survive, suggesting that an initially aggressive approach is justified in most patients. Patients <20 years, particularly children, may make remarkable recoveries after having grave early neurologic signs. In one large study of severe head injury, 55% of children had a good outcome at 1 year, compared with 21% of adults. Older age, increased ICP, early hypoxia or hypotension, and evidence on imaging of compression of the cisterns surrounding the brainstem and shift of midline structures are all poor prognostic signs. A delay in the evacuation of large intracerebral hemorrhages is also associated with a poorer prognosis.

POSTCONCUSSION SYNDROME

The *postconcussion syndrome* refers to a state of nervous instability following mild or moderate head injury. The main features are fatigue, dizziness, headache, and difficulty in concentration. The syndrome is at times difficult to distinguish from asthenia and depression. Based largely on experimental models, it has been proposed that subtle axonal shearing lesions or as yet undefined biochemical alterations account for the cognitive symptoms. In moderate and severe trauma, neuropsychological changes such as difficulty with attention, memory, and other cognitive deficits are undoubtedly present, sometimes severe, but many deficits identified by formal testing do not impact daily functioning. Test scores tend to improve rapidly during the first 6 months after injury, then more slowly for years.

Rx CONCUSSION

Management of the various symptoms of the postconcussive syndrome requires the identification and treatment of depression, sleeplessness, anxiety, persistent headache, and dizziness. A clear explanation of the problems that may follow concussion has been shown to reduce subsequent complaints. Care is taken to avoid prolonged use of drugs that produce dependence. Vestibular exercises (Chap. 30) and small doses of vestibular suppressants such as phenergan may be helpful when dizziness is the main problem. Patients who after minor or moderate injury report difficulty with memory or with complex cognitive tasks at work may also be reassured that these problems usually improve over 6–12 months. It is helpful to obtain serial and quantified neuropsychological testing in order to adjust the work environment to the patient's current abilities and to document improvement over time. Whether cognitive exercises are useful is uncertain, but patients certainly report them to be so. Previously energetic individuals usually have the best recoveries. In patients with persistent symptoms, the possibility exists of malingering or prolongation as a result of litigation.

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374 Primary and Metastatic Tumors of the Nervous System

Stephen M. Sagar, Mark A. Israel

Malignant primary tumors of the central nervous system (CNS) occur in ~16,500 individuals and account for an estimated 13,000 deaths in the United States annually, a mortality rate of 6 per 100,000. The age-adjusted incidence appears to be about the same worldwide. An approximately equal number of benign tumors of the CNS are diagnosed, with a much lower mortality rate. Glial tumors account for 50–60% of primary brain tumors, meningiomas for 25%, schwannomas for 10%, and other CNS tumors for the remainder.

Brain and vertebral metastases from systemic cancer are far more prevalent than primary CNS tumors. About 15% of patients who die of cancer (80,000 individuals each year in the United States) have symptomatic brain metastases; an additional 5% suffer spinal cord involvement. Brain and spinal metastases therefore pose a major problem in the management of systemic cancer.

APPROACH TO THE PATIENT: Brain Tumors

CLINICAL FEATURES Brain tumors usually present with one of three syndromes: (1) subacute progression of a focal neurologic deficit; (2) seizure; or (3) nonfocal neurologic disorder such as headache, dementia, personality change, or gait disorder. The presence of systemic symptoms such as malaise, weight loss, anorexia, or fever suggests a metastatic rather than a primary brain tumor.

Progressive focal neurologic deficits result from compression of neurons and white matter tracts by expanding tumor and surrounding edema. Less commonly, a brain tumor presents with a sudden stroke-like onset of a focal neurologic deficit. Although this presentation may be caused by hemorrhage into the tumor, often no hemorrhage can be demonstrated and the mechanism is obscure. Tumors frequently associated with hemorrhage include high-grade gliomas, metastatic melanoma, and choriocarcinoma.

Seizures may result from disruption of cortical circuits. Tumors that invade or compress the cerebral cortex, even small meningiomas, are more likely to be associated with seizures than subcortical neoplasms. Nonfocal neurologic dysfunction usually reflects in-

creased intracranial pressure (ICP), hydrocephalus, or diffuse tumor spread. Tumors in some areas of the brain may produce behavioral disorders; for example, frontal lobe tumors may present with personality change, dementia, or depression.

Headache may result from focal irritation or displacement of pain-sensitive structures (Chap. 15) or from a generalized increase in ICP. A headache that worsens rather than abates with recumbency is suggestive of a mass lesion. Headaches from increased ICP are usually holocephalic and episodic, occurring more than once a day. They typically develop rapidly over several minutes, persist for 20–40 min, and subside quickly. They may awaken the patient from a sound sleep, generally 60–90 min after retiring. Vomiting may occur with severe headaches. As elevated ICP becomes sustained, the headache becomes continuous but varying in intensity. Elevated ICP may cause papilledema (Chap. 29), although it is often not present in infants or patients >55 years.

The Karnofsky performance scale is useful in assessing patients with brain tumors (Chap. 77). A score ≥70 indicates that the patient is ambulatory and independent in self-care activities; it is often taken as a level of function justifying aggressive therapy.

NEUROIMAGING CT and MRI can reveal mass effect and contrast enhancement. Mass effect reflects the volume of neoplastic tissue as well as surrounding edema. Brain tumors typically produce a vasogenic pattern of edema, with accumulation of excess water in surrounding white matter. Contrast enhancement reflects a breakdown of the blood-brain barrier within the tumor, permitting leakage of contrast agent. Low-grade gliomas typically do not exhibit contrast enhancement.

Positron emission tomography (PET) and single-photon emission tomography (SPECT) have ancillary roles in the imaging of brain tumors, primarily in distinguishing tumor recurrence from tissue necrosis that can occur after irradiation (see below). Functional imaging with PET, MRI, or magnetoencephalography may be of use in surgical or radiosurgical planning to define the anatomic relationship of the tumor to critical brain regions such as the primary motor or language cortex.

LABORATORY EXAMINATION Primary brain tumors typically do not produce serologic abnormalities such as an elevated sedimentation rate or tumor-specific antigens. In contrast, metastases to the nervous system, depending on the type and extent of the primary tumor, may be associated with systemic signs of malignancy (Chap. 77). Lumbar puncture is generally not useful in the diagnosis of brain tumors. The cerebrospinal fluid (CSF) rarely contains malignant cells, with the important exceptions of leptomeningeal metastases; primary CNS lymphoma; and primitive neuroectodermal tumors, including medulloblastoma. The primary use of lumbar puncture in the evaluation of a brain tumor is to exclude other diagnoses, such as infection or demyelinating disease. Moreover, lumbar puncture may precipitate brain herniation in patients with mass lesions and should be performed only in patients in whom imaging studies have demonstrated the basilar cisterns to be patent.

Rx BRAIN TUMORS

SYMPTOMATIC Glucocorticoids decrease the volume of edema surrounding brain tumors and improve neurologic function; dexamethasone (initially 12–20 mg/d in divided doses PO or IV) is used because it has relatively little mineralocorticoid activity. Because of the toxicities of long-term glucocorticoid administration, the dexamethasone dose is rapidly tapered to the lowest dose that relieves symptoms.

The treatment of epilepsy associated with brain tumors is identical to the treatment of other forms of partial epilepsy. The first-line agents phenytoin, carbamazepine, and valproic acid are equally effective; levetiracetam and oxcarbazepine are also coming into wide use (Chap. 363). It is common practice to administer anti-epileptic drugs prophylactically to all patients with supratentorial brain tumors, although there are no good data supporting this practice.

Gliomas and primary CNS lymphomas are associated with an increased risk for deep vein thrombosis and pulmonary embolism, probably because these tumors secrete procoagulant factors into the systemic circulation. Even though hemorrhage within gliomas is a frequent histopathologic finding, patients are at no increased risk for symptomatic intracranial bleeding following treatment with an anticoagulant. Prophylaxis with low-dose SC heparin should be employed for patients with brain tumors who have lower limb immobility, which places them at risk for deep venous thrombosis.

PRIMARY BRAIN TUMORS

ETIOLOGY

Exposure to ionizing radiation is the only well-documented environmental risk factor for the development of gliomas. A number of hereditary syndromes are associated with an increased risk of brain tumors (Table 374-1). Genes that contribute to the development of brain tumors, as well as other malignancies, fall into two general classes, *tumor-suppressor genes* and *oncogenes* (Chap. 79). Whereas germ-line mutations of such genes do occur in patients with hereditary predisposition syndromes (Table 374-1), most brain tumors do not occur in patients with such recognizable syndromes. As is the case in all other tumor types, somatic mutations are almost invariably present in malignant brain tumor tissue. Amplification of the *EGFR* gene occurs in approximately one-third of cases of glioblastoma multiforme (GBM), the highest grade astrocytoma. Moreover, cytogenetic analysis often reveals characteristic changes that can signal the alteration in cancer-related genes within these chromosomal regions. In astrocytic tumors, DNA is commonly lost on chromosomes 10p, 17p, 13q, and 9. Oligodendrogliomas frequently have deletions of 1p and 19q, resulting from a centromeric translocation and loss of one of the translocated chromosomes. In meningiomas portions of 22q, which contains the gene for neurofibromatosis (NF) type 2, are often lost.

The particular constellation of genetic alterations varies among individual gliomas, even those that are histologically indistinguishable. Moreover, gliomas are genetically unstable. Genetic abnormalities tend to accumulate with time, and these changes correspond with an increasingly malignant phenotype. There are at least two genetic routes for the development of GBM (Fig. 374-1). One route involves the progression, generally over years, from a low-grade astrocytoma with deletions of chromosome 17 and inactivation of the *p53* gene to a highly malignant glioma with additional chromosomal alterations. The second route is characterized by the de novo appearance of a malignant glioma with amplification of the *EGFR* gene and an intact *p53* gene in association with other genetic abnormalities.

ASTROCYTOMAS

Tumors with astrocytic cytologic features are the most common primary intracranial neoplasms (Fig. 374-2). The most widely used histologic grading system is the World Health Organization four-tiered grading system. Grade I is reserved for special histologic variants of astrocytoma that occur mainly in childhood and can have an excellent prognosis after surgical excision. These include *juvenile pilocytic astrocytoma*, *subependymal giant cell astrocytoma* (which most often occurs in patients with tuberous sclerosis), and *pleiomorphic xanthoastrocytoma*. At the other extreme is grade IV GBM, a clinically aggressive tumor. *Astrocytoma* (grade II) and *anaplastic astrocytoma* (grade III) are intermediate in their histologic and clinical manifestations. The histologic features associated with higher grade are hypercellularity, nuclear and cytoplasmic atypia, endothelial proliferation, mitotic activity, and necrosis. Endothelial proliferation and necrosis are strong predictors of aggressive behavior.

Quantitative measures of mitotic activity also correlate with prognosis. The proliferation index can be determined by immunohistochemical staining with antibodies to the proliferating cell nuclear antigen (PCNA) or with a monoclonal antibody termed *Ki-67*, which recognizes a histone protein expressed in proliferating but not quiescent cells.

The prognosis of brain tumor patients is closely associated with the histologic grade of the tumor. In a representative Finnish population, the

TABLE 374-1 HEREDITARY SYNDROMES ASSOCIATED WITH BRAIN TUMORS

Syndrome	Gene (Locus)	Gene Product (Function)	Nervous System Neoplasms
Neurofibromatosis type 1 (von Recklinghausen's Disease)[a]	*NF1* (17q)	Neurofibromin (GTPase activating protein)	Neuroma, schwannoma, meningioma, optic glioma
Neurofibromatosis type 2[a]	*NF2* (22q)	Merlin (cytoskeletal protein)	Schwannoma, glioma, ependymoma, meningioma
Tuberous sclerosis	*TSC1* (9q) *TSC2* (16p)	Hamartin (unknown function) Tuberin (GTPase activating protein)	Astrocytoma
von Hippel-Lindau[a]	*VHL* (3p)	pVHL (modulator of cellular hypoxic response)	Hemangioblastoma of retina, cerebellum and spinal cord; pheochromocytoma
Li-Fraumeni[a]	*p53* (17p)	TP53 (cell cycle and transcriptional regulator)	Malignant glioma
Retinoblastoma[a]	*RB1* (13q)	RB (cell cycle regulator)	Retinoblastoma, pineoblastoma, malignant glioma
Turcot	*APC* (5q) (adenomatous polyposis coli)	APC (cell adhesion)	Medulloblastoma, malignant glioma
Gorlin (basal cell nevus syndrome)	*PTCH* (9q) (patched)	PTH (developmental regulator)	Medulloblastoma
Multiple endocrine neoplasia 1 (Werner syndrome)[a]	*MEN1* (11q13)	Menin (cofactor for transcription)	Pituitary adenoma, malignant schwannoma

[a]Genetic testing possible.

median survival was 93.5 months for patients with grade I or II astrocytomas, 12.4 months for patients with grade III (anaplastic astrocytoma), and 5.1 months for patients with grade IV (GBM) tumors. Although these survival rates are somewhat lower than are generally reported, they represent a population-based experience and are not influenced by selection bias. Clinical features correlating with poor prognosis include age >65 and a poor functional status, as defined by the Karnofsky performance scale.

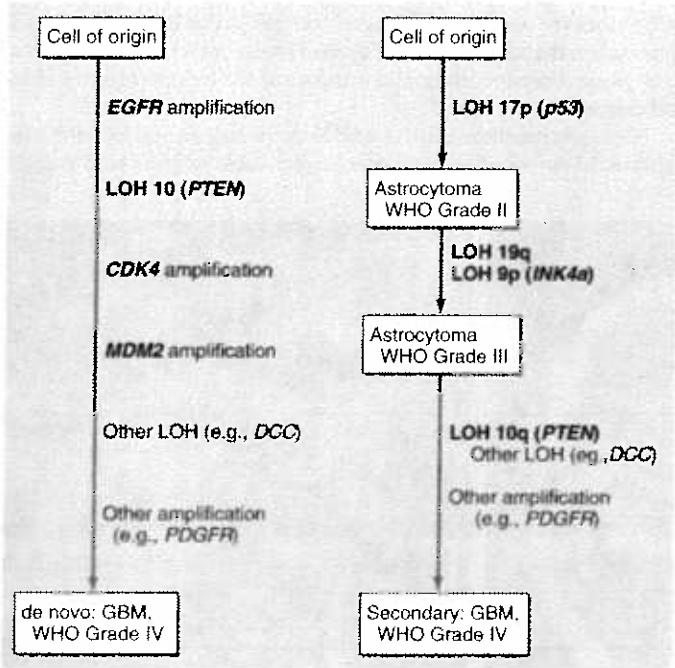

FIGURE 374-1 Model for the pathogenesis of human astrocytoma. Glioblastoma multiforme (GBM) typically presents without evidence of a precursor lesion, referred to as de novo GBM, frequently associated with amplification of the epidermal growth factor receptor (*EGFR*) gene. Less commonly, GBM arises in association with progressive genetic alterations after the diagnosis of a lower grade astrocytoma. These tumors are referred to as secondary GBM. The most widely described alterations are mutations of *p53* and *INK4a*. Other genes implicated in the development of these primary brain tumors include *CDK4*, *MDM2*, *DDC*, and *PDGFR*. LOH, loss of heterozygosity.

Low-Grade Astrocytoma Low-grade astrocytomas are more common in children than adults. Pilocytic astrocytoma, named for its characteristic spindle-shaped cells, is the most common childhood brain tumor and is typically benign. It frequently occurs in the cerebellum and is well demarcated from adjacent brain. Complete surgical excision usually produces long-term, disease-free survival.

The median overall survival of grade II astrocytoma is 5–6 years. The optimum timing of surgery and radiation therapy for these patients is unknown. Since astrocytomas infiltrate surrounding brain, total surgical excision is impossible. Moreover, they are genetically unstable and accumulate mutations over time, leading to more aggressive behavior. For patients who are symptomatic from mass effect or poorly controlled epilepsy, surgical excision can relieve symptoms. For patients who are asymptomatic or minimally symptomatic at presentation, a diagnostic biopsy should be performed and, when surgically feasible, the tumor may be resected. Whether radiation therapy is administered immediately postoperatively or at the time of tumor progression is not thought to affect overall survival, but immediate radiation therapy does delay tumor progression. No role for chemotherapy in the management of low-grade astrocytoma has been defined.

High-Grade Astrocytoma The large majority of astrocytomas arising in adults are high grade, supratentorial, and do not have a clearly defined margin between normal and malignant tissue. Neoplastic cells

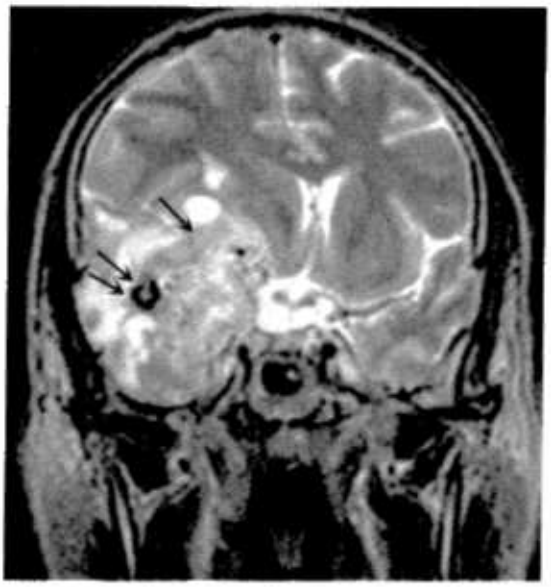

FIGURE 374-2 Malignant astrocytoma (glioblastoma). Coronal proton density–weighted MR scan through the temporal lobes demonstrates a heterogeneous right temporal lobe mass (*arrows*) compressing the third and lateral ventricles. The area of hypointense signal (*double arrows*) indicates either hemorrhage or calcification. Heterogeneous MR signal intensity is typical of glioblastoma.

migrate away from the main tumor mass and infiltrate adjacent brain, often tracking along white matter pathways. Imaging studies do not indicate the full extent of the tumor. These tumors are almost all eventually fatal. Median survival of patients with grade III astrocytoma is <3 years and for those with a grade IV tumor, <1 year. Longer survival correlates with younger age, better performance status, and greater extent of surgical resection. Late in their course, astrocytomas, especially those located in the posterior fossa, can metastasize along CSF pathways to the spine. Metastases outside the CNS are rare.

High-grade astrocytomas are managed with glucocorticoids, surgery, radiation therapy, and chemotherapy. Dexamethasone is generally administered at the time of diagnosis and continued for the duration of radiation therapy. After completion of radiation therapy, dexamethasone is tapered to the lowest possible dose.

Because astrocytomas infiltrate adjacent normal brain, total surgical excision is not possible. Nevertheless, retrospective studies indicate that the extent of tumor resection correlates with survival in younger patients. Therefore, accessible astrocytomas are generally resected aggressively. Surgery is indicated to obtain tissue for pathologic diagnosis and to control mass effect.

Postoperative radiation therapy prolongs survival and improves quality of life. Treated with dexamethasone alone following surgery, the mean survival of patients <65 years with glioblastoma is 7–9 months. Survival is prolonged to 11–13 months with radiation therapy. For primary glial tumors, radiation is generally administered to the tumor mass, as defined by contrast enhancement on a CT or MRI scan, plus a 2-cm margin. A total dose of 5000–7000 cGy is administered in 25–35 equal fractions, 5 days per week.

The roles of stereotaxic radiosurgery and interstitial brachytherapy in glioma treatment are uncertain. *Stereotaxic radiosurgery* is the administration of a focused high dose of radiation to a precisely defined volume of tissue in a single treatment. Stereotaxic radiosurgery can potentially achieve tumor ablation within the treated volume. A major limitation of stereotaxic radiosurgery is that it can be used for only relatively small tumors, generally <4 cm in maximum diameter. *Interstitial brachytherapy*, the implantation of radioactive material into the tumor mass, is generally reserved for tumor recurrence because of its associated toxicity, necrosis of adjacent brain tissue.

Chemotherapy is marginally effective and is often used as an adjuvant therapy following surgery and radiation therapy. Temozolomide, an orally administered alkylating agent, has replaced nitrosureas, including carmustine (BCNU) and lomustine (CCNU), as the most widely used chemotherapeutic agent for high-grade gliomas. Temozolomide is generally better tolerated than nitrosoureas, notably producing less fatigue and pulmonary toxicity, and has the advantage of oral administration. Moreover, a randomized trial of radiation therapy plus temozolomide for the adjuvant treatment of GBM compared to radiation therapy alone was the first clinical trial to demonstrate a clear-cut advantage of adjuvant chemotherapy for that disease. The patients who received radiation therapy plus temozolomide had a median survival $2^1/_2$ months longer than those who received radiation therapy alone. The modest survival benefit appears to be restricted to a subgroup of patients with methylation and silencing of the promoter for the *MGMT* gene coding for O^6-methylguanine-DNA methyltransferase.

An alternative approach to the chemotherapy of high-grade gliomas that has shown survival benefit in controlled trials is the surgical implantation directly into the tumor resection cavity of polymer wafers that release BCNU locally into surrounding brain. The efficacy of this approach is similar to but probably slightly less than that of temozolomide, although without the attendant systemic toxicity of chemotherapy.

Experimental approaches to brain tumor chemotherapy include efforts to bypass the blood-brain barrier using local injection of chemotherapeutic agents into the tumor mass or the intraarterial injection of chemotherapy following osmotic disruption of the blood-brain barrier. Molecularly targeted therapies are also being tested in patients with GBM. In particular, since mutation or overexpression of EGFR is common in GBM, EGFR antagonists or inhibitors of its signaling pathways are being evaluated in patients with GBM in clinical trials.

Gliomatosis cerebri is a rare form of astrocytoma in which there is diffuse infiltration of the brain by malignant astrocytes without a focal enhancing mass. It generally presents as a multifocal CNS syndrome or a more generalized disorder including dementia, personality change, or seizures. Neuroimaging studies are often nonspecific, and biopsy is required to establish the diagnosis. Gliomatosis cerebri is treated with whole-brain radiation therapy or temozolomide; in selected patients, radiation to the entire neuroaxis is employed.

OLIGODENDROGLIOMAS

Oligodendrogliomas, which comprise about 15% of gliomas in adults, have a more benign course and are more responsive to cytotoxic treatment than astrocytomas. For grade II oligodendrogliomas, the median survival is 7–8 years, and there are a substantial number of patients with prolonged survival (>10 years). For grade III or anaplastic oligodendrogliomas, median survival is ~5 years. Oligodendrogliomas occur chiefly in supratentorial locations; in adults, ~30% contain areas of calcification (Fig. 374-3).

As a rule, oligodendrogliomas are less infiltrative than astrocytomas, permitting more complete surgical excision. Histologic features of mitoses, necrosis, and nuclear atypia are associated with a more aggressive clinical course. If these features are prominent, the tumor is termed an *anaplastic oligodendroglioma*. Some gliomas contain mixtures of cells with astrocytic and oligodendroglial features. If this mixed histology is prominent, the tumor is termed a *mixed glioma*, or an *oligoastrocytoma*. The greater the oligodendroglial component, the more benign the clinical course.

