16th Edition

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PRINCIPLES OF
Internal
Medicine

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Sixteenth Edition

FURTHER READING

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359 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 are typically disseminated in time and location. MS affects ~350,000 Americans and 1.1 million individuals worldwide. In western societies, MS is second only to trauma as a cause of neurologic disability in early to middle adulthood. Manifestations of MS vary from a benign illness to a rapidly evolving and incapacitating disease requiring profound life-style adjustments.

PATHOGENESIS ■ Anatomy These lesions (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 more than half of cases, myelin-specific autoantibodies promote demyelination and stimulate macrophages and microglial cells (bone marrow–derived CNS phagocytes) that scavenge the myelin debris. As lesions evolve, astrocytes proliferate (gliosis). Surviving oligodendrocytes or those that differentiate from precursor cells may partially remyelinate the surviving naked axons, producing so-called shadow plaques. 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 deposition of antibody 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 sparing of axons is typical of MS, partial or total axonal destruction can also occur. Indirect evidence suggests that axonal loss is a major cause of irreversible neurologic disability in MS.

Physiology Nerve conduction in myelinated axons occurs in a saltatory manner, with the nerve impulse jumping from one node of Ranvier to the next without depolarization of the axonal membrane underlying the myelin sheath between nodes (Fig. 359-1). 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 the sodium channels (originally concentrated at the nodes) have had a chance to redistribute themselves along the naked axon (Fig. 359-1). This redistribution ultimately allows the continuous propagation of nerve action potentials through the demyelinated segment but, before this happens, the leakage currents are too large for the nerve impulse to jump the internode distance and conduction fails. 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 (typical of MS) that