Surgery, at minimum a stereotaxic biopsy, is necessary to establish a diagnosis. Many oligodendrogliomas are amenable to gross total surgical

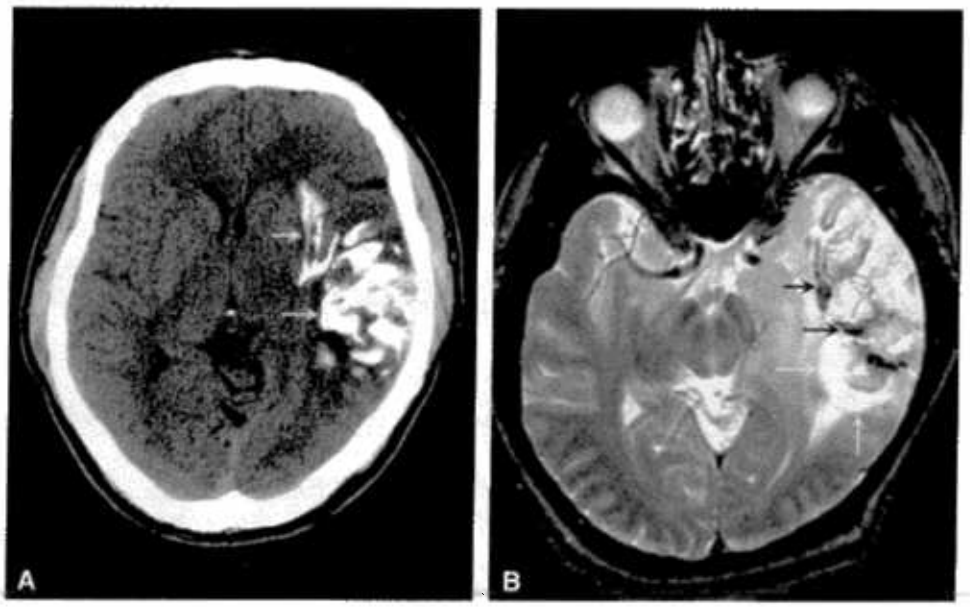

FIGURE 374-3 Oligodendroglioma. *A.* Noncontrast CT scan reveals a calcified mass involving the left temporal lobe (*arrows*) associated with mild mass effect but little edema. ***B.*** An MR T2-weighted image demonstrates a heterogeneous mass with hypointense signal (*black arrows*) surrounded by a zone of higher signal intensity (*white arrows*), consistent with a calcified temporal lobe mass. The tumor extends into the left medial temporal lobe and compresses the midbrain.

resection. In addition, oligodendrogliomas may respond dramatically to systemic combination chemotherapy with procarbazine, lomustine, and vincristine (PCV), or to temozolomide, which, although not approved by the U.S. Food and Drug Administration (FDA) for this indication, is currently much more widely used than PCV. Oligodendrogliomas with deletions of chromosome 1p always respond to chemotherapy, but only ~25% of oligodendrogliomas lacking the 1p deletion respond. The simultaneous deletion of 1p and 19q, which results from a centromeric translocation of chromosomes 1 and 19, predicts a durable response to chemotherapy (>31 months on average) and a much longer survival. It appears that the chromosomal translocation identifies a subgroup of anaplastic oligodendrogliomas with a less aggressive natural course, and response to chemotherapy is another marker of that favorable phenotype.

EPENDYMOMAS

In adults, the most frequent histologic type is myxopapillary ependymoma, which typically arises from the filum terminale of the spinal cord and appears in the lumbosacral region. The term *myxopapillary* refers to the papillary arrangement of tumor cells, which produce mucin. Ependymomas in adults may also occur intracranially or at higher levels of the spinal cord. On CT or MRI, ependymomas typically appear as diffusely enhancing masses relatively well demarcated from adjacent neural tissue. Following gross total resection, the prognosis is good, with >80% 5-year disease-free survival. Ependymomas that cannot be totally resected are treated with stereotaxic radiosurgery or with a course of external beam radiation therapy.

MEDULLOBLASTOMAS AND PRIMITIVE NEUROECTODERMAL TUMORS (PNET)

These highly cellular malignant tumors are thought to arise from neural precursor cells. Medulloblastomas occur in the posterior fossa and, along with astrocytomas, are the most frequent malignant brain tumors of children. PNET is a term applied to tumors histologically indistinguishable from medulloblastoma but occurring either in adults or supratentorially in children. In adults, >50% present in the posterior fossa. These tumors frequently disseminate along CSF pathways.

If possible, these tumors should be surgically excised; the less residual tumor left behind, the better the prognosis. In adults, surgical excision of a PNET should be followed by irradiation of the entire neuraxis, with a boost in radiation dose to the primary tumor. If the tumor is not disseminated at presentation, the prognosis is generally favorable. Aggressive treatment can result in prolonged survival, although half of adult patients relapse within 5 years of treatment. Whereas chemotherapy is widely used in medulloblastoma and PNET in children, its role in adults is not yet defined.

CNS LYMPHOMA

Primary CNS Lymphoma Primary CNS lymphoma is typically a high-grade B cell malignancy that presents within the neuraxis without evidence of systemic lymphoma. These occur most frequently in immunocompromised individuals, specifically organ transplant recipients and patients with AIDS (Chap. 182). In immunocompromised patients, CNS lymphomas are invariably associated with Epstein-Barr virus infection of the tumor cells.

In immunocompetent patients, neuroimaging studies most often reveal a uniformly enhancing mass lesion. Stereotaxic needle biopsy can be used to establish the diagnosis. There is no benefit of surgical resection unless there is a need for immediate decompression of a life-threatening mass effect. Leptomeningeal involvement is present in ~15% of patients at presentation and in 50% at some time during the course of the illness. Moreover, the disease extends to the eyes in up to 15% of patients. Therefore, a slit-lamp examination and, if indicated, anterior chamber paracentesis or vitreous biopsy is necessary to define radiation ports.

The prognosis of primary CNS lymphoma is poor compared to histologically similar lymphoma occurring outside the CNS. Many patients experience a dramatic clinical and radiographic response to glucocorticoids; however, relapse almost invariably occurs within weeks. The mainstay of definitive therapy is chemotherapy. A single dose of rituximab is generally administered prior to cytotoxic chemotherapy as long as an enhancing mass lacking a blood-tumor barrier is present. Chemotherapy includes high-dose methotrexate, but multiagent chemotherapy, usually adding vincristine and procarbazine, appears to be more effective than methotrexate alone. Chemotherapy is followed in patients <60 years with whole-brain radiation therapy (WBRT). WBRT is postponed as long as possible or administered at reduced doses in patients >60 years because of the risk of dementia, gait disorder, and incontinence as manifestations of late-delayed radiation toxicity. Consolidation therapy is typically with high-dose cytarabine. Intraarterial chemotherapy with or without blood-brain barrier disruption is an alternative. Intrathecal chemotherapy with methotrexate can be added if leptomeningeal disease is present, but it has not proven to offer added benefit if high-dose methotrexate is used. Despite aggressive therapy, >90% of patients develop recurrent CNS disease. The median survival of patients who tolerate treatment with high-dose methotrexate is >3 years.

In immunodeficient patients, primary CNS lymphoma may be ring-enhancing rather than diffusely enhancing on CT or MRI (Fig. 374-4). It may therefore be impossible by imaging criteria to distinguish primary CNS lymphoma from metastatic malignancies or infections, particularly toxoplasmosis. The standard approach to this dilemma in a neurologically stable patient is to administer antibiotics to treat toxoplasmosis for 2–3 weeks and then repeat neuroimaging. If the imaging shows clear improvement, antibiotic treatment is continued. If not, a stereotaxic brain biopsy, which has substantially more risk in an immunodeficient than an immunocompetent patient, is performed. Alternatively, when the clinical situation permits a safe lumbar puncture, a CSF examination demonstrating Epstein-Barr virus DNA in CSF in an immunodeficient patient with neuroimaging findings consistent with lymphoma is diagnostic of primary CNS lymphoma. In organ transplant recipients, reversal of the immunosuppressed state can improve outcome. Survival with AIDS-related primary CNS lymphoma is very poor, generally ≤3 months; pretreatment performance status, the degree of immunosuppression, and the extent of CNS dissemination at diagnosis all appear to influence outcome.

Secondary CNS Lymphoma Secondary CNS lymphoma is a manifestation of systemic disease and almost always occurs in adults with progressive B cell lymphoma or B cell leukemia who have tumor involvement of bone, bone marrow, testes, or the cranial sinuses. The leptomeninges are the most common site of CNS metastasis. Leptomeningeal lymphoma is usually detectable with contrast-enhanced CT or gadolinium-enhanced MRI of the brain and spine or by CSF examination. Treatment consists of systemic chemotherapy, intrathecal chemotherapy, and CNS irradiation. It is usually possible to suppress the leptomeningeal disease effectively, although the overall prognosis is determined by the course of the systemic lymphoma. Intraparenchymal lymphoma metastases may be treated with radiation therapy or systemic chemotherapy.

MENINGIOMAS

Meningiomas are derived from mesoderm, probably from cells giving rise to the arachnoid granulations. These tumors are usually benign and attached to the dura. They may invade the skull but only infrequently invade the brain. Meningiomas most often occur along the sagittal sinus, over the cerebral convexities, in the cerebellar-pontine angle, and along the dorsum of the spinal cord. They are more frequent in women than men, with a peak incidence in middle age.

Meningiomas may be found incidentally on a CT or MRI scan or may present with a focal seizure, a slowly progressive neurologic deficit, or symptoms of raised ICP. The radiologic image of a dural-based, extraaxial mass with dense, uniform contrast enhancement is essentially diagnostic, although a dural metastasis must also be considered (Fig. 374-5). A meningioma may have a "dural tail," a streak of dural enhancement flanking the main tumor mass; however, this finding may also be present with other dural tumors.

Total surgical resection of benign meningiomas is curative. If a total resection cannot be achieved, local external beam radiotherapy or ster-

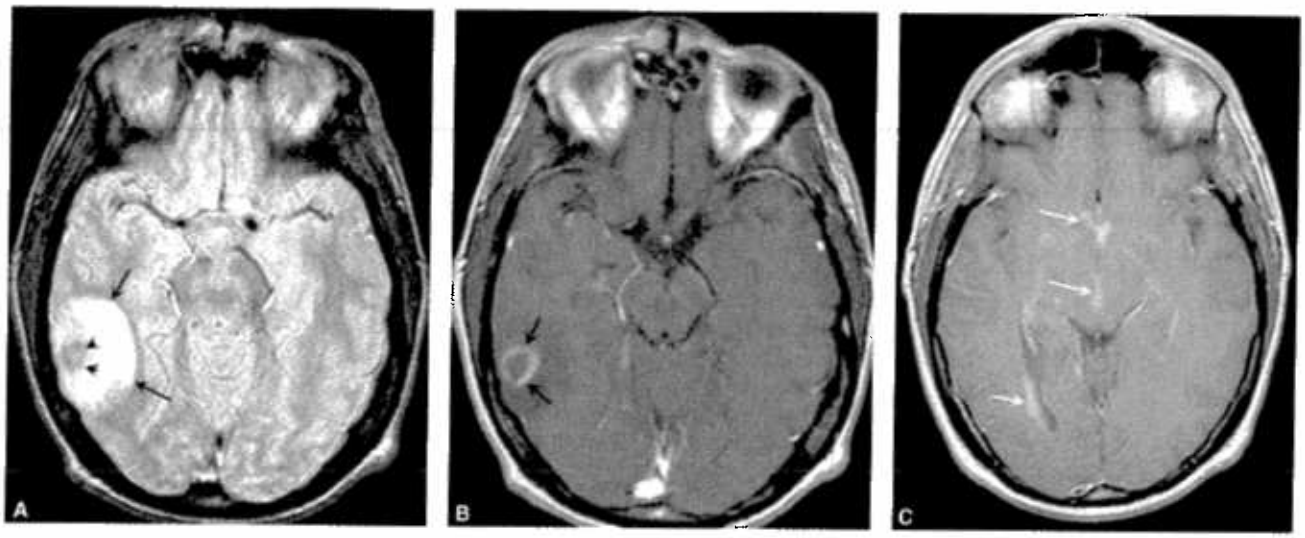

FIGURE 374-4 CNS lymphoma. *A.* Proton density–weighted MR image through the temporal lobe demonstrates a low signal intensity nodule (*small arrows*) surrounded by a ring of high signal intensity edema (*larger arrows*). ***B.*** T1-weighted contrast-enhanced axial MRI demonstrates ring enhancement surrounded by a nonenhanced rim of edema. In this patient with AIDS, a solitary lesion of this type is consistent with either lymphoma or toxoplasmosis; the presence of multiple lesions favors toxoplasmosis. ***C.*** In a different patient with lymphomatous meningitis, an axial postcontrast T1-weighted MRI through the midbrain demonstrates multiple areas of abnormal enhancement in periventricular and subependymal regions (*arrows*). Lymphoma tends to spread subependymally at interfaces of CSF and brain parenchyma.

eotaxic radiosurgery reduces the recurrence rate to <10%. For meningiomas that are not surgically accessible, radiosurgery is the treatment of choice. Small asymptomatic meningiomas incidentally discovered in older patients can safely be followed radiologically; these tumors grow at an average rate of a few millimeters in diameter per year and only rarely become symptomatic.

Rare meningiomas invade the brain or have histologic evidence of malignancy such as nuclear pleomorphism and cellular atypia. A high mitotic index is also predictive of aggressive behavior. *Hemangiopericytoma*, although not strictly a meningioma, is a meningeal tumor with an especially aggressive behavior. Meningiomas with features of aggressiveness and hemangiopericytomas, even if totally excised by gross inspection, frequently recur and should receive postoperative radiotherapy. Chemotherapy has no proven benefit.

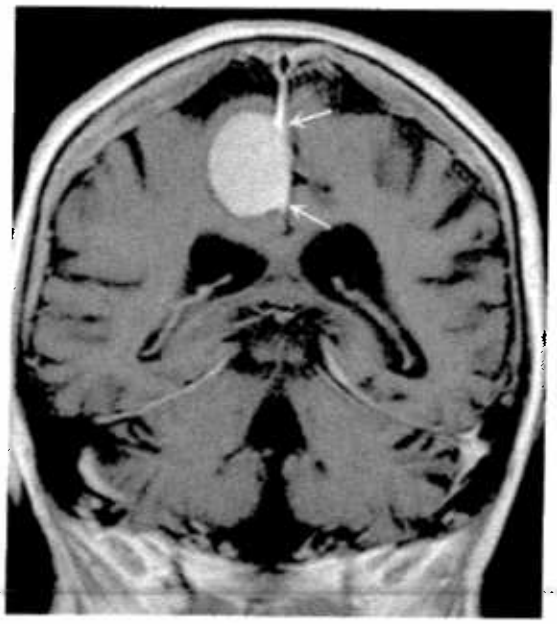

FIGURE 374-5 Meningioma. Coronal postcontrast T1-weighted MR image demonstrates an enhancing extraaxial mass arising from the falx cerebri (*arrows*). There is a "dural tail" of contrast enhancement extending superiorly along the intrahemispheric septum.

SCHWANNOMAS

These tumors are also called *neuromas*, *neurinomas*, or *neurolemmomas*. They arise from Schwann cells of nerve roots, most frequently in the eighth cranial nerve (*vestibular schwannoma*, formerly termed *acoustic schwannoma* or *acoustic neuroma*). The fifth cranial nerve is the second most frequent site; however, schwannomas may arise from any cranial or spinal root except the optic and olfactory nerves, which are myelinated by oligodendroglia rather than Schwann cells. Neurofibromatosis (NF) type 2 (see below) strongly predisposes to vestibular schwannoma. Schwannomas of spinal nerve roots also occur in patients with NF type 2 as well as patients with NF type 1.

Eighth cranial nerve schwannomas typically arise from the vestibular division of the nerve. On MRI they are densely and uniformly enhancing neoplasms (Fig. 374-6). Vestibular schwannomas enlarge the internal auditory canal, an imaging feature that helps distinguish them from other cerebellopontine angle masses. Because the vestibular system adapts to slow destruction of the eighth nerve, patients with vestibular schwannomas characteristically present with progressive unilateral hearing loss rather than with dizziness or other vestibular symptoms. Unexplained unilateral hearing loss merits evaluation with audiometry and an MRI scan (Chap. 30). As a vestibular schwannoma grows, it can compress the cerebellum, pons, or facial nerve. With rare exceptions schwannomas are histologically and clinically benign.

Whenever possible, schwannomas should be surgically excised. When the tumors are small, it is usually possible to preserve hearing in the involved ear. In the case of large tumors, the patient is usually deaf at presentation; nonetheless, surgery is indicated to prevent further compression of posterior fossa structures. Stereotaxic radiosurgery is also effective treatment for schwannoma and has a complication rate equivalent to that of surgery.

OTHER BENIGN BRAIN TUMORS

Epidermoid tumors are cystic tumors with proliferative epidermal cells at the periphery and more mature epidermal cells towards the center of the cyst. The mature cells desquamate into the liquid center of the cyst. Epidermoid tumors are thought to arise from embryonic epidermal rests within the cranium. They occur extraaxially near the midline, in the middle cranial fossa, the suprasellar region, or the cerebellopontine angle. These well-demarcated lesions are amenable to complete surgical excision. Postoperative radiation therapy is unnecessary.

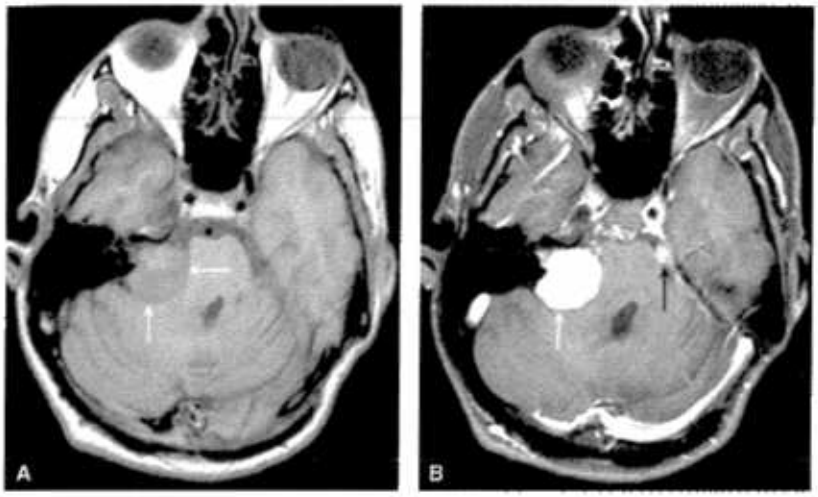

FIGURE 374-6 Vestibular schwannoma. *A.* Axial noncontrast MR scan through the cerebellopontine angle demonstrates an extraaxial mass that extends into a widened internal auditory canal, displacing the pons (*arrows*). ***B.*** Postcontrast T1-weighted image demonstrates intense enhancement of the vestibular schwannoma (*white arrow*). Abnormal enhancement of the left fifth nerve (*black arrow*) most likely represents another schwannoma in this patient with neurofibromatosis type 2.

Dermoid cysts are thought to arise from embryonic rests of skin tissue trapped within the CNS during closure of the neural tube. The most frequent locations are in the midline supratentorially or at the cerebellopontine angle. Histologically, they are composed of multiple elements of the dermis including epidermis, hair follicles, and sweat glands; they frequently calcify. Treatment is surgical excision.

Craniopharyngiomas are thought to arise from remnants of Rathke's pouch, the mesodermal structure from which the anterior pituitary gland is derived (Chap. 333). Craniopharyngiomas typically present as suprasellar masses. Because of their location, they may present as growth failure in children, endocrine dysfunction in adults, or visual loss in either age group. Histologically, craniopharyngiomas resemble epidermoid tumors; they are usually cystic, and in adults 80% are calcified. Treatment is surgical excision; postoperative external beam radiation or stereotaxic radiosurgery is added if total surgical removal cannot be achieved.

Colloid cysts are benign tumors of unknown cellular origin that occur within the third ventricle and can obstruct CSF flow. Other *rare benign primary brain tumors* include neurocytomas, subependymomas, and pleomorphic xanthoastrocytomas. Surgical excision of these neoplasms is the primary treatment and can be curative.

Pituitary tumors are discussed in Chap. 333.

NEUROCUTANEOUS SYNDROMES

This group of genetic disorders, also known as the *phakomatoses*, produces a variety of developmental abnormalities of skin along with an increased risk of nervous system tumors (Table 374-1). These disorders are inherited as autosomal dominant conditions with variable penetrance.

NEUROFIBROMATOSIS TYPE 1 (VON RECKLINGHAUSEN'S DISEASE)

NF1 is characterized by cutaneous *neurofibromas*, pigmented lesions of the skin called *café au lait spots*, freckling in non-sun-exposed areas such as the axilla, hamartomas of the iris termed *Lisch nodules*, and pseudoarthrosis of the tibia. Neurofibromas are benign peripheral nerve tumors composed of proliferating Schwann cells and fibroblasts. They present as multiple, palpable, rubbery, cutaneous tumors. They are generally asymptomatic; however, if they grow in an enclosed space, e.g., the intervertebral foramen, they may produce a compressive radiculopathy or neuropathy. Aqueductal stenosis with hydrocephalus, scoliosis, short stature, hypertension, epilepsy, and mental retardation may also occur.

Patients with NF1 are at increased risk of developing nervous system neoplasms, including plexiform neurofibromas, optic pathway gliomas, ependymomas, meningiomas, astrocytomas, and pheochromocytomas. Neurofibromas may undergo secondary malignant degeneration and become sarcomatous.

Mutation of the *NF1* gene on chromosome 17 causes von Recklinghausen's disease. The *NF1* gene is a tumor-suppressor gene; it encodes a protein, *neurofibromin*, which modulates signal transduction through the *ras* GTPase pathway.

NEUROFIBROMATOSIS TYPE 2

NF2 is characterized by the development of bilateral vestibular schwannomas in >90% of individuals who inherit the gene. Patients with NF2 also have a predisposition for the development of meningiomas, gliomas, and schwannomas of cranial and spinal nerves. In addition, a characteristic type of cataract, juvenile posterior subcapsular lenticular opacity, occurs in NF2. Multiple café au lait spots and peripheral neurofibromas occur rarely.

In patients with NF2, vestibular schwannomas are usually associated with progressive unilateral deafness early in the third decade of life. Bilateral vestibular schwannomas are generally detectable by MRI at that time (Fig. 374-6). Surgical management is designed to treat the underlying tumor and preserve hearing as long as possible.

This syndrome is caused by mutation of the *NF2* gene on chromosome 22q. *NF2* encodes a protein called *neurofibromin 2*, *schwannomin*, or *merlin*, with homology to a family of cytoskeletal proteins that includes moesin, ezrin, and radixin.

TUBEROUS SCLEROSIS (BOURNEVILLE'S DISEASE)

Tuberous sclerosis is characterized by cutaneous lesions, seizures, and mental retardation. The cutaneous lesions include adenoma sebaceum (facial angiofibromas), ash leaf–shaped hypopigmented macules (best seen under ultraviolet illumination with a Wood's lamp), shagreen patches (yellowish thickenings of the skin over the lumbosacral region of the back), and depigmented nevi. Recognizable by neuroimaging studies, the presence of subependymal nodules, which may be calcified, is characteristic. Tuberous sclerosis patients are at increased risk of developing ependymomas and childhood astrocytomas, of which >90% are *subependymal giant cell astrocytomas*. These are benign neoplasms that may develop in the retina or along the border of the lateral ventricles. They may obstruct the foramen of Monro and produce hydrocephalus. Rhabdomyomas of the myocardium and angiomyomas of the kidney, liver, adrenals, and pancreas may also occur.

Treatment is symptomatic. Anticonvulsants for seizures, shunting for hydrocephalus, and behavioral and educational strategies for mental retardation are the mainstays of management. Severely affected individuals generally die before age 30.

Mutations in either the *TSC-1* gene at 9q or the *TSC-2* gene at 16p are associated with tuberous sclerosis. These genes encode *tuberins*, proteins that modulate the GTPase activity of other cellular signaling proteins.

VON HIPPEL–LINDAU SYNDROME

This syndrome consists of retinal, cerebellar, and spinal hemangioblastomas, which are slowly growing cystic tumors. Hypernephroma, renal cell carcinoma, pheochromocytoma, and benign cysts of the kidneys, pancreas, epididymis, or liver may also occur. Erythropoietin produced by hemangioblastomas may result in polycythemia. Mutation of the von Hippel–Lindau (*VHL*) gene on chromosome 3p, a tumor-suppressor gene, causes this disorder. *VHL* encodes a protein with multiple functions, including modulation of signal transduction in response to cellular hypoxia.

TUMORS METASTATIC TO BRAIN

MECHANISMS OF BRAIN METASTASES

Brain metastases arise from hematogenous spread. The anatomic distribution of brain metastases generally parallels regional cerebral blood flow, with a predilection for the gray matter–white matter junction and

TABLE 374-2 FREQUENCY OF NERVOUS SYSTEM METASTASES BY COMMON PRIMARY TUMORS

Site of Primary Tumor	Brain Metastases, %	Leptomeningeal Metastases, %	Spinal Cord Compression, %
Lung	40	24	18
Breast	19	41	24
Melanoma	10	12	4
Gastrointestinal tract	7	13	6
Genitourinary tract	7		18
Other	17	10	30

for the border zone between middle cerebral and posterior cerebral artery distributions. The lung is the most common origin of brain metastases; both primary lung cancer and cancers metastatic to the lung frequently metastasize to the brain. Breast cancer (especially ductal carcinoma) has a propensity to metastasize to the cerebellum and the posterior pituitary gland. Other common origins of brain metastases are gastrointestinal malignancies and melanoma (Table 374-2). Certain less common tumors have a special propensity to metastasize to brain, including germ cell tumors and thyroid cancer. By contrast, prostate cancer, ovarian cancer, and Hodgkin's disease rarely metastasize to the brain.

EVALUATION OF METASTASES FROM KNOWN CANCER

On MRI scans brain metastases typically appear as well-demarcated, approximately spherical lesions that are hypointense or isointense relative to brain on T1-weighted images and bright on T2-weighted images. They invariably enhance with gadolinium, reflecting extravasation of gadolinium through tumor vessels that lack a blood-tumor barrier (Fig. 374-7). Small metastases often enhance uniformly. Larger metastases typically produce ring enhancement surrounding a central mass of nonenhancing necrotic tissue that develops as the metastasis outgrows its blood supply. Metastases are surrounded by variable amounts of edema. Blood products may also be seen, reflecting hemorrhage of abnormal tumor vessels.

The radiologic appearance of a brain metastasis is not specific. The differential diagnosis of ring-enhancing lesions includes brain abscess, radiation necrosis, toxoplasmosis, granulomas, tuberculosis, sarcoidosis, demyelinating lesions, primary brain tumors, primary CNS lymphoma, stroke, hemorrhage, and trauma. Contrast-enhanced CT scanning is less sensitive than MRI for the detection of brain metastases. Cytologic examination of the CSF is not indicated, since intraparenchymal brain metastases almost never shed cells into the CSF.

BRAIN METASTASES WITHOUT A KNOWN PRIMARY TUMOR

In general hospital populations, up to one-third of patients presenting with brain metastases do not have a previously known underlying cancer. These patients generally present with either a seizure or a progressive neurologic deficit. Neuroimaging studies typically demonstrate one or multiple ring-enhancing lesions. In individuals who are not immunocompromised and not at risk for brain abscesses, this radiologic pattern is most likely due to brain metastasis.

Diagnostic evaluation begins with a search for the primary tumor. Blood tests should include carcinoembryonic antigen and liver function tests. Examination of the skin for melanoma and the thyroid gland for masses should be carried out. The search for a primary cancer most often discloses lung cancer (particularly small cell lung cancer) or melanoma. In 30% of patients no primary tumor can be identified, even after extensive evaluation. A CT scan of the chest, abdomen, and pelvis should be obtained. If these are all negative, further imaging studies, including bone scan, other radionuclide scans, mammography, and upper and lower gastrointestinal barium studies, are unlikely to be productive.

A tissue diagnosis is essential. If a primary tumor is found, it will usually be more accessible to biopsy than a brain lesion. If a single brain lesion is found in a surgically accessible location, if a primary tumor is not found, or if the primary tumor is in a location difficult to biopsy, the brain metastasis should be biopsied or resected.

Rx TUMORS METASTATIC TO BRAIN

Once a systemic cancer metastasizes to the brain it is, with rare exception, incurable. Therapy is therefore palliative, designed to prevent disability and suffering and, if possible, to prolong life. Published outcome studies have focused on survival as the primary endpoint, leaving questions regarding quality of life unanswered. There is, however, widespread agreement that glucocorticoids, anticonvulsants, radiation therapy, and surgery (see below) can contribute to the management of these patients.

GENERAL MEASURES Glucocorticoids frequently ameliorate symptoms of brain metastases. Improvement is often dramatic, occurring within 24 h, and is sustained with continued administration, although the toxicity of glucocorticoids is cumulative. Therefore, if possible, a more definitive therapy for metastases should be instituted to permit withdrawal of glucocorticoid therapy. One-third of patients with brain metastases have one or more seizures; anticonvulsants are used empirically for seizure prophylaxis.

SPECIFIC MEASURES Radiation Therapy

Radiation therapy is the primary treatment for brain metastases. Since multiple microscopic deposits of tumor cells throughout the brain are likely to be present in addition to metastases visualized by neuroimaging studies, WBRT is usually used. Its benefit has been established in controlled studies, but no clear dose response has been shown. Usually, 30–37.5 Gy is administered in 10–15 fractions; an additional dose ("boost") of focal irradiation to a single or large metastasis may also be administered. Stereotaxic radiosurgery is of benefit in patients with four or fewer metastases demonstrable by MRI. The addition of WBRT to stereotaxic radiosurgery delays tumor recurrence in the brain but does not prolong survival.

Surgery Up to 40% of patients with brain metastases have only a single tumor mass identified by CT. Accessible single metastases may be surgically excised as a palliative measure. If the systemic disease is under control, total resection of a single brain lesion has been demonstrated to improve survival and minimize disability. Survival is further improved if surgery is followed by WBRT.

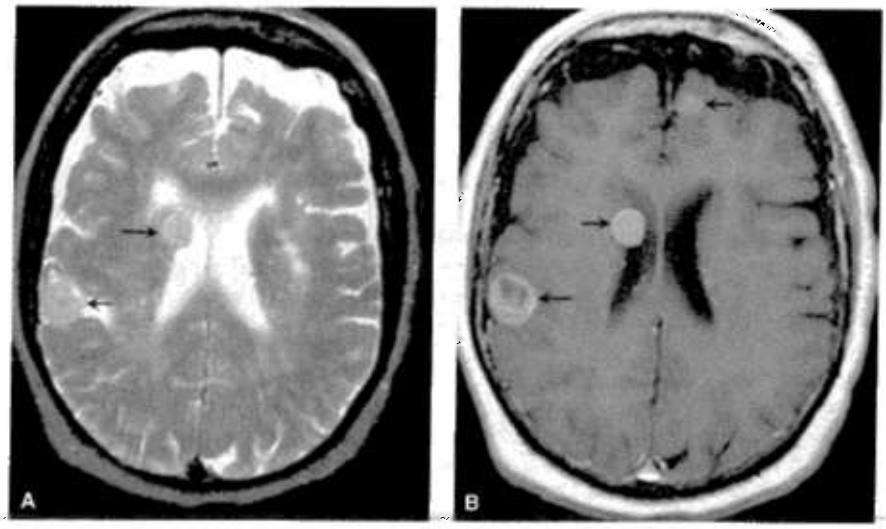

FIGURE 374-7 Brain metastasis. *A.* Axial T2-weighted MRI through the lateral ventricles reveals two isodense masses, one in the subependymal region and one near the cortex (*arrows*). ***B.*** T1-weighted postcontrast image at the same level as ***A*** reveals enhancement of the two masses seen on the T2-weighted image as well as a third mass in the left frontal lobe (*arrows*).

Chemotherapy Brain metastases of certain tumors, including breast cancer, small cell lung cancer, and germ cell tumors, are often responsive to systemic chemotherapy. Although metastases frequently do not respond as well as the primary tumor, dramatic responses to systemic chemotherapy or hormonal therapy may occur in some cases. In patients who are neurologically asymptomatic, two to four cycles of systemic chemotherapy may be administered initially to reduce tumor mass and render the residual tumor more amenable to radiation therapy. Even if a complete radiologic remission is achieved from chemotherapy, WBRT should then be administered. Gene therapy, immunotherapy, intraarterial chemotherapy, and chemotherapy administered following osmotic disruption of the blood-brain barrier are currently under investigation.

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases are also called *carcinomatous meningitis, meningeal carcinomatosis*, and, in the case of specific tumors, *leukemic meningitis* or *lymphomatous meningitis*. Clinical evidence of leptomeningeal metastases is present in 8% of patients with metastatic solid tumors; at necropsy, the prevalence is as high as 19%. Among solid tumors, adenocarcinomas of the breast, lung, and gastrointestinal tract and melanoma are the most common cause of leptomeningeal metastases (Table 374-2). In one-quarter of patients the systemic cancer is under control, and especially in these patients the effective control of leptomeningeal disease can improve the quality and duration of life.

Cancer usually metastasizes to the meninges via the bloodstream. Alternatively, cells may invade the subarachnoid space directly from a superficially located parenchymal brain metastasis. Some tumors, including squamous cell carcinoma of the skin and some non-Hodgkin's lymphomas, have a propensity to grow along peripheral nerves and may seed the meninges by that route.

CLINICAL FEATURES

Leptomeningeal metastases present with signs and symptoms at multiple levels of the nervous system, most often in a setting of known systemic malignancy. Encephalopathy is frequent, and cranial neuropathy or spinal radiculopathy from nodular nerve root compression is characteristic. Hydrocephalus can result from obstruction of CSF outflow. Focal neurologic deficits reflect coexisting intraparenchymal metastases.

LABORATORY AND IMAGING EVALUATION

Leptomeningeal metastases are diagnosed by cytologic demonstration of malignant cells in the CSF, by MRI demonstration of nodular tumor deposits or diffuse enhancement in the meninges (Fig. 374-8), and by meningeal biopsy. CSF findings are usually those of an inflammatory meningitis consisting of lymphocytic pleocytosis, elevated protein levels, and normal or low CSF glucose. A positive CSF cytology is unequivocal evidence of tumor spread to the subarachnoid space. CSF examination is more likely to be informative when larger volumes of CSF are submitted for cytology and when up to three CSF examinations are performed. A complete MRI examination of the neuraxis is indicated in all cases of suspected leptomeningeal metastases; in addition to nodular meningeal lesions, hydrocephalus due to obstruction of CSF pathways may be found.

Rx LEPTOMENINGEAL METASTASES

Although the prognosis of patients with leptomeningeal metastases is poor, ~20% of patients treated aggressively can expect a response of ≥6 months. Intrathecal therapy exposes meningeal tumor implants to high concentrations of chemotherapy with minimal systemic toxicity. Methotrexate can be safely administered intrathecally and is effective against leptomeningeal metastases from a variety of solid tumors including lymphoma; cytarabine and thiotepa are alternative agents. Liposomal cytarabine provides prolonged cytotoxic levels of cytarabine in the CSF, requiring administration only every 2 weeks, in contrast to weekly or twice weekly administration of other agents. Intrathecal chemotherapy may be administered either by repeated lumbar puncture or through an indwelling Ommaya reservoir, which consists of a catheter in one lateral ventricle attached to a reservoir implanted under the scalp. If there is a question of patency of CSF pathways, a radionuclide flow study through the reservoir may be performed.

Large, nodular deposits of tumor on the meninges or along nerve roots are unlikely to respond to intrathecal chemotherapy, as the barrier to diffusion is too great. Therefore, external beam radiation is employed, and these patients may also benefit from systemic chemotherapy. Hydrocephalus is treated with a ventriculoperitoneal shunt, although seeding of the peritoneum by tumor is a risk.

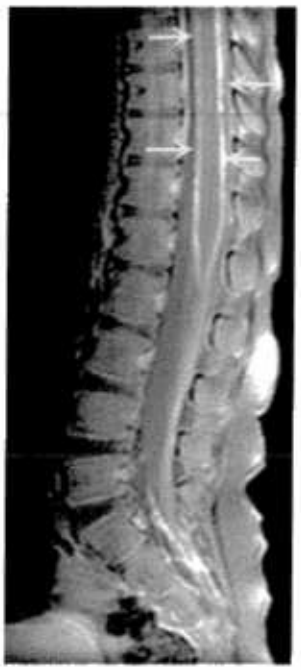

FIGURE 374-8 Carcinomatous meningitis. Sagittal postcontrast MRI through the lower thoracic region demonstrates diffuse pial enhancement along the surface of the spinal cord (*arrows*), typical of CSF spread of neoplasm.

MALIGNANT SPINAL CORD COMPRESSION

Spinal cord compression from solid tumor metastases usually results from growth of a vertebral metastasis into the epidural space. Primary tumors that frequently metastasize to bone include lung, breast, and prostate cancer. Back pain is usually the first symptom and is prominent at presentation in 90% of patients. The pain is typically dull, aching, and may be associated with localized tenderness. If a nerve root is compressed, radicular pain is also present. The thoracic cord is most often affected. Weakness, sensory loss, and autonomic dysfunction (urinary urgency and incontinence, fecal incontinence, and sexual impotence in men) are hallmarks of spinal cord compression. Once signs of spinal cord compression appear, they tend to progress rapidly. It is thus essential to recognize and treat this serious complication of malignancy promptly to prevent irreversible neurologic deficits. Diagnosis and management are discussed in Chap. 372.

METASTASES TO THE PERIPHERAL NERVOUS SYSTEM

Systemic cancer may compress or invade peripheral nerves. Compression of the brachial plexus may occur by direct extension of Pancoast's tumors (cancer of the apex of the lung), by lymphoma, or by extension of local lymph node metastases in breast or lung cancer. The lumbosacral plexus may be compressed by retroperitoneal tumor invasion such as occurs in cases of prostate or ovarian cancer or lymphoma. Skull metastases may compress cranial nerve branches as they pass through the skull, and pituitary metastases may extend into the cavernous sinus.

The epineurium generally provides an effective barrier to invasion of the peripheral nerves by solid tumors, but certain tumors characteristically invade and spread along peripheral nerves. Squamous cell carcinoma of the skin may spread along the trigeminal nerve and extend intracranially. Non-Hodgkin's lymphoma may be neurotrophic and cause polyradiculopathy or a syndrome resembling mononeuropathy multiplex (Chap. 379). Focal external beam radiation may reduce

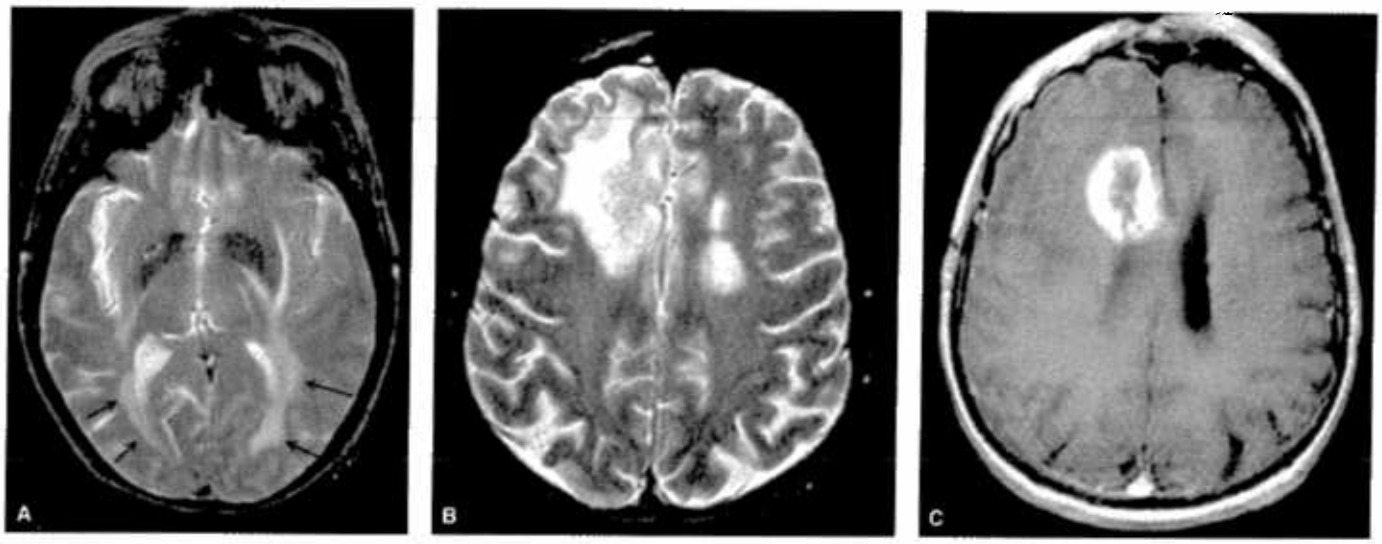

FIGURE 374-9 Radiation injury. *A.* Late delayed radiation injury 1 year after whole-brain radiation (5500 cGy). T2-weighted MR image at the level of the temporal lobes reveals high signal intensity abnormality in periventricular white matter (*arrows*). ***B*** and ***C.*** Focal radiation necrosis 3 years after radiotherapy (7000 cGy) for carcinoma of the nasopharynx. Axial T2-weighted MRI (***B***) demonstrates a mass in the right frontal lobe with surrounding vasogenic edema. Abnormal signal changes are also present on the left. T1-weighted postcontrast MRI (***C***) reveals a heterogeneously enhancing mass in the right cingulate gyrus.

pain, prevent irreversible loss of peripheral nerve function, and possibly restore function.

In patients with cancer who have brachial or lumbosacral plexopathy, it may be difficult to distinguish tumor invasion from radiation injury. High radiation dose or the presence of myokymia (rippling contractions of muscle) suggests radiation injury, whereas pain suggests tumor. Radiographic imaging studies may be equivocal, and surgical exploration is sometimes required.

COMPLICATIONS OF THERAPY

RADIATION TOXICITY

The nervous system is vulnerable to injury by therapeutic radiation. Histologically, there is demyelination, degeneration of small arterioles, and eventually brain infarction and necrosis.

Acute radiation injury to the brain occurs during or immediately after therapy. It is rarely seen with current protocols of external beam radiation but may occur after stereotaxic radiosurgery. Manifestations include headache, sleepiness, and worsening of preexisting neurologic deficits.

Early delayed radiation injury occurs within 4 months of therapy. It is associated with an increased white matter T2 signal on MRI scans. In children, the *somnolence syndrome* is a common form of early delayed radiation injury in which somnolence and ataxia develop after WBRT. Irradiation of the cervical spine may cause Lhermitte's phenomenon, an electricity-like sensation evoked by neck flexion. Symptoms resulting from acute and early delayed radiation injury often respond to glucocorticoid administration, are self-limited, and usually resolve without residual deficits. These injuries do not increase the risk of late radiation injury.

Late delayed radiation injury produces permanent damage to the nervous system. It occurs >4 months (generally 8–24 months) after completion of therapy; onset as late as 15 years after therapy has been described. Following focal brain irradiation, radiation necrosis can occur within the radiation field, producing a contrast-enhancing (frequently ring-enhancing) mass with surrounding white matter signal abnormalities (Fig. 374-9). MRI or CT scans are often unable to distinguish radiation necrosis from recurrent tumor, but PET or SPECT scans may demonstrate the increased glucose metabolism typical of tumor tissue or the decreased metabolism of necrotic tissue. Magnetic resonance spectroscopy may demonstrate a high lactate concentration with relatively low choline concentration in areas of necrosis. Biopsy is frequently required to establish the correct diagnosis. Peripheral nerves, including the brachial and lumbosacral plexuses, may also develop late delayed radiation injury.

If untreated, radiation necrosis of the CNS may act as an expanding mass lesion. Symptoms may resolve spontaneously or respond to treatment with glucocorticoids. Progressive radiation necrosis is best treated with surgical resection if the patient has a life expectancy of at least 6 months and a Karnofsky performance score >70. There are anecdotal reports that anticoagulation with heparin or warfarin may be beneficial. After WBRT, progressive dementia can occur, often accompanied by gait apraxia and urinary incontinence. Radiation injury of large arteries also accelerates the development of atherosclerosis, but an increase in the risk of stroke becomes significant only years after radiation treatment.

Endocrine dysfunction resulting in hypopituitarism frequently follows exposure of the hypothalamus or pituitary gland to therapeutic radiation. Growth hormone is the pituitary hormone most sensitive to radiation therapy, and thyroid-stimulating hormone is the least sensitive; ACTH, prolactin, and the gonadotropins have an intermediate sensitivity.

Development of a second neoplasm is another risk of therapeutic radiation that generally occurs many years after radiation exposure. Depending on the irradiated field, the risk of gliomas, meningiomas, sarcomas, and thyroid cancer is increased.

TOXICITIES OF CHEMOTHERAPY

Chemotherapy regimens used to treat primary brain tumors generally include alkylating agents, either temozolomide or nitrosoureas, and are relatively well tolerated. Infrequently, drugs used to treat CNS neoplasms are associated with the development of altered mental states (e.g., confusion, depression), ataxia, and seizures. Chemotherapy for systemic malignancy is a more frequent cause of nervous system toxicity and is more often toxic to the peripheral than the central nervous system. Cisplatin commonly produces tinnitus and high-frequency bilateral hearing loss, especially in younger patients. At cumulative doses > 450 mg/m^2, cisplatin can produce a symmetric, large-fiber axonal neuropathy that is predominantly sensory; paclitaxel (Taxol) produces a similar picture. Fluorouracil and high-dose cytarabine can cause cerebellar dysfunction that resolves after discontinuation of therapy. Vincristine, which is commonly used to treat lymphoma, may cause an acute ileus and is frequently associated with development of a progressive distal, symmetric sensory motor neuropathy with foot drop and paresthesias.

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375 Multiple Sclerosis and Other Demyelinating Diseases

Stephen L. Hauser, Douglas S. Goodin

Demyelinating disorders are characterized by inflammation and selective destruction of central nervous system (CNS) myelin. The peripheral nervous system (PNS) is spared, and most patients have no evidence of an associated systemic illness.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is characterized by a triad of inflammation, demyelination, and gliosis (scarring); the course can be relapsing-remitting or progressive. Lesions of MS typically occur at different times and in different CNS locations (i.e., disseminated in time and space). MS affects ~350,000 individuals in the United States and 2.5 million individuals worldwide. In Western societies, MS is second only to trauma as a cause of neurologic disability beginning in early to middle adulthood. Manifestations of MS vary from a benign illness to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments.

PATHOGENESIS

Anatomy The lesions of MS (plaques) vary in size from 1 or 2 mm to several centimeters. Acute MS lesions are characterized by perivenular cuffing with inflammatory mononuclear cells, predominantly T cells and macrophages, which also infiltrate the surrounding white matter. At sites of inflammation, the blood-brain barrier (BBB) is disrupted, but unlike vasculitis, the vessel wall is preserved. In many lesions, myelin-specific autoantibodies are present, presumably promoting demyelination directly as well as stimulating macrophages and microglial cells (bone marrow–derived CNS phagocytes) that scavenge the myelin debris. As lesions evolve, there is prominent astrocytic proliferation (gliosis). Surviving oligodendrocytes or those that differentiate from precursor cells may partially remyelinate the surviving naked axons, producing so-called shadow plaques. In many lesions, oligodendrocyte precursors are present in large numbers but fail to remyelinate. Ultrastructural studies of MS lesions suggest that fundamentally different underlying pathologies may exist in different patients. Heterogeneity has been observed in terms of (1) whether the inflammatory cell infiltrate is associated with antibody deposition and activation of complement, and (2) whether the target of the immunopathologic process is the myelin sheath itself or the cell body of the oligodendrocyte. Although relative sparing of axons is typical of MS, partial or total axonal destruction can also occur, especially within highly inflammatory lesions. Evidence also suggests that axonal loss is a major contributor to irreversible neurologic disability in MS (see "Neurodegeneration," below).

Physiology Nerve conduction in myelinated axons occurs in a saltatory manner, with the nerve impulse jumping from one node of Ranvier to the next without depolarization of the axonal membrane underlying the myelin sheath between nodes (Fig. 375-1). This produces considerably faster conduction velocities (~70 m/s) than the slow velocities (~1 m/s) produced by continuous propagation in unmyelinated nerves. Conduction block occurs when the nerve impulse is unable to traverse the demyelinated segment. This can happen when the resting axon membrane becomes hyperpolarized due to the exposure of voltage-dependent potassium channels that are normally buried underneath the myelin sheath. A temporary conduction block often follows a demyelinating event before sodium channels (originally concentrated at the nodes) redistribute along the naked axon (Fig. 375-1). This redistribution ultimately allows continuous propagation of nerve action potentials through the demyelinated segment. On occasion, conduction block is incomplete, affecting, for example, high- but not low-frequency volleys of impulses. Variable conduction block can occur with raised body temperature or metabolic alterations and may explain clinical fluctuations that vary from hour to hour or appear with fever or exercise. Conduction slowing occurs when the demyelinated segments support only (slow) continuous nerve impulse propagation.

Epidemiology MS is approximately threefold more common in women than men. The age of onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present across the lifespan. Approximately 10% of cases begin before age 18 years of age, and extremes with onset as early as 1–2 years of age or as late as the eighth decade have been described.

Geographical gradients have been repeatedly observed in MS, with prevalence rates increasing at higher latitudes. The highest known prevalence for MS (250 per 100,000) occurs in the Orkney Islands, located north of Scotland, and similarly high rates are found throughout northern Europe, the northern United States, and Canada. By contrast, the prevalence is low in Japan (6 per 100,000), in other parts of Asia, in equatorial Africa, and in the Middle East.

One proposed explanation for the latitude effect on MS is that there is a protective effect of sun exposure. Ultraviolet radiation from sun is the most important source of vitamin D in most individuals, and low levels of vitamin D are common at high latitudes where sun exposure

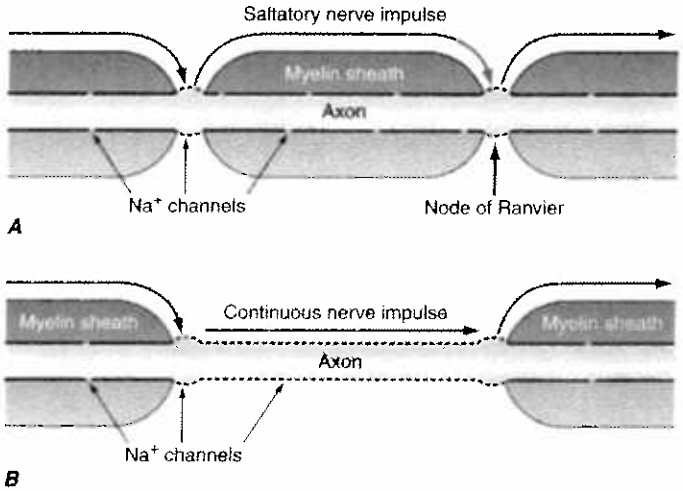

FIGURE 375-1 Nerve conduction in myelinated and demyelinated axons. *A.* Saltatory nerve conduction in myelinated axons occurs with the nerve impulse jumping from one node of Ranvier to the next. Sodium channels (shown as breaks in the solid black line) are concentrated at the nodes where axonal depolarization occurs. ***B.*** Following demyelination, additional sodium channels are redistributed along the axon itself, thereby allowing continuous propagation of the nerve action potential despite the absence of myelin.

may be low, particularly during winter months. Prospective studies have confirmed that vitamin D deficiency is associated with an increase in MS risk. Immunoregulatory effects of vitamin D could explain this possible relationship.

Migration studies and identification of possible point epidemics provide additional support for an environmental effect on MS risk. Migration studies suggest that some MS-related exposure occurs in childhood and years before MS is clinically evident. In some studies, migration early in life from a low- to high-risk area was found to increase MS risk, and conversely, migration from a high- to a low-risk area decreased risk. With respect to possible point epidemics, the most convincing example occurred in the Faeroe Islands north of Denmark after the British occupation during World War II.

The prevalence of MS appears to have steadily increased over the past century; furthermore, this increase has occurred primarily in women. Interestingly, recent epidemiologic data suggests that the latitude effect on MS may currently be decreasing, for unknown reasons.

MS risk also correlates with high socioeconomic status, which may reflect improved sanitation and delayed initial exposures to infectious agents. By analogy, some viral infections (e.g., poliomyelitis and measles viruses) produce neurologic sequelae more frequently when the age of initial infection is delayed. Occasional reports seem to implicate a specific infectious agent such as human herpes virus type 6 (HHV-6) or *Chlamydia pneumoniae*, although, in general, the available reports have been inconsistent.

Most intriguingly, the evidence of a remote Epstein-Barr virus (EBV) infection playing some role in MS is supported by a number of epidemiologic and laboratory studies. A higher risk of infectious mononucleosis (associated with relatively late EBV infection) and higher-antibody titers to latency-associated EBV nuclear antigen are associated with MS; conversely, individuals never infected with EBV are at low MS risk. At this time, however, a causal role for EBV or for any specific infectious agent in MS remains uncertain.

GENETIC CONSIDERATIONS Evidence also supports an important genetic influence on MS. Caucasians are inherently at higher risk for MS than Africans or Asians, even when residing in a similar environment. MS also aggregates within some families, and adoption, half-sibling, twin, and spousal studies indicate that familial aggregation is due to genetic, and not environmental, factors (**Table 375-1**).

Susceptibility to MS is polygenic, with each gene contributing a relatively small amount to the overall risk. The major histocompatibility complex (MHC) on chromosome 6 is the strongest MS susceptibility region in the genome. Fine mapping studies implicate primarily the class II region of the MHC (encoding HLA molecules involved in presenting peptide antigens to T cells) and specifically the DR2 (molecular designation DRB1*1501) allele. Other recently identified MS susceptibility genes encode receptors for two proinflammatory cytokines, the IL-7 receptor alpha chain (CD127) and the IL-2 receptor alpha chain (CD25); the MS associated variant of the IL-7 receptor increases the amount of soluble compared to membrane bound receptor. It is also likely that genetic heterogeneity is present in MS, meaning that there are different causative genes in different individuals.

Immunology An autoimmune cause for MS is supported by the laboratory model of experimental allergic encephalomyelitis (EAE) and by studies of the immune system in MS patients.

AUTOREACTIVE T LYMPHOCYTES Myelin basic protein (MBP) is an important T cell antigen in EAE and probably also in human MS. Activated MBP-reactive T cells have been identified in the blood, in cerebrospinal fluid (CSF), and within MS lesions. Moreover, DR2 may influence the autoimmune response because it binds with high affinity to a fragment of MBP (spanning amino acids 89–96), stimulating T cell responses to this self-protein.

TABLE 375-1 RISK OF DEVELOPING MS

1 in 3	If an identical twin has MS
1 in 15	If a fraternal twin has MS
1 in 25	If a sibling has MS
1 in 50	If a parent or half-sibling has MS
1 in 100	If a first cousin has MS
1 in 1000	If a spouse has MS
1 in 1000	If no one in the family has MS

HUMORAL AUTOIMMUNITY B cell activation and antibody responses also appear to be necessary for the full development of demyelinating lesions to occur, both in experimental models and in human MS. Increased numbers of clonally expanded B cells with properties of post-germinal center memory or antibody-producing lymphocytes are present in MS lesions and in CSF. Myelin-specific autoantibodies, some directed against myelin oligodendrocyte glycoprotein (MOG), have been detected bound to vesiculated myelin debris in MS plaques. In the CSF, elevated levels of locally synthesized immunoglobulins and oligoclonal antibodies derived from expansion of clonally restricted plasma cells are also characteristic of MS. The pattern of oligoclonal banding is unique to each individual, and attempts to identify the targets of these antibodies have been largely unsuccessful, although one recent report indicated that some bands recognized EBV antigens.

CYTOKINES Cytokines and chemokines appear to regulate many of the cellular interactions that operate in MS. Proinflammatory T_H1 cytokines including interleukin (IL) 2, tumor necrosis factor (TNF) α, and interferon (IFN) γ play key roles in activating and maintaining autoimmune responses, and TNF-α and IFN-γ may directly injure oligodendrocytes or the myelin membrane.

TRIGGERS Studies reveal that in patients with early relapsing remitting MS, serial MRI has demonstrated bursts of focal inflammatory disease activity occurring far more frequently than would have been predicted by the frequency of relapses. Thus, early in MS, most disease activity is clinically silent. The triggers causing these bursts are unknown, although the fact that patients may experience relapses after nonspecific upper respiratory infections suggests that either molecular mimicry between viruses and myelin antigens or viral superantigens activating pathogenic T cells may play a role in MS pathogenesis (Chap. 312).

Neurodegeneration Axonal damage occurs in every newly formed MS lesion, and cumulative axonal loss is considered to be the major cause of progressive and irreversible neurological disability in MS. As many as 70% of axons are lost from the lateral corticospinal tracts in patients with advanced paraparesis from MS, and longitudinal MRI studies suggest there is progressive axonal loss over time within established, inactive, lesions. Knowledge of the mechanisms responsible for axonal injury is incomplete, and it is even unclear whether demyelination is a prerequisite for axonal injury in MS. Demyelination can result in reduced trophic support for axons, redistribution of ion channels, and destabilization of action potential membrane potentials. Axons can initially adapt, but eventually distal and retrograde degeneration occurs. Therefore the early promotion of remyelination and preservation of oligodendrocytes remain important therapeutic goals in MS. Some evidence suggests that axonal damage is mediated directly by resident and invading inflammatory cells and their toxic products, in particular by microglia, macrophages, and CD8 T lymphocytes. Activated microglia are particularly likely to cause axonal injury through the release of NO and oxygen radicals and via glutamate, which is toxic to oligodendrocytes and neurons.

CLINICAL MANIFESTATIONS

The onset of MS may be abrupt or insidious. Symptoms may be severe or seem so trivial that a patient may not seek medical attention for months or years. Indeed, at autopsy some individuals who were asymptomatic during life will be found, unexpectedly, to have MS. In others, an MRI scan obtained for an unrelated reason may show evidence of asymptomatic MS. Symptoms of MS are extremely varied and depend on the location and severity of lesions within the CNS

TABLE 375-2 INITIAL SYMPTOMS OF MS

Symptom	Percent of Cases	Symptom	Percent of Cases
Sensory loss	37	Lhermitte	3
Optic neuritis	36	Pain	3
Weakness	35	Dementia	2
Paresthesias	24	Visual loss	2
Diplopia	15	Facial palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal attacks	4	Epilepsy	1
Bladder	4	Falling	1

Source: After WB Matthews et al, *McAlpine's Multiple Sclerosis*, New York, Churchill Livingstone, 1991.

(Table 375-2). Examination generally reveals evidence of neurologic dysfunction, often in asymptomatic locations. For example, a patient may present with symptoms in one leg but signs in both.

Weakness of the limbs may manifest as loss of strength or dexterity, fatigue, or a disturbance of gait. Exercise-induced weakness is a characteristic symptom of MS. The weakness is of the upper motor neuron type (Chap. 23) and is usually accompanied by other pyramidal signs such as spasticity, hyperreflexia and Babinski signs. Occasionally a tendon reflex may be lost (simulating a lower motor neuron lesion) if an MS lesion disrupts the afferent reflex fibers in the spinal cord.

Spasticity (Chap. 23) is often associated with spontaneous and movement-induced muscle spasms. More than 30% of MS patients have moderate to severe spasticity, especially in the legs. This is often accompanied by painful spasms, interfering with ambulation, work, or self-care. Occasionally spasticity provides support for the body weight during ambulation, and in these cases treatment of spasticity may actually do more harm than good.

Optic neuritis (ON) presents as diminished visual acuity, dimness, or decreased color perception (desaturation) in the central field of vision. These symptoms may be mild or may progress to severe visual loss. Rarely, there is complete loss of light perception. Visual symptoms are generally monocular but may be bilateral. Periorbital pain (aggravated by eye movement) often precedes or accompanies the visual loss. An afferent pupillary defect (Chap. 29) is usually present. Funduscopic examination may be normal or reveal optic disc swelling (papillitis). Pallor of the optic disc (optic atrophy) commonly follows ON. Uveitis is rare and should raise the possibility of alternative diagnoses.

Visual blurring in MS may result from ON or diplopia; if the symptom resolves when either eye is covered, the cause is diplopia.

Diplopia may result from internuclear ophthalmoplegia (INO) or from palsy of the sixth cranial nerve (rarely the third or fourth). An INO consists of impaired adduction of one eye due to a lesion in the ipsilateral medial longitudinal fasciculus (Chap. 29). Prominent nystagmus is often observed in the abducting eye, along with a small skew deviation. A bilateral INO is particularly suggestive of MS. Other common gaze disturbances in MS include (1) a horizontal gaze palsy, (2) a "one and a half" syndrome (horizontal gaze palsy plus an INO), and (3) acquired pendular nystagmus.

Sensory symptoms are varied and include both paresthesias (e.g., tingling, prickling sensations, formications, "pins and needles," or painful burning) and hypesthesia (e.g., reduced sensation, numbness, or a "dead" feeling). Unpleasant sensations (e.g., feelings that body parts are swollen, wet, raw, or tightly wrapped) are also common. Sensory impairment of the trunk and legs below a horizontal line on the torso (a sensory level) indicates that the spinal cord is the origin of the sensory disturbance. It is often accompanied by a bandlike sensation of tightness around the torso. Pain is a common symptom of MS, experienced by >50% of patients. Pain can occur anywhere on the body and can change locations over time.

Ataxia usually manifests as cerebellar tremors (Chap. 368). Ataxia may also involve the head and trunk or the voice, producing a characteristic cerebellar dysarthria (scanning speech).

Bladder dysfunction is present in >90% of MS patients, and in a third of patients, dysfunction results in weekly or more frequent episodes of incontinence. During normal reflex voiding, relaxation of the bladder sphincter (α-adrenergic innervation) is coordinated with contraction of the detrusor muscle in the bladder wall (muscarinic cholinergic innervation). *Detrusor hyperreflexia*, due to impairment of suprasegmental inhibition, causes urinary frequency, urgency, nocturia, and uncontrolled bladder emptying. *Detrusor sphincter dyssynergia*, due to loss of synchronization between detrusor and sphincter muscles, causes difficulty in initiating and/or stopping the urinary stream, producing hesitancy, urinary retention, overflow incontinence, and recurrent infection.

Constipation occurs in >30% of patients. Fecal urgency or *bowel incontinence* is less common (15%) but can be socially debilitating.

Cognitive dysfunction can include memory loss, impaired attention, difficulties in problem solving, slowed information processing, and problems shifting between cognitive tasks. Euphoria (elevated mood) was once thought to be characteristic of MS but is actually uncommon, occurring in <20% of patients. Cognitive dysfunction sufficient to impair activities of daily living is rare.

Depression, experienced by approximately half of patients, can be reactive, endogenous, or part of the illness itself and can contribute to fatigue. Suicide in MS patients is 7.5-fold more common than in age-matched controls.

Fatigue is experienced by 90% of patients; this symptom is the most common reason for work-related disability in MS. Fatigue can be exacerbated by elevated temperatures, by depression, by expending exceptional effort to accomplish basic activities of daily living, or by sleep disturbances (e.g., from frequent nocturnal awakenings to urinate).

Sexual dysfunction may manifest as decreased libido, impaired genital sensation, impotence in men, and diminished vaginal lubrication or adductor spasms in women.

Facial weakness due to a lesion in the pons may resemble idiopathic Bell's palsy (Chap. 371). Unlike Bell's palsy, facial weakness in MS is usually not associated with ipsilateral loss of taste sensation or retroauricular pain.

Vertigo may appear suddenly from a brainstem lesion, superficially resembling acute labyrinthitis (Chap. 22). *Hearing loss* may also occur in MS but is uncommon.

Ancillary Symptoms *Heat sensitivity* refers to neurologic symptoms produced by an elevation of the body's core temperature. For example, unilateral visual blurring may occur during a hot shower or with physical exercise (*Uhthoff's symptom*). It is also common for MS symptoms to worsen transiently, sometimes dramatically, during febrile illnesses (see "Acute Attacks or Initial Demyelinating Episodes," below). Such heat-related symptoms probably result from transient conduction block (see above).

Lhermitte's symptom is an electric shocklike sensation (typically induced by flexion or other movements of the neck) that radiates down the back into the legs. Rarely, it radiates into the arms. It is generally self-limited but may persist for years. Lhermitte's symptom can also occur with other disorders of the cervical spinal cord (e.g., cervical spondylosis).

Paroxysmal symptoms are distinguished by their brief duration (10 s to 2 min), high frequency (5–40 episodes per day), lack of any alteration of consciousness or change in background electroencephalogram during episodes, and a self-limited course (generally lasting weeks to months). They may be precipitated by hyperventilation or movement. These syndromes may include Lhermitte's symptom; tonic contractions of a limb, face, or trunk (tonic seizures); paroxysmal dysarthria and ataxia; paroxysmal sensory disturbances; and several other less well-characterized syndromes. Paroxysmal symptoms probably result from spontaneous discharges, arising at the edges of demyelinated plaques and spreading to adjacent white matter tracts.

Trigeminal neuralgia, hemifacial spasm, and *glossopharyngeal neuralgia* (Chap. 371) can occur when the demyelinating lesion involves the root entry (or exit) zone of the fifth, seventh, and ninth cranial

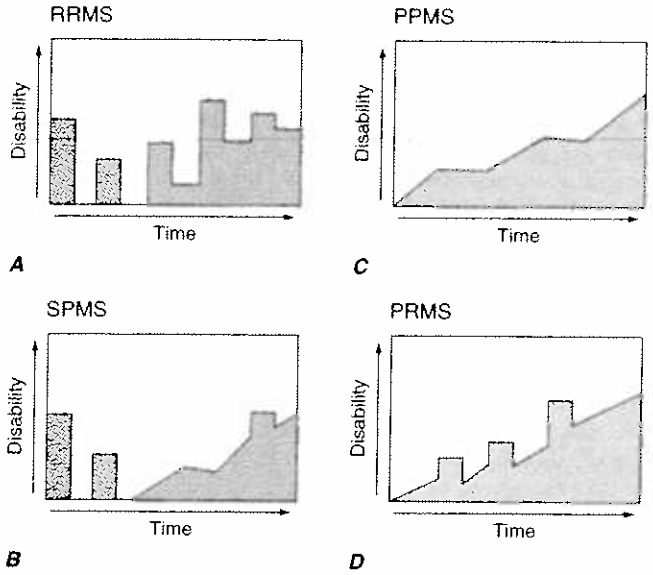

FIGURE 375-2 Clinical course of multiple sclerosis (MS). *A.* Relapsing/remitting MS. ***B.*** Secondary progressive MS. ***C.*** Primary progressive MS. ***D.*** Progressive/relapsing MS.

nerve, respectively. Trigeminal neuralgia (tic douloureux) is a very brief lancinating facial pain often triggered by an afferent input from the face or teeth. Most cases of trigeminal neuralgia are not MS-related; however, atypical features such as onset before age 50 years, bilateral symptoms, objective sensory loss, or nonparoxysmal pain should raise concerns that MS could be responsible.

Facial myokymia consists of either persistent rapid flickering contractions of the facial musculature (especially the lower portion of the orbicularis oculus) or a contraction that slowly spreads across the face. It results from lesions of the corticobulbar tracts or brainstem course of the facial nerve.

DISEASE COURSE

Four clinical types of MS have been described (Fig. 375-2):

1. *Relapsing/remitting MS* (RRMS) accounts for 85% of MS cases at onset and is characterized by discrete attacks that generally evolve over days to weeks (rarely over hours). There is often complete recovery over the ensuing weeks to months (Fig. 375-2*A*). However, when ambulation is severely impaired during an attack, approximately half will fail to improve. Between attacks, patients are neurologically stable.
2. *Secondary progressive MS* (SPMS) always begins as RRMS (Fig. 375-2*B*). At some point, however, the clinical course changes so that the patient experiences a steady deterioration in function unassociated with acute attacks (which may continue or cease during the progressive phase). SPMS produces a greater amount of fixed neurologic disability than RRMS. For a patient with RRMS, the risk of developing SPMS is ~2.5% each year, meaning that the great majority of RRMS ultimately evolves into SPMS. SPMS appears to represent a late stage of the same underlying illness as RRMS.
3. *Primary progressive MS* (PPMS) accounts for ~15% of cases. These patients do not experience attacks but only a steady functional decline from disease onset (Fig. 375-2*C*). Compared to RRMS, the sex distribution is more even, the disease begins later in life (mean age ~40 years), and disability develops faster (at least relative to the onset of the first clinical symptom). Whether PPMS is an uncommon form of the same underlying illness as RRMS or whether these are distinct illnesses is uncertain.
4. *Progressive/relapsing MS* (PRMS) overlaps PPMS and SPMS and accounts for ~5% of MS patients. Like patients with PPMS, these patients experience a steady deterioration in their condition from disease onset. However, like SPMS patients, they experience occasional attacks superimposed upon their progressive course (Fig. 375-2*D*).

TABLE 375-3 DIAGNOSTIC CRITERIA FOR MS

1. Examination must reveal *objective* abnormalities of the CNS.
2. Involvement must reflect predominantly disease of white matter long tracts, usually including (a) pyramidal pathways, (b) cerebellar pathways, (c) medial longitudinal fasciculus, (d) optic nerve, and (e) posterior columns.
3. Examination or history must implicate involvement of two or more areas of the CNS.
   a. MRI may be used to document a second lesion when only one site of abnormality has been demonstrable on examination. A confirmatory MRI must have either four lesions involving the white matter or three lesions if one is periventricular in location. Acceptable lesions must be >3 mm in diameter. For patients older than 50 years, two of the following criteria must also be met: (a) lesion size >5 mm, (b) lesions adjacent to the bodies of the lateral ventricles, and (c) lesion(s) present in the posterior fossa.
   b. Evoked response testing may be used to document a second lesion not evident on clinical examination.
4. The clinical pattern must consist of (a) two or more separate episodes of worsening involving different sites of the CNS, each lasting at least 24 h and occurring at least 1 month apart, or (b) gradual or stepwise progression over at least 6 months if accompanied by increased IgG synthesis or two or more oligoclonal bands. MRI may be used to document dissemination in time if a new T2 lesion or a Gd-enhancing lesion is seen 3 or more months after a clinically isolated syndrome.
5. The patient's neurologic condition could not better be attributed to another disease.

Diagnostic Categories

1. *Definite MS:* All five criteria fulfilled.
2. *Probable MS: All* five criteria fulfilled except (a) only one objective abnormality despite two symptomatic episodes or (b) only one symptomatic episode despite two or more objective abnormalities.
3. *At risk for MS:* Criteria 1, 2, 3, and 5 fulfilled; patient has only one symptomatic episode and one objective abnormality.

Note: CNS, central nervous system; MRI, magnetic resonance imaging; Gd, gadolinium.

DIAGNOSIS

There is no definitive diagnostic test for MS. Diagnostic criteria for clinically definite MS require documentation of two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS (Table 375-3). Symptoms must last for >24 h and occur as distinct episodes that are separated by a month or more. At least one of the two required signs must be present on neurologic examination. The second may be documented by abnormal paraclinical tests such as MRI or evoked potentials (EPs). Similarly, in the most recent diagnostic scheme, the second clinical event (in time) may be supported solely by paraclinical information, usually the development of new focal white matter lesions on MRI. In patients who experience gradual progression of disability for ≥6 months without superimposed relapses, documentation of intrathecal IgG may be used to support the diagnosis.

DIAGNOSTIC TESTS

Magnetic Resonance Imaging MRI has revolutionized the diagnosis and management of MS (Fig. 375-3); characteristic abnormalities are found in >95% of patients. An increase in vascular permeability from a breakdown of the BBB is detected by leakage of intravenous gadolinium (Gd) into the parenchyma. Such leakage occurs early in the development of an MS lesion and serves as a useful marker of inflammation. Gd enhancement persists for approximately 1 month, and the residual MS plaque remains visible indefinitely as a focal area of hyperintensity (a lesion) on spin-echo (T2-weighted) and proton-density images. Lesions are frequently oriented perpendicular to the ventricular surface, corresponding to the pathologic pattern of perivenous demyelination (Dawson's fingers). Lesions are multifocal within the brain, brainstem, and spinal cord. Lesions larger than 6 mm located in the corpus callosum, periventricular white matter, brainstem, cerebellum, or spinal cord are particularly helpful diagnostically. Different criteria for the use of MRI in the diagnosis of MS have been proposed (Table 375-3).

The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical

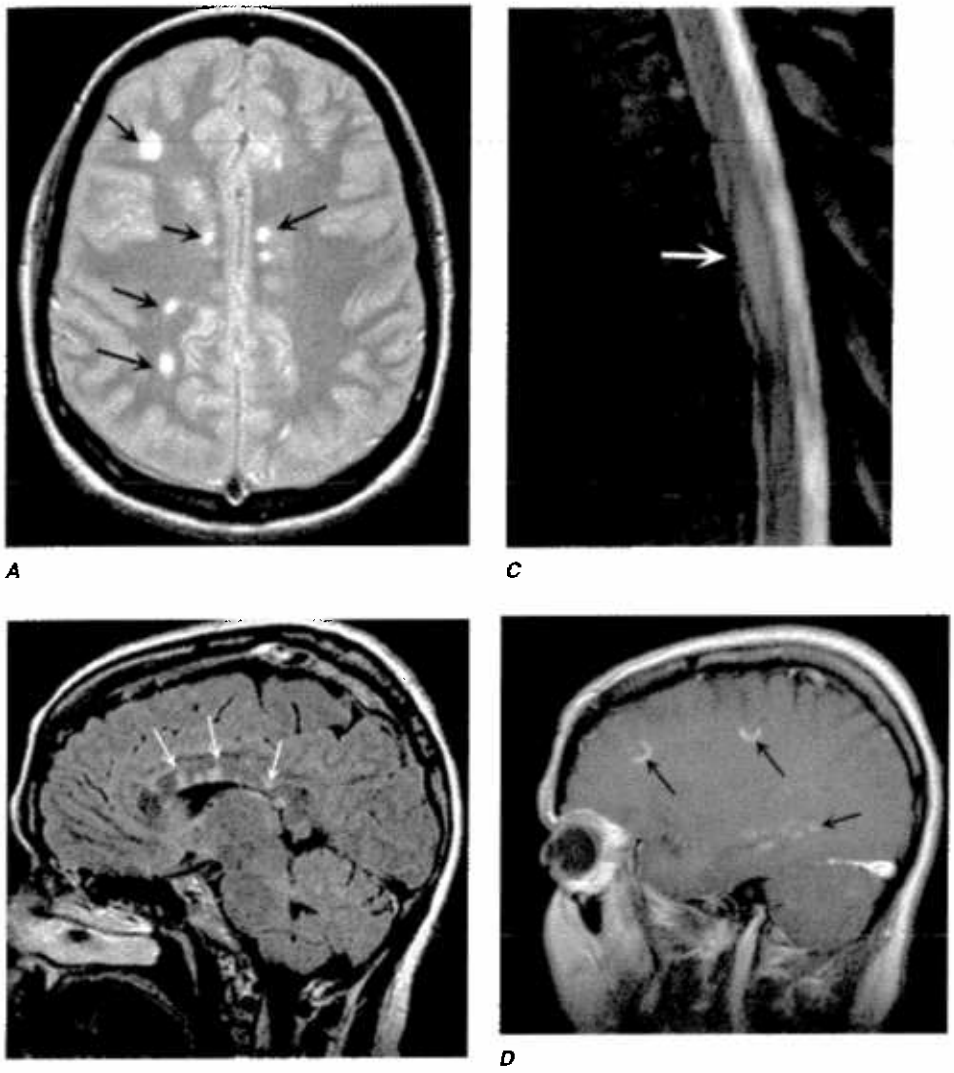

FIGURE 375-3 MRI findings in MS. ***A.*** Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. ***B.*** Sagittal T2-weighted FLAIR (fluid attenuated inversion recovery) image in which the high signal of CSF has been suppressed. CSF appears dark, while areas of brain edema or demyelination appear high in signal as shown here in the corpus callosum (*arrows*). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. ***C.*** Sagittal T2-weighted fast spin echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the mid thoracic spinal cord. ***D.*** Sagittal T1-weighted image obtained after the intravenous administration of gadolinium DTPA reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (*arrows*).

disability, as do measures of brain atrophy. Approximately one-third of T2-weighted lesions appear as hypointense lesions (black holes) on T1-weighted imaging. Black holes may be a marker of irreversible demyelination and axonal loss, although even this measure depends on the timing of the image acquisition (e.g., most acute Gd-enhancing T2 lesions are T1 dark).

Newer MRI measures such as magnetization transfer ratio (MTR) imaging and proton magnetic resonance spectroscopic imaging (MRSI) may ultimately serve as surrogate markers of clinical disability. For example, MRSI can quantitate molecules such as *N*-acetyl aspartate, which is a marker of axonal integrity, and MTR may be able to distinguish demyelination from edema.

Evoked Potentials EP testing assesses function in afferent (visual, auditory, and somatosensory) or efferent (motor) CNS pathways. EPs use computer averaging to measure CNS electric potentials evoked by repetitive stimulation of selected peripheral nerves or of the brain. These tests provide the most information when the pathways studied are clinically uninvolved. For example, in a patient with a remitting and relapsing spinal cord syndrome with sensory deficits in the legs, an abnormal somatosensory EP following posterior tibial nerve stimulation provides little new information. By contrast, an abnormal visual EP in this circumstance would permit a diagnosis of clinically definite MS (Table 375-3). Abnormalities on one or more EP modalities occur in 80–90% of MS patients. EP abnormalities are not specific to MS, although a marked delay in the latency of a specific EP component (as opposed to a reduced amplitude or distorted waveshape) is suggestive of demyelination.

Cerebrospinal Fluid CSF abnormalities found in MS include a mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG. The total CSF protein is usually normal or slightly elevated. Various formulas distinguish intrathecally synthesized IgG from IgG that may have entered the CNS passively from the serum. One formula, the CSF IgG index, expresses the ratio of IgG to albumin in the CSF divided by the same ratio in the serum. The IgG synthesis rate uses serum and CSF IgG and albumin measurements to calculate the rate of CNS IgG synthesis. The measurement of oligoclonal banding (OCB) in the CSF also assesses intrathecal production of IgG. OCBs are detected by agarose gel electrophoresis. Two or more OCBs are found in 75–90% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients the number of bands may increase with time. It is important that paired serum samples be studied to exclude a peripheral (i.e., non-CNS) origin of any OCBs detected in the CSF.

A mild CSF pleocytosis (>5 cells/μL) is present in ~25% of cases, usually in young patients with RRMS. A pleocytosis of >75 cells/μL, the presence of polymorphonuclear leukocytes, or a protein concentration of >1.0 g/L (>100 mg/dL) in CSF should raise concern that the patient may not have MS.

DIFFERENTIAL DIAGNOSIS

No single clinical sign or test is diagnostic of MS. The diagnosis is readily made in a young adult with relapsing and remitting symptoms involving different areas of CNS white matter. The possibility of an alternative diagnosis should always be considered (Table 375-4), particularly when (1) symptoms are localized exclusively to the posterior fossa, craniocervical junction, or spinal cord; (2) the patient is <15 or >60 years of age; (3) the clinical course is progressive from onset; (4) the patient has never experienced visual, sensory, or bladder symptoms; or (5) laboratory findings (e.g., MRI, CSF, or EPs) are atypical. Similarly, uncommon or rare symptoms in MS (e.g., aphasia, parkinsonism, chorea, isolated dementia, severe muscular atrophy, peripheral neuropathy, episodic loss of consciousness, fever, headache, seizures, or coma) should increase concern about an alternative diagnosis. Diagnosis is also difficult in patients with a rapid or explosive (strokelike) onset or with mild symptoms and a normal neurologic examination. Rarely, intense inflammation and swelling may produce a mass lesion that mimics a primary or metastatic

TABLE 375-4 DISORDERS THAT CAN MIMIC MS

Acute disseminated encephalomyelitis (ADEM)
Antiphospholipid antibody syndrome
Behçet's disease
Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
Human immunodeficiency virus (HIV) infection
Ischemic optic neuropathy (arteritic and nonarteritic)
Lyme disease
Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
Neoplasms (e.g., lymphoma, glioma, meningioma)
Sarcoid
Sjögren's syndrome
Stroke and ischemic cerebrovascular disease
Syphilis
Systemic lupus erythematosus and related collagen vascular disorders
Tropical spastic paraparesis (HTLV I/II infection)
Vascular malformations (especially spinal dural AV fistulas)
Vasculitis (primary CNS or other)
Vitamin B_{12} deficiency

Note: HTLV, human T cell lymphotropic virus; AV, arteriovenous; CNS, central nervous system.

tumor. The specific tests required to exclude alternative diagnoses will vary with each clinical situation; however, an erythrocyte sedimentation rate, serum B_{12} level, ANA, and treponemal antibody should probably be obtained in all patients with suspected MS.

PROGNOSIS

Most patients with MS ultimately experience progressive neurologic disability. Fifteen years after onset, only 20% of patients have no functional limitation; between one-third and one-half will have progressed to SPMS and will require assistance with ambulation. Twenty-five years after onset, ~80% of MS patients will have reached this level of disability. In 1998, it was estimated that the total annual economic burden of MS in the United States exceeded $6.8 billion.

However, even if the prognosis for disability is grave for the average patient, the prognosis in an individual is difficult to establish. Certain clinical features suggest a more favorable prognosis, including ON or sensory symptoms at onset; fewer than two relapses in the first year of illness; and minimal impairment after 5 years. By contrast, patients with truncal ataxia, action tremor, pyramidal symptoms, or a progressive disease course are more likely to become disabled.

Importantly, some MS patients have a benign variant of MS and never develop neurologic disability. The likelihood of having benign MS is thought to be <20%. Patients with benign MS 15 years after onset who have entirely normal neurologic examinations are likely to maintain their benign course.

In patients with their first demyelinating event (i.e., a clinically isolated syndrome), the brain MRI provides prognostic information. With three or more typical T2-weighted lesions, the risk of developing MS after 10 years is 70–80%. Conversely, with a normal brain MRI, the likelihood of developing MS is <20%. Similarly, two or more Gd-enhancing lesions at baseline is highly predictive of future MS, as is the appearance of either new T2-weighted lesions or new Gd enhancement ≥3 months after the initial episode.

Mortality as a direct consequence of MS is uncommon, although it has been estimated that the 25-year survival is only 85% of expected. Death can occur during an acute MS attack, although this is distinctly rare. More commonly, death occurs as a complication of MS (e.g., pneumonia in a debilitated individual). Death also results from suicide.

Effect of Pregnancy Pregnant MS patients experience fewer attacks than expected during gestation (especially in the last trimester), but more attacks than expected in the first 3 months postpartum. When considering the pregnancy year as a whole (i.e., 9 months pregnancy plus 3 months postpartum), the overall disease course is unaffected. Decisions about childbearing should thus be made based on (1) the mother's physical state, (2) her ability to care for the child, and (3) the availability of social support. Disease-modifying therapy is generally discontinued during pregnancy, although the actual risk from the interferons and glatiramer acetate (see below) appears to be low.

MULTIPLE SCLEROSIS

Therapy for MS can be divided into several categories: (1) treatment of acute attacks as they occur, (2) treatment with disease-modifying agents that reduce the biological activity of MS, and (3) symptomatic therapy. Treatments that promote remyelination or neural repair do not currently exist but would be highly desirable.

The Kurtzke Expanded Disability Status Score (EDSS) is a useful measure of neurologic impairment in MS (**Table 375-5**). Most patients with EDSS scores <3.5 have RRMS, walk normally, and are generally not disabled; by contrast, patients with EDSS scores >5.5 have progressive MS (SPMS or PPMS), are gait-impaired and, typically, are occupationally disabled.

ACUTE ATTACKS OR INITIAL DEMYELINATING EPISODES

When patients experience acute deterioration, it is important to consider whether this change reflects new disease activity or a "pseudoexacerbation" resulting from an increase in ambient temperature, fever, or an infection. In such instances, glucocorticoid treatment is inappropriate. Glucocorticoids are used to manage either first attacks or acute exacerbations. They provide short-term clinical benefit by reducing the severity and shortening the duration of attacks. Whether treatment provides any long-term benefit on the course of the illness is less clear. Therefore, mild attacks are often not treated. Physical and occupational therapy can help with mobility and manual dexterity.

Glucocorticoid treatment is usually administered as intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks. Outpatient treatment is usually possible. If intravenous therapy is unavailable or inconvenient, oral glucocorticoids can be substituted.

Side effects of short-term glucocorticoid therapy include fluid retention, potassium loss, weight gain, gastric disturbances, acne, and emotional lability. Concurrent use of a low-salt, potassium-rich diet and avoidance of potassium-wasting diuretics is advisable. Lithium carbonate (300 mg orally bid) may help to manage emotional lability and insomnia associated with glucocorticoid therapy. Patients with a history of peptic ulcer disease may require cimetidine (400 mg bid) or ranitidine (150 mg bid).

Plasma exchange (seven exchanges: 40–60 mL/kg per exchange, every other day for 14 days) may benefit patients with fulminant attacks of demyelination (not only MS) that are unresponsive to glucocorticoids. However, the cost is high, and the evidence of efficacy is only preliminary.

DISEASE-MODIFYING THERAPIES FOR RELAPSING FORMS OF MS (RRMS, SPMS WITH EXACERBATIONS) Five such agents are approved in the United States: (1) IFN-β-1a (Avonex), (2) IFN-β-1a (Rebif), (3) IFN-β-1b (Betaseron), (4) glatiramer acetate (Copaxone), and (5) natalizumab (Tysabri). Each of these treatments is also used in SPMS patients who continue to experience attacks, because SPMS can be difficult to distinguish from RRMS, and because clinical trials suggest that such patients also derive therapeutic benefit. In Phase III clinical trials, recipients of IFN-β-1b, IFN-β-1a, glatiramer acetate, and natalizumab experienced fewer clinical exacerbations and fewer new MRI lesions compared to placebo recipients (**Table 375-6**). Mitoxantrone (Novantrone), an immune suppressant, has also been approved in the United States, although it is generally reserved for patients with progressive disability who have failed other treatments because of its potential toxicity.

Interferon β, Glatiramer Acetate, and Natalizumab IFN-β is a class I interferon originally identified by its antiviral properties. Efficacy in MS probably results from immunomodulatory properties including (1) downregulating expression of MHC molecules on antigen-presenting cells, (2) inhibiting proinflammatory and increasing regulatory cytokine levels, (3) inhibition of T cell proliferation, and (4) limiting the trafficking of inflammatory cells in the CNS. Glatiramer acetate is a synthetic, random polypeptide composed of four amino acids (L-glutamic acid, L-lysine, L-alanine, and L-tyrosine). Its mechanism of action may include (1) induction of antigen-specific suppressor T cells; (2) binding to MHC molecules, thereby displacing bound MBP; or (3) altering the balance between proinflammatory and regulatory cytokines.

TABLE 375-5 SCORING SYSTEMS FOR MS

Kurtzke Expanded Disability Status Score (EDSS)

0.0 = Normal neurologic exam (all grade 0 in functional status (FS))
1.0 = No disability, minimal signs in one FS (i.e., grade 1)
1.5 = No disability, minimal signs in more than one FS (more than one grade 1)
2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0 = Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0 = Ambulatory without aid or rest for ≥ 500 m
4.5 = Ambulatory without aid or rest for ≥ 300 m
5.0 = Ambulatory without aid or rest for ≥ 200 m
5.5 = Ambulatory without aid or rest for ≥ 100 m
6.0 = Unilateral assistance required to walk about 100 m with or without resting
6.5 = Constant bilateral assistance required to walk about 20 m without resting
7.0 = Unable to walk beyond about 5 m even with aid; essentially restricted to wheelchair; wheels self and transfers alone
7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer
8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5 = Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0 = Helpless bed patient; can communicate and eat
9.5 = Totally helpless bed patient; unable to communicate or eat
10.0 = Death due to MS

Functional Status (FS) Score

A. Pyramidal functions
- 0 = Normal
- 1 = Abnormal signs without disability
- 2 = Minimal disability
- 3 = Mild or moderate paraparesis or hemiparesis, or severe monoparesis
- 4 = Marked paraparesis or hemiparesis, moderate quadriparesis, or monoplegia
- 5 = Paraplegia, hemiplegia, or marked quadriparesis
- 6 = Quadriplegia

B. Cerebellar functions
- 0 = Normal
- 1 = Abnormal signs without disability
- 2 = Mild ataxia
- 3 = Moderate truncal or limb ataxia
- 4 = Severe ataxia all limbs
- 5 = Unable to perform coordinated movements due to ataxia

C. Brainstem functions
- 0 = Normal
- 1 = Signs only
- 2 = Moderate nystagmus or other mild disability
- 3 = Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
- 4 = Marked dysarthria or other marked disability
- 5 = Inability to swallow or speak

D. Sensory functions
- 0 = Normal
- 1 = Vibration or figure-writing decrease only, in 1 or 2 limbs
- 2 = Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in 1 or 2 limbs, or vibratory decrease alone in 3 or 4 limbs
- 3 = Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in 1 or 2 limbs, or mild decrease in touch or pain, and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs
- 4 = Marked decrease in touch or pain or loss of proprioception, alone or combined, in 1 or 2 limbs or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than 2 limbs
- 5 = Loss (essentially) of sensation in 1 or 2 limbs or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
- 6 = Sensation essentially lost below the head

E. Bowel and bladder functions
- 0 = Normal
- 1 = Mild urinary hesitancy, urgency, or retention
- 2 = Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence
- 3 = Frequent urinary incontinence
- 4 = In need of almost constant catheterization
- 5 = Loss of bladder function
- 6 = Loss of bowel and bladder function

F. Visual (or optic) functions
- 0 = Normal
- 1 = Scotoma with visual acuity (corrected) better than 20/30
- 2 = Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59
- 3 = Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99
- 4 = Worse eye with marked decrease of fields and maximal acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
- 5 = Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
- 6 = Grade 5 plus maximal visual acuity of better eye of 20/60 or less

G. Cerebral (or mental) functions
- 0 = Normal
- 1 = Mood alteration only (does not affect EDSS score)
- 2 = Mild decrease in mentation
- 3 = Moderate decrease in mentation
- 4 = Marked decrease in mentation
- 5 = Chronic brain syndrome—severe or incompetent

Source: After JF Kurtzke: Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 33:1444, 1983.

Natalizumab is a humanized monoclonal antibody directed against the α_4 subunit of $\alpha_4\beta_1$ integrin, a cellular adhesion molecule expressed on the surface of lymphocytes. It prevents lymphocytes from binding to endothelial cells, thereby preventing lymphocytes from penetrating the BBB and entering the CNS.

IFN-β reduces the attack rate and improves disease severity measures such as EDSS progression and MRI documented disease burden. IFN-β should be considered in patients with either RRMS or SPMS with superimposed relapses. In patients with SPMS but without relapses, efficacy has not been established. Higher IFN-β doses appear to have slightly greater efficacy but are also more likely to induce neutralizing antibodies, which may reduce the clinical benefit (see below).

Glatiramer acetate also reduces the attack rate (whether measured clinically or by MRI) in RRMS. Glatiramer acetate may also benefit disease severity measures, although this is less well-established than for the relapse rate. Therefore, glatiramer acetate should be considered in RRMS patients. Its usefulness in progressive disease is entirely unknown.

Natalizumab dramatically reduces the attack rate and significantly improves all measures of disease severity in MS. However, because of the development of progressive multifocal leukoencephalopathy (PML) in two patients treated with natalizumab in combination with IFN-β 1a (Avonex), and a third case in a patient treated (in combination with other immunosuppressant drugs) for Crohn's disease, natalizumab is currently recommended only for patients who have failed other therapies or who have particularly aggressive presentations. Its usefulness in the treatment of progressive disease has not been studied.

The long-term efficacy of these treatments remains uncertain, although several recent studies suggest that these agents can improve the long-term outcome of MS when administered in the RRMS stage of the illness. Beneficial effects seen in early MS include a reduction in the relapse rate and a reduction in CNS inflammation as measured by MRI. Unfortunately, already established progressive symptoms do not respond to treatment with these disease-modifying therapies. Because progressive symptoms are likely to result from delayed effects of earlier focal demyelinating epi-

TABLE 375-6 TWO-YEAR OUTCOMES FOR FDA-APPROVED THERAPIES FOR MULTIPLE SCLEROSIS[a]

Dose, Route, and Schedule	Clinical Outcomes[b]		MRI Outcomes[c]	
	Attack Rate, Mean	Change in Disease Severity	New T2 Lesions[d]	Total Burden of Disease
IFN-β-1b, 250 μg SC qod	-34%[e]	-29% (ns)	-83%[f]	-17%[e]
IFN-β-1a, 30 μg IM qw	-18%[g]	-37%[g]	-36%[f]	-4% (ns)
IFN-β-1a, 44 μg SC tiw	-32%[e]	-30%[g]	-78%[e]	-15%[e]
GA, 20 mg SC qd	-29%[f]	-12% (ns)	-38%[f]	-8%[f]
MTX, 12 mg/m^2 IV q3mo	-66%[e]	-75%[g]	-79%[g]	nr
NTZ, 300 mg IV qmo	-68%[e]	-42%[e]	-83%[e]	-18%[e]

[a]Percentage reductions (or increases) have been calculated by dividing the reported rates in the treated group by the comparable rates in the placebo group, except for MRI disease burden, which was calculated as the difference in the median % change between the treated and placebo groups.
[b]Severity = 1 point EDSS progression, sustained for 3 months (in the IFN-β-1a 30 μg qw trial, this change was sustained for 6 months; in the IFN-β-1b trial, this was over 3 years).
[c]Different studies measured these MRI measures differently, making comparisons difficult (numbers for new T2 represent the best case scenario for each trial).
[d]New lesions seen on T_2-weighted MRI.
[e]$p = .001$.
[f]$p = .01$.
[g]$p = .05$.
Abbreviations: IFN-β, interferon β; GA, glatiramer acetate; MTX, mitoxantrone; NTZ, natalizumab; IM, intramuscular; SC, subcutaneous; IV, intravenous; qod, every other day; qw, once per week; tiw, three times per week; qd, daily; q3mo, once every 3 months; qmo, once per month; ns, not significant; nr, not reported.

sodes, many experts now believe that very early treatment with a disease-modifying drug is appropriate for most MS patients. It is reasonable to delay initiating treatment in patients with (1) normal neurologic exams, (2) a single attack or a low attack frequency, and (3) a low burden of disease as assessed by brain MRI. Untreated patients should be followed closely with periodic brain MRI scans; the need for therapy is reassessed if scans reveal evidence of ongoing, subclinical disease.

Most treated patients with relapsing forms of MS receive IFN-β or glatiramer acetate as first-line therapy. Regardless of which agent is chosen first, treatment should probably be changed in patents who continue to have frequent attacks or progressive disability (**Fig. 375-4**). The value of combination therapy is unknown.

IFN-β-1a (Avonex), 30 μg, is administered by intramuscular injection once every week. IFN-β-1a (Rebif), 44 μg, is administered by subcutaneous injection three times per week. IFN-β-1b (Betaseron), 250 μg, is administered by subcutaneous injection every other day. Glatiramer acetate, 20 mg, is administered by subcutaneous injection every day. Natalizumab, 300 μg, is administered by IV infusion each month. Common side effects of IFN-β therapy include flulike symptoms (e.g., fevers, chills, and myalgias) and mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia). Rarely, more severe hepatotoxicity may occur. Subcutaneous IFN-β also causes reactions at the injection site (e.g., pain, redness, induration, or, rarely, skin necrosis). Side effects can usually be managed with concomitant nonsteroidal anti-inflammatory medications and with the use of an autoinjector. Depression, increased spasticity, and cognitive changes have been reported, although these symptoms can also be due to the underlying disease. In any event, side effects to IFN-β therapy usually subside with time.

Approximately 2–10% of IFN-β-1a (Avonex) recipients, 15–25% of IFN-β-1a (Rebif) recipients, and 30–40% of IFN-β-1b (Betaseron) recipients develop neutralizing antibodies to IFN-β, which may disappear over time. Some evidence suggests that neutralizing antibodies reduce efficacy, especially for MRI outcomes. The current clinical data, however, are quite conflicted.

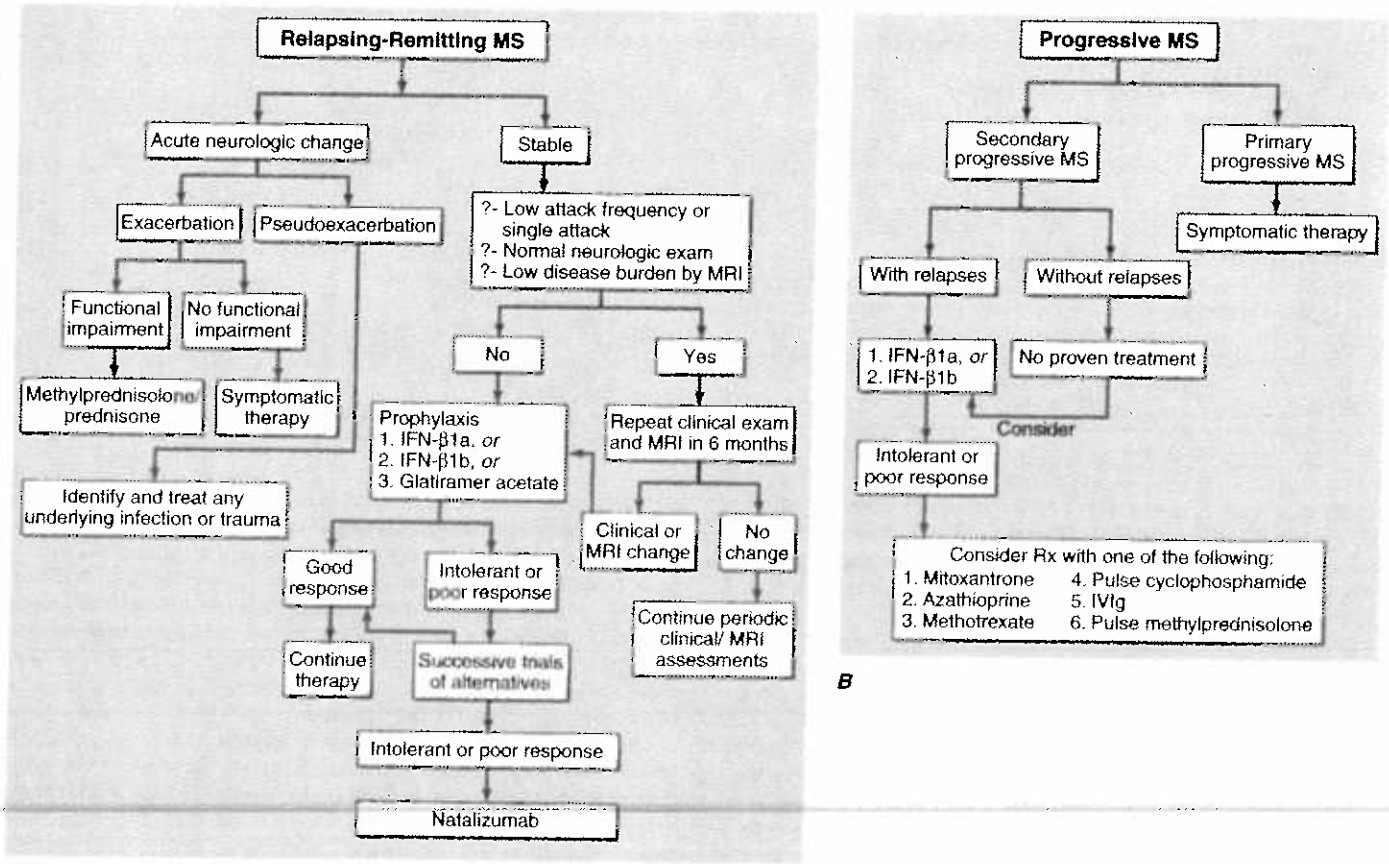

FIGURE 375-4 Therapeutic decision-making for MS.

Moreover, there are few situations where measurement of antibodies is necessary. Thus, for a patient doing well on therapy, the presence of antibodies should not affect treatment. Conversely, for a patient doing poorly on therapy, alternative treatment should be considered, even if there are no detectable antibodies.

Injection-site reactions also occur with glatiramer acetate but are less severe than with IFN-β-1b. Approximately 15% of patients experience one or more episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety after injection. This systemic reaction is unpredictable, brief (duration <1 h), and tends not to recur.

Treatment with natalizumab is, in general, well tolerated. A small percentage (<10%) of patients experience hypersensitivity reactions (including anaphylaxis) and ~6% develop neutralizing antibodies to the molecule. As noted above, of greater potential concern was the occurrence of PML in three patients.

Mitoxantrone Hydrochloride Mitoxantrone (Novantrone), an anthracenedione, exerts its antineoplastic action by (1) intercalating into DNA and producing both strand breaks and interstrand cross-links, (2) interfering with RNA synthesis, and (3) inhibiting topoisomerase II (involved in DNA repair). The U.S. Food and Drug Administration (FDA) approved mitoxantrone on the basis of a single (relatively small) phase III clinical trial in Europe, in addition to an even smaller phase II study completed earlier. Mitoxantrone received (from the FDA) the broadest indication of any current treatment for MS. Thus, mitoxantrone is indicated for use in SPMS, in PRMS, and in patients with worsening RRMS (defined as patients whose neurologic status remains significantly abnormal between MS attacks). Despite this broad indication, however, the data supporting its efficacy are weaker than for other approved therapies.

Mitoxantrone can be cardiotoxic (e.g., cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure). As a result, a cumulative dose >140 mg/m^2 is not recommended. At currently approved doses (12 mg/m^2 every 3 months), the maximum duration of therapy can be only 2–3 years. Furthermore, >40% of women will experience amenorrhea, which may be permanent. Finally, there is risk of acute leukemia, and this complication has already been reported in several mitoxantrone-treated MS patients.

Given these risks, mitoxantrone should not be used as a first-line agent in either RRMS or relapsing SPMS. It is reasonable to consider mitoxantrone in selected patients with a progressive course who have failed other approved therapies.

DISEASE-MODIFYING THERAPIES FOR SPMS High-dose IFN-β probably has a beneficial effect in patients with SPMS who are still experiencing acute relapses. IFN-β is probably ineffective in patients with SPMS who are not having acute attacks. Glatiramer acetate and natalizumab have not been studied in this patient population.

Although mitoxantrone has been approved for patients with progressive MS, this is not the population studied in the pivotal trial. Therefore no evidence-based recommendation can be made with regard to its use in this setting.

PPMS No currently available therapies have shown any promise for treating PPMS at this time. A phase III clinical trial of glatiramer acetate in PPMS was recently stopped because of lack of efficacy. Trials of mitoxantrone and rituximab in PPMS are currently underway.

OFF-LABEL TREATMENT OPTIONS FOR RRMS AND SPMS *Azathioprine* (2–3 mg/kg/per day) has been used primarily in SPMS. Meta-analysis of published trials suggests that azathioprine is marginally effective at lowering relapse rates, although a benefit on disability progression has not been demonstrated.

Methotrexate (7.5–20 mg/wk) was shown in one study to slow the progression of upper-extremity dysfunction in SPMS. Because of the possibility of developing irreversible liver damage, some experts recommend a blind liver biopsy after 2 years of therapy.

Cyclophosphamide (700 mg/m^2, every other month) may be helpful for treatment-refractory patients who are (1) otherwise in good health, (2) ambulatory, and (3) <40 years of age. Because cyclophosphamide can be used for periods in excess of 3 years, it may be preferable to mitoxantrone in these circumstances.

Intravenous immunoglobulin (IVIg), administered in monthly pulses (up to 1 g/kg) for up to 2 years, appears to reduce annual exacerbation rates. However, its use is limited because of its high cost, questions about optimal dose, and uncertainty about its effect on long-term disability outcome.

Methylprednisolone administered in one study as monthly high-dose intravenous pulses, reduced disability progression (see above).

OTHER THERAPEUTIC CLAIMS Many purported treatments for MS have never been subjected to scientific scrutiny. These include dietary therapies (e.g., the Swank diet in addition to others), megadose vitamins, low-dose naltrexone, calcium orotate, bee stings, cow colostrum, hyperbaric oxygen, procain (a combination of histamine and caffeine), chelation, acupuncture, acupressure, various Chinese herbal remedies, and removal of mercury-amalgam tooth fillings, among many others. Patients should avoid costly or potentially hazardous unproven treatments. Many such treatments lack biologic plausibility. For example, no reliable case of mercury poisoning resembling typical MS has ever been described.

Although potential roles for EBV, HHV-6, or chlamydia have been suggested for MS, these reports are unconfirmed, and treatment with antiviral agents or antibiotics is not currently appropriate.

SYMPTOMATIC THERAPY Potassium channel blockers (e.g., 4-aminopyridine, 10–40 mg/d; and 3,4-diaminopyridine, 40–80 mg/d) may be helpful for *weakness*, especially for heat-sensitive symptoms. At high doses they may cause seizures. These agents are not FDA-approved but can be obtained from compounding pharmacies around the United States.

Ataxia/tremor is often intractable. Clonazepam, 1.5–20 mg/d; mysoline, 50–250 mg/d; propranolol, 40–200 mg/d; or ondansetron, 8–16 mg/d may help. Wrist weights occasionally reduce tremor in the arm or hand. Thalamotomy or deep-brain stimulation has been tried with mixed success.

Spasticity and *spasms* may improve with physical therapy, regular exercise, and stretching. Avoidance of triggers (e.g., infections, fecal impactions, bed sores) is extremely important. Effective medications include lioresal (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydrochloride (10–60 mg/d). For severe spasticity, a lioresal pump (delivering medication directly into the CSF) can provide substantial relief.

Pain is treated with anticonvulsants (carbamazepine, 100–1000 mg/d; phenytoin, 300–600 mg/d; gabapentin, 300–3600 mg/d; or pregabalin, 50–300 mg/d), antidepressants (amitriptyline, 25–150 mg/d; nortriptyline, 25–150 mg/d; desipramine, 100–300 mg/d; or venlafaxine, 75–225 mg/d), or antiarrhythmics (mexiletine, 300–900 mg/d). If these approaches fail, patients should be referred to a comprehensive pain management program.

Bladder dysfunction management is best guided by urodynamic testing. Evening fluid restriction or frequent voluntary voiding may help *detrusor hyperreflexia*. If these methods fail, propantheline bromide (10–15 mg/d), oxybutynin (5–15 mg/d), hyoscyamine sulfate (0.5–0.75 mg/d), tolterodine tartrate (2–4 mg/d), or solifenacin (5–10 mg/d) may help. Coadministration of pseudoephedrine (30–60 mg) is sometimes beneficial.

Detrusor/sphincter dyssynergia may respond to phenoxybenzamine (10–20 mg/d) or terazosin hydrochloride (1–20 mg/d). Loss of reflex bladder wall contraction may respond to bethanechol (30–150 mg/d). However, both conditions often require catheterization.

Urinary tract infections should be treated promptly. Patients with large post-void residual urine volumes are predisposed to infections. Prevention by urine acidification (with cranberry juice or vitamin C) inhibits some bacteria. Prophylactic administration of antibiotics is sometimes necessary but may lead to colonization by resistant organisms. Intermittent catheterization may help to prevent recurrent infections.

Treatment of *constipation* includes high-fiber diets and fluids. Natural or other laxatives may help. *Fecal incontinence* may respond to a reduction in dietary fiber.

Depression should be treated. Useful drugs include the selective serotonin reuptake inhibitors (fluoxetine, 20–80 mg/d, or sertraline, 50–200 mg/d); the tricyclic antidepressants (amitriptyline, 25–150 mg/d, nortriptyline, 25–150 mg/d, or desipramine, 100–300 mg/d); and the nontricyclic antidepressants (venlafaxine, 75–225 mg/d).

Fatigue may improve with assistive devices, help in the home, or successful management of spasticity. Patients with frequent nocturia may benefit from anticholinergic medication at bedtime. Primary MS fatigue may respond to amantadine (200 mg/d), methylphenidate (5–25 mg/d), or modafinil (100–400 mg/d).

Cognitive problems may respond to the cholinesterase inhibitor donepezil hydrochloride (10 mg/d).

Paroxysmal symptoms respond dramatically to low-dose anticonvulsants (acetazolamide, 200–600 mg/d; carbamazepine, 50–400 mg/d; phenytoin, 50–300 mg/d; or gabapentin, 600–1800 mg/d).

Heat sensitivity may respond to heat avoidance, air-conditioning, or cooling garments.

Sexual dysfunction may be helped by lubricants to aid in genital stimulation and sexual arousal. Management of pain, spasticity, fatigue, and bladder/bowel dysfunction may also help. Sildenafil (50–100 mg) taken 1–2 h before sex, is now the standard treatment for maintaining erections.

PROMISING EXPERIMENTAL THERAPIES Numerous clinical trials are currently underway. These include: (1) combination therapies; (2) higher-dose IFN-β than currently prescribed; (3) monoclonal antibodies against CD20 to deplete B cells, against the IL-2 receptor, or against CD52 to induce global lymphocyte depletion; (4) an oral sphingosine-1-phosphate receptor antagonist to sequester lymphocytes in the secondary lymphoid organs; (5) use of MBP, or an altered peptide ligand resembling MBP, to induce antigen-specific tolerance; (6) an oral inhibitor of the enzyme dihydroorotate dehydrogenase involved in pyrimidine synthesis; (7) use of statins as immunomodulators; (8) estriol to induce a pregnancy-like state; and (9) bone marrow transplantation.

CLINICAL VARIANTS OF MS

Neuromyelitis optica (NMO), or Devic's syndrome, consists of separate attacks of acute ON and myelitis. ON may be unilateral or bilateral and precede or follow an attack of myelitis by days, months, or years. In contrast to MS, patients with NMO do not experience brainstem, cerebellar, and cognitive involvement, and the brain MRI is typically normal. A focal enhancing region of swelling and cavitation, extending over three or more spinal cord segments, is typically seen on MRI. Histopathology of these lesions may reveal thickening of blood-vessel walls and deposition of antibody and complement. Occasional patients with apparent NMO also have brain MRI changes indicating involvement of the cerebral hemispheres.

NMO, which is uncommon in Caucasians compared with Asians and Africans, is best understood as a syndrome with diverse causes. Some patients have a systemic autoimmune disorder, often systemic lupus erythematosus, Sjögren's syndrome, p-ANCA (perinuclear antineutrophil cytoplasmic antibody) associated vasculitis, or mixed connective tissue disease. In others, onset may be associated with acute infection with varicella-zoster virus, EBV, HIV, or tuberculosis. More frequently, however, NMO is idiopathic and probably represents an MS variant; in such cases the course can be monophasic but is more often recurrent.

A highly specific autoantibody directed against the water channel protein aquaporin-4 is present in the sera of more than half of patients who have a clinical diagnosis of NMO. Aquaporin-4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces. The role of aquaporin-4 antibodies in the pathogenesis of NMO, however, is unknown.

Disease-modifying therapies for MS have not been rigorously studied in NMO. Acute attacks are usually treated with high-dose glucocorticoids as for MS exacerbations (see above). Because of the possibility that NMO is antibody-mediated, plasma exchange has also been used empirically for acute episodes that fail to respond to glucocorticoids. Immunosuppressants (cyclophosphamide or azathioprine with glucocorticoids) are sometimes used in the hope that further relapses will be prevented. More recently, in a small open-case series, B cell depletion with anti-CD20 monoclonal antibody (rituxan) appeared to show promise in preventing relapses of NMO.

Acute MS (Marburg's variant) is a fulminant demyelinating process that in some cases progresses inexorably to death within 1–2 years. Typically, there are no remissions. When acute MS presents as a solitary, usually cavitary, lesion, a brain tumor is often suspected. In such cases a brain biopsy is usually required to establish the diagnosis. An antibody-mediated process appears to be responsible for most cases. Marburg's variant does not seem to follow infection or vaccination, and it is unclear whether this syndrome represents an extreme form of MS or another disease altogether. No controlled trials of therapy exist; high-dose glucocorticoids, plasma exchange, and cyclophosphamide have been tried, with uncertain benefit.

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

ADEM has a monophasic course and is frequently associated with antecedent immunization (postvaccinal encephalomyelitis) or infection (postinfectious encephalomyelitis). The hallmark of ADEM is the presence of widely scattered small foci of perivenular inflammation and demyelination. In its most explosive form, acute hemorrhagic leukoencephalitis, the lesions are vasculitic and hemorrhagic, and the clinical course is devastating.

Postvaccinal encephalomyelitis may follow the administration of smallpox and certain rabies vaccines. Postinfectious encephalomyelitis is most frequently associated with the viral exanthems of childhood. Infection with measles virus is the most common antecedent (1 in 1000 cases). Worldwide, measles encephalomyelitis is still common, although use of the live measles vaccine has dramatically reduced its incidence in developed countries. An ADEM-like illness rarely follows vaccination with live measles vaccine (1–2 in 10^6 immunizations). ADEM is now most frequently associated with varicella (chickenpox) infections (1 in 4000–10,000 cases). It may also follow infection with rubella, mumps, influenza, parainfluenza, infectious mononucleosis viruses, and *Mycoplasma*. Some patients may have a nonspecific upper respiratory infection or no known antecedent illness.

All forms of ADEM presumably result from a cross-reactive immune response to the infectious agent or vaccine that then triggers an inflammatory demyelinating response. Autoantibodies to MBP and to other myelin antigens have been detected in the CSF from many patients with ADEM. Attempts to demonstrate direct viral invasion of the CNS have been unsuccessful.

CLINICAL MANIFESTATIONS

In severe cases, onset is abrupt and progression rapid (hours to days). In postinfectious ADEM, the neurologic syndrome generally begins late in the course of the viral illness as the exanthem is fading. Fever reappears, and headache, meningismus, and lethargy progressing to coma may develop. Seizures are common. Signs of disseminated neurologic disease are consistently present (e.g., hemiparesis or quadriparesis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss and brainstem involvement). In ADEM due to chickenpox, cerebellar involvement is often conspicuous. CSF protein is modestly elevated [0.5–1.5 g/L (50–150 mg/dL)]. Lymphocytic pleocytosis, generally 200 cells/μl, occurs in 80% of patients. Occasional patients have higher counts or a mixed polymorphonuclear-lymphocytic pattern during the initial days of the illness. Transient CSF oligoclonal banding has been reported. MRI may reveal extensive gadolinium enhancement of white matter in brain and spinal cord.

DIAGNOSIS

The diagnosis is easily established when there is a history of recent vaccination or exanthematous illness. In severe cases with predominantly cerebral involvement, acute encephalitis due to infection with herpes simplex or other viruses may be difficult to exclude. The simultaneous onset of disseminated symptoms and signs is common in ADEM and rare in MS. Similarly, meningismus, drowsiness, coma, or seizures suggest ADEM rather than MS. Unlike in MS, in ADEM optic nerve involvement is generally bilateral and transverse myelopathy complete. MRI findings that may support a diagnosis of ADEM include extensive and relatively symmetric white matter abnormalities and Gd enhancement of all abnormal areas, indicating active disease and a monophasic course.

℞ ACUTE DISSEMINATED ENCEPHALOMYELITIS

Initial treatment is with high-dose glucocorticoids as for exacerbations of MS (see above); depending on the response, treatment may need to be continued for 4–8 weeks. Patients who fail to respond within a few days may benefit from a course of plasma exchange or intravenous immunoglobulin. The prognosis reflects the severity of the underlying acute illness. Measles en-

cephalomyelitis is associated with a mortality rate of 5–20%, and most survivors have permanent neurologic sequelae. Children who recover may have persistent seizures and behavioral and learning disorders.

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376 Meningitis, Encephalitis, Brain Abscess, and Empyema

Karen L. Roos, Kenneth L. Tyler

Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision-making, and rapid institution of therapy can be lifesaving. These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis. Each may present with a nonspecific prodrome of fever and headache, which in a previously healthy individual may initially be thought to be benign, until (with the exception of viral meningitis) altered consciousness, focal neurologic signs, or seizures appear. Key goals of early management are to emergently distinguish between these conditions, identify the responsible pathogen, and initiate appropriate antimicrobial therapy.

APPROACH TO THE PATIENT

(Fig. 376-1) The first task is to identify whether an infection predominantly involves the subarachnoid space (*meningitis*) or whether there is evidence of either generalized or focal involvement of brain tissue in the cerebral hemispheres, cerebellum, or brainstem. When brain tissue is directly injured by a viral infection the disease is referred to as *encephalitis*, whereas focal bacterial, fungal, or parasitic infections involving brain tissue are classified as either *cerebritis* or *abscess*, depending on the presence or absence of a capsule.

Nuchal rigidity ("stiff neck") is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs of meningeal irritation. *Kernig's sign* is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. *Brudzinski's sign* is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. Although commonly tested on physical examinations, the sensitivity and specificity of Kernig's and Brudzinski's signs are uncertain. Both may be absent or reduced in very young or elderly patients, immunocompromised individuals, or patients with a severely depressed mental status. The high prevalence of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity.

Initial management can be guided by several considerations: (1) Empirical therapy should be initiated promptly whenever bacterial meningitis is a significant diagnostic consideration. (2) All patients who have had recent head trauma, are immunocompromised, have known malignant lesions or central nervous system (CNS) neoplasms, or have focal neurologic findings that include papilledema or a depressed level of consciousness should undergo CT or MRI of the brain prior to lumbar puncture (LP). In these cases empirical antibiotic therapy should not be delayed pending test results but should be administered prior to neuroimaging and LP. (3) A significantly depressed level of consciousness (e.g., somnolence, coma), seizures, or focal neurologic deficits do not occur in viral (*aseptic*) meningitis; patients with these symptoms should be hospitalized for further evaluation and treated empirically for bacterial and viral meningoencephalitis. (4) Immunocompetent patients with a normal level of consciousness, no prior antimicrobial treatment, and a cerebrospinal fluid (CSF) profile consistent with viral meningitis (lymphocytic pleocytosis and a normal glucose concentration) can often be treated as outpatients if appropriate contact and monitoring can be ensured. Failure of a patient with suspected viral meningitis to improve within 48 h should prompt a reevaluation including follow-up neurologic and general medical examination and repeat imaging and laboratory studies, often including a second LP.

ACUTE BACTERIAL MENINGITIS

DEFINITION

Bacterial meningitis is an acute purulent infection within the subarachnoid space. It is associated with a CNS inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. The meninges, the subarachnoid space, and the brain parenchyma are all frequently involved in the inflammatory reaction (*meningoencephalitis*).

EPIDEMIOLOGY

Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of >2.5 cases/100,000 population. The epidemiology of bacterial meningitis has changed significantly in recent years, reflecting a dramatic decline in the incidence of meningitis due to *Haemophilus influenzae*, and a smaller decline in that due to *Neisseria meningitidis*, following the introduction and increasingly widespread use of vaccines for both these organisms. Currently, the organisms most commonly responsible for community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *N. meningitidis* (~25%), group B streptococci (~15%), and *Listeria monocytogenes* (~10%). *H. influenzae* now accounts for <10% of cases of bacterial meningitis in most series.

ETIOLOGY

S. pneumoniae (Chap. 130) is the most common cause of meningitis in adults >20 years of age, accounting for nearly half the reported cases (1.1

per 100,000 persons per year). There are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia. Additional risk factors include coexisting acute or chronic pneumococcal sinusitis or otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and CSF rhinorrhea. Mortality remains ~20% despite antibiotic therapy.

N. meningitidis (Chap. 136) accounts for 25% of all cases of bacterial meningitis (0.6 cases per 100,000 persons per year) and for up to 60% of cases in children and young adults between the ages of 2 and 20. The presence of petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection. In some patients the disease is fulminant, progressing to death within hours of symptom onset. Infection may be initiated by nasopharyngeal colonization, which can result in either an asymptomatic carrier state or invasive meningococcal disease. The risk of invasive disease following nasopharyngeal colonization depends on both bacterial virulence factors and host immune defense mechanisms, including the host's capacity to produce antimeningococcal antibodies and to lyse meningococci by both classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections.

Enteric gram-negative bacilli are an increasingly common cause of meningitis in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with chronic urinary tract infections. Gram-negative meningitis can also complicate neurosurgical procedures, particularly craniotomy.

Group B streptococcus, or *S. agalactiae*, was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals >50 years of age, particularly those with underlying diseases.

L. monocytogenes (Chap. 132) has become an increasingly important cause of meningitis in neonates (<1 month of age), pregnant women, individuals >60 years, and immunocompromised individuals of all ages. Infection is acquired by ingesting foods contaminated by *Listeria*. Foodborne human listerial infection has been reported from contaminated coleslaw, milk, soft cheeses, and several types of "ready-to-eat" foods, including delicatessen meat and uncooked hotdogs.

The frequency of *H. influenzae* type b meningitis in children has declined dramatically since the introduction of the Hib conjugate vaccine, although rare cases of Hib meningitis in vaccinated children have been reported. More frequently, *H. influenzae* causes meningitis in unvaccinated children and adults.

Staphylococcus aureus and coagulase-negative staphylococci (Chap. 129) are important causes of meningitis that occurs following invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or as a complication of the use of subcutaneous Ommaya reservoirs for administration of intrathecal chemotherapy.

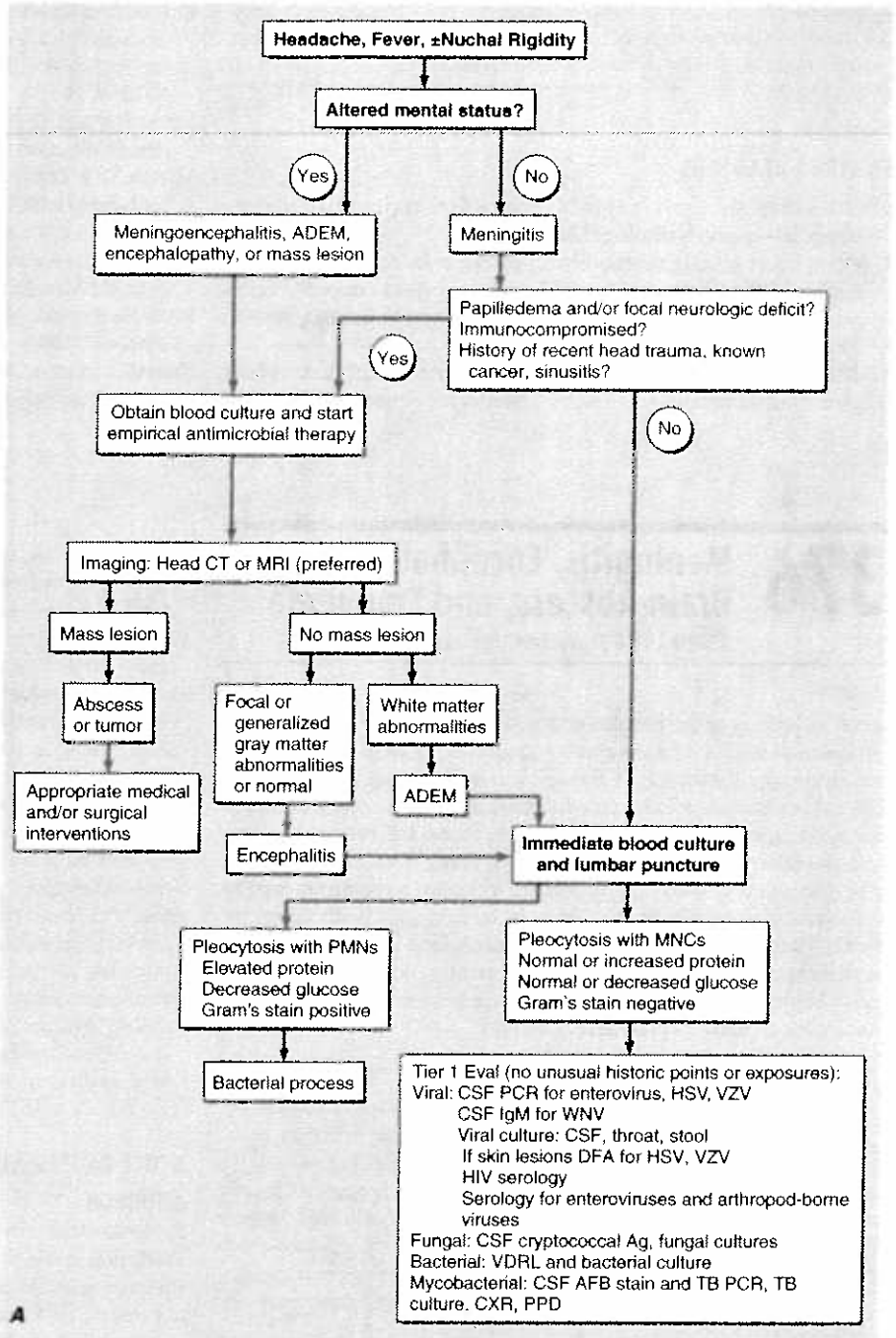

FIGURE 376-1 The management of patients with suspected CNS infection. ADEM, acute disseminated encephalomyelitis; CT, computed tomography; MRI, magnetic resonance imaging; PMNs, polymorphonuclear leukocytes; MNCs, mononuclear cells; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; HSV, herpes simplex virus; VZV, varicella-zoster virus; WNV, West Nile virus; DFA, direct fluorescent antibody; Ag, antigen; VDRL, Venereal Disease Research Laboratory; AFB, acid-fast bacillus; TB, tuberculosis; CXR, chest x-ray; PPD, purified protein derivative; EBV, Epstein-Barr virus; CTFV, Colorado tick fever virus; HHV, human herpesvirus; LCMV, lymphocytic choriomeningitis virus.

PATHOPHYSIOLOGY

The most common bacteria that cause meningitis, *S. pneumoniae* and *N. meningitidis*, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement–mediated bactericidal activity because of the presence of a polysaccharide

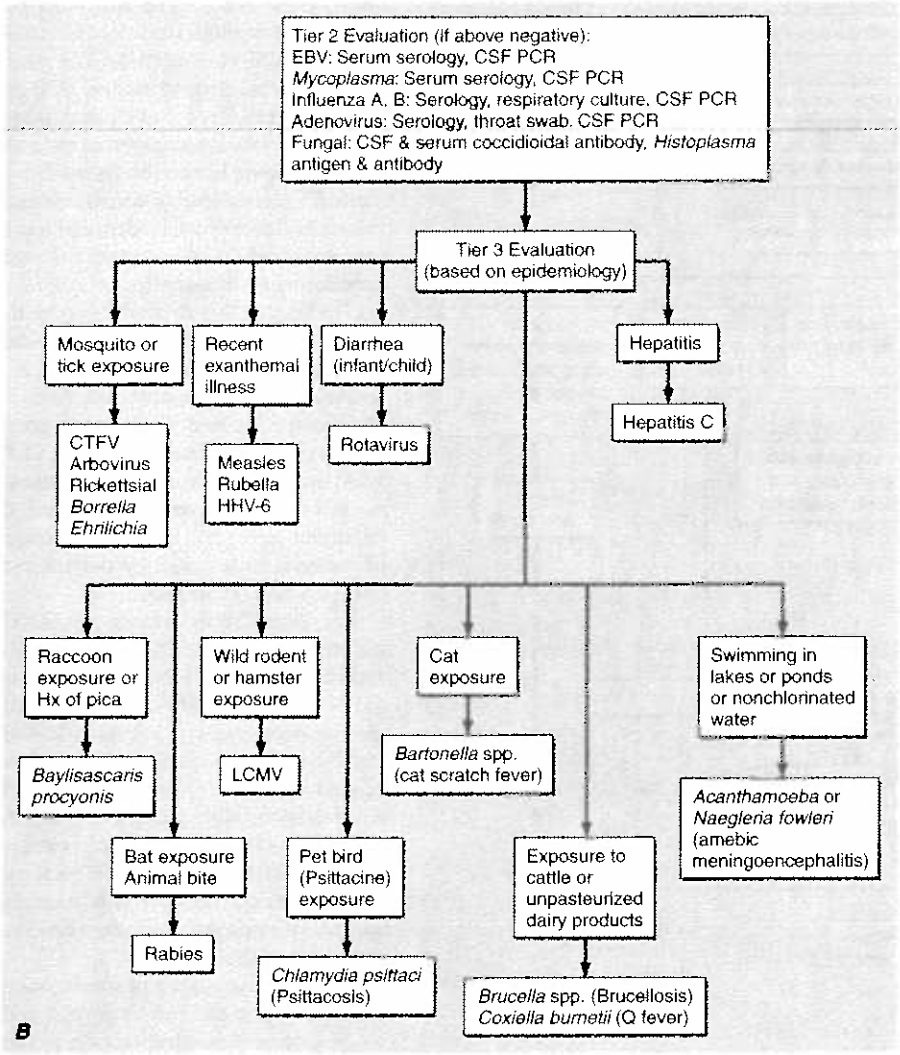

FIGURE 376-1 ***(Continued.)***

capsule. Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells, and gain access to the CSF. Some bacteria, such as *S. pneumoniae*, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white blood cells (WBCs) and relatively small amounts of complement proteins and immunoglobulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Many of the neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen rather than from direct bacteria-induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy.

The lysis of bacteria with the subsequent release of cell-wall components into the subarachnoid space is the initial step in the induction of the inflammatory response and the formation of a purulent exudate in the subarachnoid space (Fig. 376-2). Bacterial cell-wall components, such as the lipopolysaccharide (LPS) molecules of gram-negative bacteria and teichoic acid and peptidoglycans of *S. pneumoniae*, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and CSF leukocytes. In experimental models of meningitis, cytokines including tumor necrosis factor (TNF) and interleukin 1 (IL-1) are present in CSF within 1–2 h of intracisternal inoculation of LPS. This cytokine response is quickly followed by an increase in CSF protein concentration and leukocytosis. Chemokines (cytokines that induce chemotactic migration in leukocytes) and a variety of other proinflammatory cytokines are also produced and secreted by leukocytes and tissue cells that are stimulated by IL-1 and TNF. In addition, bacteremia and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that can induce death of brain cells.

Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF and IL-1 act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the subarachnoid space (Fig. 376-2). The subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema.

Inflammatory cytokines upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, promoting leukocyte adherence to vascular endothelial cells and subsequent migration into the CSF. The adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of plasma proteins into the CSF, which adds to the inflammatory exudate. Neutrophil degranulation results in the release of toxic metabolites that contribute to cytotoxic edema, cell injury, and death. Contrary to previous beliefs, CSF leukocytes probably do little to contribute to the clearance of CSF bacterial infection.

During the very early stages of meningitis, there is an increase in cerebral blood flow, soon followed by a decrease in cerebral blood flow and a loss of cerebrovascular autoregulation (Chap. 269). Narrowing of the large arteries at the base of the brain due to encroachment by the purulent exudate in the subarachnoid space and infiltration of the arterial wall by inflammatory cells with intimal thickening (*vasculitis*) also occur and may result in ischemia and infarction, obstruction of branches of the middle cerebral artery by thrombosis, thrombosis of the major cerebral venous sinuses, and thrombophlebitis of the cerebral cortical veins. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised ICP and coma. Cerebral herniation usually results from the effects of cerebral edema, either focal or generalized; hydrocephalus and dural sinus or cortical vein thrombosis may also play a role.

CLINICAL PRESENTATION

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity. A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma. Nausea, vomiting, and photophobia are also common complaints.

Seizures occur as part of the initial presentation of bacterial meningitis or during the course of the illness in 20–40% of patients. Focal

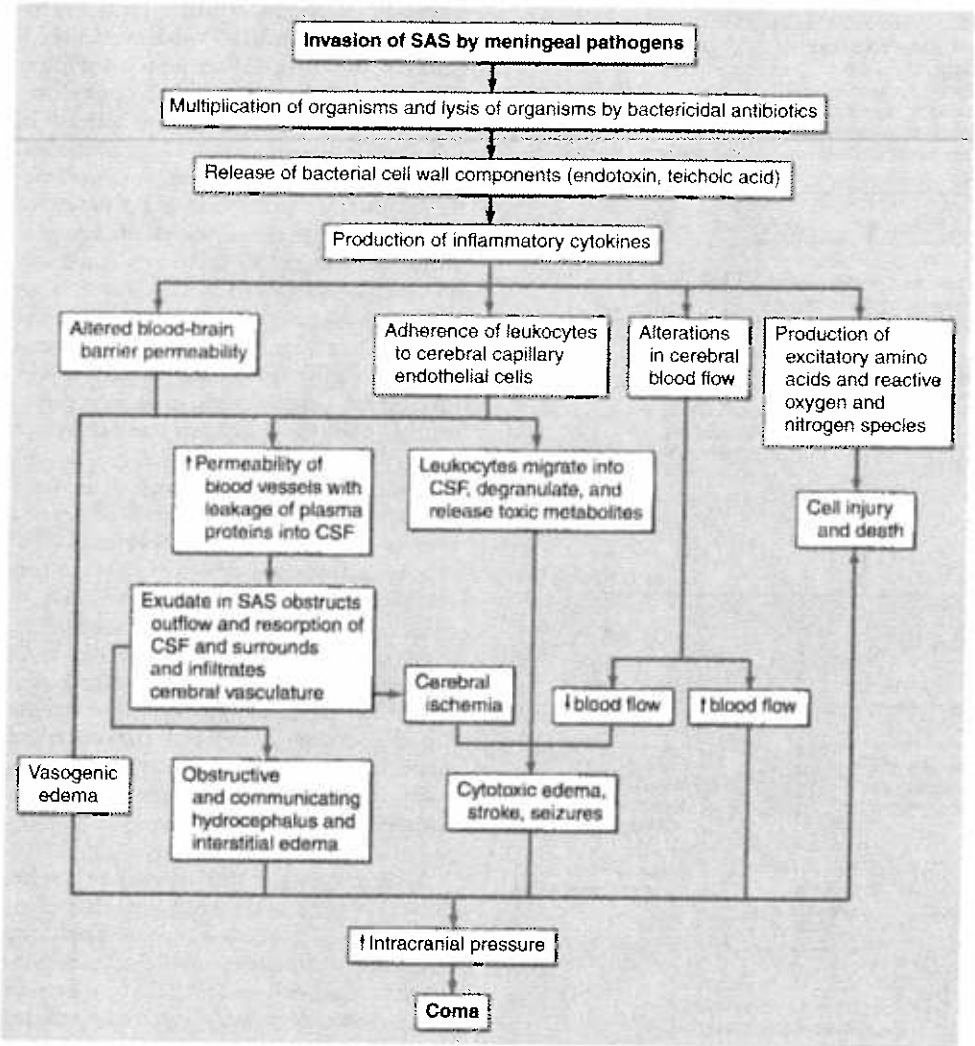

FIGURE 376-2 The pathophysiology of the neurologic complications of bacterial meningitis. SAS, subarachnoid space; CSF, cerebrospinal fluid.

seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema. Generalized seizure activity and status epilepticus may be due to hyponatremia, cerebral anoxia, or, less commonly, the toxic effects of antimicrobial agents such as high-dose penicillin.

Raised ICP is an expected complication of bacterial meningitis and the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mmH_2O, and 20% have opening pressures >400 mmH_2O. Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations). The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases.

Specific clinical features may provide clues to the diagnosis of individual organisms and are discussed in more detail in specific chapters devoted to individual pathogens. The most important of these clues is the rash of meningococcemia, which begins as a diffuse erythematous maculopapular rash resembling a viral exanthem; however, the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles.

DIAGNOSIS

When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial therapy initiated without delay (Table 376-1). The diagnosis of bacterial meningitis is made by examination of the CSF (Table 376-2). The need to obtain neuroimaging studies (CT or MRI) prior to LP requires clinical judgment. In an immunocompetent patient with no known history of recent head trauma, a normal level of consciousness, and no evidence of papilledema or focal neurologic deficits, it is considered safe to perform LP without prior neuroimaging studies. If LP is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated after blood cultures are obtained. Antibiotic therapy initiated a few hours prior to LP will not significantly alter the CSF WBC count or glucose concentration, nor is it likely to prevent visualization of organisms by Gram's stain or detection of bacterial nucleic acid by polymerase chain reaction (PCR) assay.

The classic CSF abnormalities in bacterial meningitis (Table 376-2) are (1) polymorphonuclear (PMN) leukocytosis (>100 cells/μL in 90%), (2) decreased glucose concentration [<2.2 mmol/L (<40 mg/dL) and/or CSF/serum glucose ratio of <0.4 in ~60%], (3) increased protein concentration [>0.45 g/L (>45 mg/dL) in 90%], and (4) increased opening pressure (>180 mmH_2O in 90%). CSF bacterial cultures are positive in >80% of patients, and CSF Gram's stain demonstrates organisms in >60%.

CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal, and a CSF glucose concentration of zero can be seen in bacterial meningitis. Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration. The CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6. A CSF/serum glucose ratio <0.4 is highly suggestive of bacterial meningitis but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis. It takes from 30 min to several hours for the concentration of CSF glucose to reach equilibrium with blood glucose levels; therefore, administration of 50 mL of 50% glucose (D50) prior to LP, as commonly occurs in emergency room settings, is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and LP.

A broad-range PCR can detect small numbers of viable and nonviable organisms in CSF and is expected to be useful for making a diagnosis of bacterial meningitis in patients who have been pretreated with oral or parenteral antibiotics and in whom Gram's stain and CSF culture are negative. When the broad-range PCR is positive, a PCR that uses specific bacterial primers to detect the nucleic acid of *S. pneumoniae, N. meningitidis, Escherichia coli, L. monocytogenes, H. influenzae,* and *S. agalactiae* can be obtained based on the clinical suspicion of the meningeal pathogen. The latex agglutination (LA) test for the detection of bacterial antigens of *S. pneumoniae, N. meningitidis, H. influenzae* type b, group B streptococcus, and *E. coli* K1 strains in the CSF has been useful for making a diagnosis of bacterial meningitis but is being replaced by the CSF bacterial PCR assay. The CSF LA test has a *specificity* of 95–100% for *S. pneumoniae* and *N. meningitidis*, so a positive test is virtually diagnostic of bacterial meningitis caused by these organisms. However, the *sensitivity* of the CSF LA test is only 70–100% for detection of *S. pneumoniae* and 33–70% for detection of *N. menin-*

TABLE 376-1 ANTIBIOTICS USED IN EMPIRICAL THERAPY OF BACTERIAL MENINGITIS AND FOCAL CNS INFECTIONS[a]

Indication	Antibiotic
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 mos	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 mos and adults <55	Cefotaxime or ceftriaxone + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime or ceftriaxone + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime + vancomycin

Antimicrobial Agent	Total Daily Dose and Dosing Interval	
	Child (>1 month)	Adult
Ampicillin	200 (mg/kg)/d, q4h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	200 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h[b]	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	3 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	60 (mg/kg)/d, q6h	2 g/d, q12h[b]

[a]All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function.

[b]Doses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 μg/mL; trough: <2 μg/mL; vancomycin therapeutic level: peak: 25–40 μg/mL; trough: 5–15 μg/mL.

gitidis antigens, so a negative test does not exclude infection by these organisms. The Limulus amebocyte lysate assay is a rapid diagnostic test for the detection of gram-negative endotoxin in CSF and thus for making a diagnosis of gram-negative bacterial meningitis. The test has a specificity of 85–100% and a sensitivity approaching 100%. Thus, a positive Limulus amebocyte lysate assay occurs in virtually all patients with gram-negative bacterial meningitis, but false positives may occur.

Almost all patients with bacterial meningitis will have neuroimaging studies performed during the course of their illness. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is often seen after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability.

Petechial skin lesions, if present, should be biopsied. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram's stain.

TABLE 376-2 CEREBROSPINAL FLUID (CSF) ABNORMALITIES IN BACTERIAL MENINGITIS

Opening pressure	>180 mmH_2O
White blood cells	10/μL to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
Latex agglutination	May be positive in patients with meningitis due to *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b, *E. coli*, group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis
PCR	Detects bacterial DNA

Note: PCR, polymerase chain reaction.

DIFFERENTIAL DIAGNOSIS

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis, can mimic the clinical presentation of bacterial meningitis (see "Encephalitis," below). HSV encephalitis typically presents with headache, fever, altered consciousness, focal neurologic deficits (e.g., dysphasia, hemiparesis), and focal or generalized seizures. The findings on CSF studies, neuroimaging, and electroencephalogram (EEG) distinguish HSV encephalitis from bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. MRI abnormalities (other than meningeal enhancement) are not seen in uncomplicated bacterial meningitis. By contrast, in HSV encephalitis, on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI images, high signal intensity lesions are seen in the orbitofrontal, anterior, and medial temporal lobes in the majority of patients within 48 h of symptom onset. Some patients with HSV encephalitis have a distinctive periodic pattern on EEG (see below).

Rickettsial disease can resemble bacterial meningitis (Chap. 167). Rocky Mountain spotted fever (RMSF) is transmitted by a tick bite and caused by the bacteria *Rickettsia rickettsii*. The disease may present acutely with high fever, prostration, myalgia, headache, nausea, and vomiting. Most patients develop a characteristic rash within 96 h of the onset of symptoms. The rash is initially a diffuse erythematous maculopapular rash that may be difficult to distinguish from that of meningococcemia. It progresses to a petechial rash, then to a purpuric rash and, if untreated, to skin necrosis or gangrene. The color of the lesions changes from bright red to very dark red, then yellowish-green to black. The rash typically begins in the wrist and ankles and then spreads distally and proximally within a matter of a few hours, involving the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens. Ehrlichioses are also transmitted by a tick bite. These are small gram-negative coccobacilli of which two species cause human disease. *Anaplasma phagocytophilum* causes human granulocytic ehrlichiosis (anaplasmosis), and *Ehrlichia chaffeensis* causes human monocytic ehrlichiosis. The clinical and laboratory manifestations of the infections are similar. Patients present with fever, headache, nausea, and vomiting. Twenty percent of patients have a maculopapular or petechial rash. There is laboratory evidence of leukopenia, thrombocytopenia and anemia, and mild to moderate elevations in alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase. Patients with RMSF and those with ehrlichial infections may have an altered level of consciousness ranging from mild lethargy to coma, confusion, focal neurologic signs, cranial nerve palsies, hyperreflexia, and seizures.

Focal suppurative CNS infections (see below), including subdural and epidural empyema and brain abscess, should also be considered, especially when focal neurologic findings are present. MRI should be performed promptly in all patients with suspected meningitis who have focal features, both to detect the intracranial infection and to search for associated areas of infection in the sinuses or mastoid bones.

A number of noninfectious CNS disorders can mimic bacterial meningitis. Subarachnoid hemorrhage (SAH; Chap. 269) is generally the major consideration. Other possibilities include chemical meningitis due to rupture of tumor contents into the CSF (e.g., from a cystic glioma or craniopharyngioma epidermoid or dermoid cyst); drug-induced hypersensitivity meningitis; carcinomatous or lymphomatous meningitis; meningitis associated with inflammatory disorders such as sarcoid, systemic lupus erythematosus (SLE), and Behçet's syndrome; pituitary apoplexy; and uveomeningitic syndromes (Vogt-Koyanagi-Harada syndrome).

On occasion, subacutely evolving meningitis (Chap. 377) may be considered in the differential diagnosis of acute meningitis. The principal causes include *Mycobacterium tuberculosis* (Chap. 158), *Cryptococcus neoformans* (Chap. 195), *Histoplasma capsulatum* (Chap. 192), *Coccidioides immitis* (Chap. 193), and *Treponema pallidum* (Chap. 162).

℞ ACUTE BACTERIAL MENINGITIS

EMPIRICAL ANTIMICROBIAL THERAPY (Table 376-1) Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy

within 60 min of a patient's arrival in the emergency room. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF Gram's stain and culture are known. *S. pneumoniae* (Chap. 128) and *N. meningitidis* (Chap. 136) are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant *S. pneumoniae*, empirical therapy of community-acquired suspected bacterial meningitis in children and adults should include a combination of dexamethasone, a third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) and vancomycin, plus acyclovir, as HSV encephalitis is the leading disease in the differential diagnosis, and doxycycline during tick season to treat tick-borne bacterial infections. Ceftriaxone or cefotaxime provide good coverage for susceptible *S. pneumoniae*, group B streptococci, and *H. influenzae* and adequate coverage for *N. meningitidis*. Cefepime is a broad-spectrum fourth-generation cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against *S. pneumoniae* and *N. meningitidis* and greater activity against *Enterobacter* species and *Pseudomonas aeruginosa*. In clinical trials, cefepime has been demonstrated to be equivalent to cefotaxime in the treatment of penicillin-sensitive pneumococcal and meningococcal meningitis, and it has been used successfully in some patients with meningitis due to *Enterobacter* species and *P. aeruginosa*. Ampicillin should be added to the empirical regimen for coverage of *L. monocytogenes* in individuals <3 months of age, those >55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy. In hospital-acquired meningitis, and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms including *P. aeruginosa* are the most common etiologic organisms. In these patients, empirical therapy should include a combination of vancomycin and ceftazidime, cefepime, or meropenem. Ceftazidime, cefepime, or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients, as ceftriaxone and cefotaxime do not provide adequate activity against CNS infection with *P. aeruginosa*. Meropenem is a carbapenem antibiotic that is highly active in vitro against *L. monocytogenes*, has been demonstrated to be effective in cases of meningitis caused by *P. aeruginosa*, and shows good activity against penicillin-resistant pneumococci. In experimental pneumococcal meningitis, meropenem was comparable to ceftriaxone and inferior to vancomycin in sterilizing CSF cultures. The number of patients with bacterial meningitis enrolled in clinical trials of meropenem has not been sufficient to definitively assess the efficacy of this antibiotic.

SPECIFIC ANTIMICROBIAL THERAPY **Meningococcal Meningitis** **(Table 376-3)** Although ceftriaxone and cefotaxime provide adequate empirical coverage for *N. meningitidis*, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of *N. meningitidis* with moderate resistance to penicillin have been identified, but patients infected with these strains have still been successfully treated with penicillin. CSF isolates of *N. meningitidis* should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of ciprofloxacin (750 mg), one dose of azithromycin (500 mg), or one intramuscular dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes.

TABLE 376-3 ANTIMICROBIAL THERAPY OF CNS BACTERIAL INFECTIONS BASED ON PATHOGEN[a]

Organism	Antibiotic
Neisseria meningitides	
Penicillin-sensitive	Penicillin G or ampicillin
Penicillin-resistant	Ceftriaxone or cefotaxime
Streptococcus pneumoniae	
Penicillin-sensitive	Penicillin G
Penicillin-intermediate	Ceftriaxone or cefotaxime
Penicillin-resistant	(Ceftriaxone or cefotaxime) + vancomycin
Gram-negative bacilli (except *Pseudomonas* spp.)	Ceftriaxone or cefotaxime
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococci spp.	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or cefotaxime
Streptococcus agalactiae	Penicillin G or ampicillin
Bacteroides fragilis	Metronidazole
Fusobacterium spp.	Metronidazole

[a]Doses are as indicated in Table 376-1.

Pneumococcal Meningitis Antimicrobial therapy of pneumococcal meningitis is initiated with a cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin. All CSF isolates of *S. pneumoniae* should be tested for sensitivity to penicillin and the cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 376-3). For *S. pneumoniae* meningitis, an isolate of *S. pneumoniae* is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) <0.06 μg/mL, to have intermediate resistance when the MIC is 0.1–1.0 μg/mL, and to be highly resistant when the MIC >1.0 μg/mL. Isolates of *S. pneumoniae* that have cephalosporin MICs ≤0.5 μg/mL are considered sensitive to the cephalosporins (cefotaxime, ceftriaxone, cefepime). Those with MICs of 1 μg/mL are considered to have intermediate resistance, and those with MICs ≥2 μg/mL are considered resistant. For meningitis due to pneumococci with cefotaxime or ceftriaxone MICs ≤0.5 μg/mL, treatment with cefotaxime or ceftriaxone is usually adequate. If the MIC >1 μg/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone. A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis.

Patients with *S. pneumoniae* meningitis should have a repeat LP performed 24–36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24–36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of *S. pneumoniae* who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration.

***Listeria* Meningitis** Meningitis due to *L. monocytogenes* is treated with ampicillin for at least 3 weeks (Table 376-3). Gentamicin is often added (2 mg/kg loading dose, then 7.5 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim [10–20 (mg/kg)/d] and sulfamethoxazole [50–100 (mg/kg)/d] given every 6 h may provide an alternative in penicillin-allergic patients.

Staphylococcal Meningitis Meningitis due to susceptible strains of *S. aureus* or coagulase-negative staphylococci is treated with nafcillin (Table 376-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intraventricular or intrathecal vancomycin, 20 mg once daily, can be added.

Gram-Negative Bacillary Meningitis The third-generation cephalosporins—cefotaxime, ceftriaxone, and ceftazidime—are equally efficacious for the treatment of gram-negative bacillary meningitis, with the exception of meningitis due to *P. aeruginosa*, which should be treated with ceftazidime, cefepime, or meropenem (Table 376-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli.

ADJUNCTIVE THERAPY The release of bacterial cell-wall components by bactericidal antibiotics leads to the production of the inflammatory cytokines IL-1 and TNF in the subarachnoid space. Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1 and TNF at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the

blood-brain barrier. The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF production once it has been induced. The results of clinical trials of dexamethasone therapy in children, predominantly with meningitis due to *H. influenzae* and *S. pneumoniae*, have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae such as the incidence of sensorineural hearing loss.

A prospective European trial of adjunctive therapy for acute bacterial meningitis in 301 adults found that dexamethasone reduced the number of unfavorable outcomes (15% vs. 25%, $p = .03$) including death (7% vs. 15%, $p = .04$). The benefits were most striking in patients with pneumococcal meningitis. Dexamethasone (10 mg intravenously) was administered 15–20 min before the first dose of an antimicrobial agent, and the same dose was repeated every 6 h for 4 days. These results were confirmed in a second trial of dexamethasone in adults with pneumococcal meningitis. Therapy with dexamethasone should ideally be started 20 min before, or not later than concurrent with, the first dose of antibiotics. It is unlikely to be of significant benefit if started >6 h after antimicrobial therapy has been initiated. Dexamethasone may decrease the penetration of vancomycin into CSF, and it delays the sterilization of CSF in experimental models of *S. pneumoniae* meningitis. As a result, its potential benefit should be carefully weighed when vancomycin is the antibiotic of choice. Alternatively, vancomycin can be administered by the intraventricular route.

INCREASED INTRACRANIAL PRESSURE Emergency treatment of increased ICP includes elevation of the patient's head to 30–45°, intubation and hyperventilation (Pa_{CO_2} 25–30 mmHg), and mannitol. Patients with increased ICP should be managed in an intensive care unit; accurate ICP measurements are best obtained with an ICP monitoring device. **Treatment of increased intracranial pressure is discussed in detail in Chap. 269.**

PROGNOSIS

Mortality is 3–7% for meningitis caused by *H. influenzae*, *N. meningitidis*, or group B streptococci; 15% for that due to *L. monocytogenes*; and 20% for *S. pneumoniae*. In general, the risk of death from bacterial meningitis increases with (1) decreased level of consciousness on admission, (2) onset of seizures within 24 h of admission, (3) signs of increased ICP, (4) young age (infancy) and age >50, (5) the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and (6) delay in the initiation of treatment. Decreased CSF glucose concentration [<2.2 mmol/L (<40 mg/dL)] and markedly increased CSF protein concentration [>3 g/L (>300 mg/dL)] have been predictive of increased mortality and poorer outcomes in some series. Moderate or severe sequelae occur in ~25% of survivors, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

ACUTE VIRAL MENINGITIS

CLINICAL MANIFESTATIONS

Patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with an inflammatory CSF profile (see below). The headache of viral meningitis is usually frontal or retroorbital and is often associated with photophobia and pain on moving the eyes. Nuchal rigidity is present in most cases but may be mild and present only near the limit of neck anteflexion. Constitutional signs can include malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Patients often have mild lethargy or drowsiness; however, profound alterations in consciousness, such as stupor, coma, or marked confusion, are unusual in viral meningitis and suggest the presence of encephalitis or other alternative diagnoses. Similarly, seizures or focal neurologic signs or symptoms or neuroimaging abnormalities indicative of brain parenchymal involvement are not typical of viral meningitis and suggest the presence of encephalitis or another CNS infectious or inflammatory process.

TABLE 376-4 VIRUSES CAUSING ACUTE MENINGITIS AND ENCEPHALITIS IN NORTH AMERICA

Acute Meningitis

Common	Less Common
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71)	Varicella zoster virus
Herpes simplex virus 2	Epstein-Barr virus
Arthropod-borne viruses	Lymphocytic choriomeningitis virus
HIV	

Acute Encephalitis

Common	Less Common
Herpesviruses	Rabies
Herpes simplex virus 1	Eastern equine encephalitis virus
Varicella zoster virus	Western equine encephalitis virus
Epstein-Barr virus	Powassan virus
Arthropod-borne viruses	Cytomegalovirus[a]
La Crosse virus	Enteroviruses[a]
West Nile virus	Colorado tick fever
St. Louis encephalitis virus	Mumps

[a]Immunocompromised host.

ETIOLOGY

Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 75–90% of cases of viral meningitis. The most important agents are enteroviruses, HSV type 2 (HSV-2), and arboviruses (Table 376-4). CSF cultures are positive in 30–70% of patients, the frequency of isolation depending on the specific viral agent. Approximately two-thirds of culture-negative cases of aseptic meningitis have a specific viral etiology identified by CSF PCR testing (see below).

EPIDEMIOLOGY

Viral meningitis is not a nationally reportable disease; however, it has been estimated that the incidence is ~75,000 cases per year. In temperate climates, there is a substantial increase in cases during the summer and early fall months, reflecting the seasonal predominance of enterovirus and arthropod-borne virus (arbovirus) infections, with a peak monthly incidence of about 1 reported case per 100,000 population.

LABORATORY DIAGNOSIS

CSF Examination The most important laboratory test in the diagnosis of viral meningitis is examination of the CSF. The typical profile is a lymphocytic pleocytosis (25–500 cells/μL), a normal or slightly elevated protein concentration [0.2–0.8 g/L (20–80 mg/dL)], a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH_2O). Organisms are *not* seen on Gram's or acid-fast stained smears or India ink preparations of CSF. Rarely, PMNs may predominate in the first 48 h of illness, especially with infections due to echovirus 9, eastern equine encephalitis (EEE) virus, or mumps. A pleocytosis of polymorphonuclear neutrophils also occurs in 45% of patients with West Nile virus (WNV) meningitis and can persist for a week or longer before shifting to a lymphocytic pleocytosis. Despite these exceptions, the presence of a CSF PMN pleocytosis in a patient with suspected viral meningitis should always prompt consideration of alternative diagnoses, including bacterial meningitis or parameningeal infections. The total CSF cell count in viral meningitis is typically 25–500/μL, although cell counts of several thousand/μL are occasionally seen, especially with infections due to lymphocytic choriomeningitis virus (LCMV) and mumps virus. The CSF glucose concentration is typically normal in viral infections, although it may be decreased in 10–30% of cases due to mumps or LCMV. Rare instances of decreased CSF glucose concentration occur in cases of meningitis due to echoviruses and other enteroviruses, HSV-2, and varicella-zoster virus (VZV). As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal or tuberculous meningitis, *Listeria* meningoencephalitis, or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

A number of tests measuring levels of various CSF proteins, enzymes, and mediators—including C-reactive protein, lactic acid, lactate dehydrogenase, neopterin, quinolinate, IL-1β, IL-6, soluble IL-2 receptor, β_2-microglobulin, and TNF—have been proposed as potential discriminators between viral and bacterial meningitis or as markers of specific types of viral infection (e.g., infection with HIV), but they remain of uncertain sensitivity and specificity and are not widely used for diagnostic purposes.

Polymerase Chain Reaction Amplification of Viral Nucleic Acid Amplification of viral-specific DNA or RNA from CSF using PCR amplification has become the single most important method for diagnosing CNS viral infections. In both enteroviral and HSV infections of the CNS, PCR has become the diagnostic procedure of choice and is substantially more sensitive than viral cultures. HSV PCR is also an important diagnostic test in patients with recurrent episodes of "aseptic" meningitis, many of whom have amplifiable HSV DNA in CSF despite negative viral cultures. CSF PCR is also used routinely to diagnose CNS viral infections caused by cytomegalovirus (CMV), Epstein-Barr virus (EBV), VZV, and human herpesvirus 6 (HHV-6). CSF PCR tests are available for WNV but are not as sensitive as CSF IgM. PCR is also useful in the diagnosis of CNS infection caused by *Mycoplasma pneumoniae,* which can mimic viral meningitis and encephalitis.

Viral Culture The sensitivity of CSF cultures for the diagnosis of viral meningitis and encephalitis, in contrast to its utility in bacterial infections, is generally poor. In addition to CSF, specific viruses may also be isolated from throat swabs, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and LCMV in blood; mumps and CMV in urine; and enteroviruses, mumps, and adenoviruses in throat washings. During enteroviral infections, viral shedding in stool may persist for several weeks. The presence of enterovirus in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection; it also occurs in some asymptomatic individuals during enteroviral epidemics.

Serologic Studies For some viruses, including many arboviruses such as WNV, serologic studies remain a crucial diagnostic tool. Serum antibody determination is less useful for viruses with high seroprevalence rates in the general population such as HSV, VZV, CMV, and EBV. For viruses with low seroprevalence rates, diagnosis of acute viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (typically obtained after 2–4 weeks) or by demonstrating the presence of virus-specific IgM antibodies. Documentation of synthesis of virus-specific antibodies in CSF, as shown by an increased IgG index or the presence of CSF IgM antibodies, is more useful than serum serology alone and can provide presumptive evidence of CNS infection. Although serum and CSF IgM antibodies generally persist for only a few months after acute infection, there are exceptions to this rule. For example, WNV IgM has been shown to persist in some patients for >1 year following acute infection. Unfortunately, the delay between onset of infection and the host's generation of a virus-specific antibody response often means that serologic data are useful mainly for the retrospective establishment of a specific diagnosis, rather than in aiding acute diagnosis or management.

CSF oligoclonal gamma globulin bands occur in association with a number of viral infections. The associated antibodies are often directed against viral proteins. Oligoclonal bands occur commonly in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., neurosyphilis, Lyme neuroborreliosis).

Other Laboratory Studies All patients with suspected viral meningitis should have a complete blood count and differential, liver and renal function tests, erythrocyte sedimentation rate (ESR) and C-reactive protein, electrolytes, glucose, creatine kinase, aldolase, amylase, and lipase. Neuroimaging studies (MRI, CT) are not necessary in patients with uncomplicated viral meningitis but should be performed in patients with altered consciousness, seizures, focal neurologic signs or symptoms, or atypical CSF profiles.

DIFFERENTIAL DIAGNOSIS

The most important issue in the differential diagnosis of viral meningitis is to consider diseases that can mimic viral meningitis, including (1) untreated or partially treated bacterial meningitis; (2) early stages of meningitis caused by fungi, mycobacteria, or *Treponema pallidum* (neurosyphilis), in which a lymphocytic pleocytosis is common, cultures may be slow growing or negative, and hypoglycorrhachia may not be present early; (3) meningitis caused by agents such as *Mycoplasma, Listeria* spp., *Brucella* spp., *Coxiella* spp., *Leptospira* spp., and *Rickettsia* spp.; (4) parameningeal infections; (5) neoplastic meningitis; and (6) meningitis secondary to noninfectious inflammatory diseases, including hypersensitivity meningitis, SLE and other rheumatologic diseases, sarcoidosis, Behçet's syndrome, and the uveomeningitic syndromes.

SPECIFIC VIRAL ETIOLOGIES

Enteroviruses (Chap. 184) are the most common cause of viral meningitis, accounting for >75% of cases in which a specific etiology can be identified. CSF reverse transcriptase PCR (RT-PCR) is the diagnostic procedure of choice and is both sensitive (>95%) and specific (>100%). Enteroviruses are the most likely cause of viral meningitis in the summer months, especially in children (<15 years), although cases occur at reduced frequency year round. Although the incidence of enteroviral meningitis declines with increasing age, some outbreaks have preferentially affected older children and adults. Meningitis outside the neonatal period is usually benign. Patients present with sudden onset of fever; headache; nuchal rigidity; and often constitutional signs, including vomiting, anorexia, diarrhea, cough, pharyngitis, and myalgias. The physical examination should include a careful search for stigmata of enterovirus infection, including exanthemata, hand-foot-mouth disease, herpangina, pleurodynia, myopericarditis, and hemorrhagic conjunctivitis. The CSF profile is typically a lymphocytic pleocytosis (100–1000 cells/μL) with normal glucose and normal or mildly elevated protein concentration. In rare cases, PMNs may predominate during the first 48 h of illness. Treatment is supportive, and patients usually recover without sequelae. Chronic and severe infections can occur in neonates and in individuals with hypo- or agammaglobulinemia.

Arbovirus infections (Chap. 189) occur predominantly in the summer and early fall. Arboviral meningitis should be considered when clusters of meningitis and encephalitis cases occur in a restricted geographic region during the summer or early fall. In WNV epidemics, avian deaths may serve as sentinel infections for subsequent human disease. A history of tick exposure or travel or residence in the appropriate geographic area should suggest the possibility of Colorado tick fever virus or Powassan virus infection, although nonviral tick-borne diseases, including RMSF and Lyme neuroborreliosis, may present similarly. Arbovirus meningoencephalitis is typically associated with a CSF lymphocytic pleocytosis, normal glucose concentration, and normal or mildly elevated protein concentration. However, 40–45% of patients with WNV meningoencephalitis have CSF neutrophilia, which can persist for a week or more. The rarity of hypoglycorrhachia in WNV infection as well as the absence of positive Gram's stains and the negative cultures helps distinguish these patients from those with bacterial meningitis. The presence of increased numbers of plasmacytoid cells or Mollaret-like large mononuclear cells in the CSF may be a clue to the diagnosis of WNV infection. Definitive diagnosis of arboviral meningoencephalitis is based on demonstration of viral-specific IgM in CSF or seroconversion. CSF PCR tests are available for some viruses in selected diagnostic laboratories and at the Centers for Disease Control and Prevention (CDC), but in the case of WNV, sensitivity (~70%) of CSF PCR is less than that of CSF serology.

HSV-2 meningitis (Chap. 172) occurs in ~25% of women and 11% of men at the time of an initial (primary) episode of genital herpes. Of these patients, 20% go on to have recurrent attacks of meningitis. HSV-2 has been increasingly recognized as a major cause of viral meningitis in adults, and overall it is probably second in importance to enteroviruses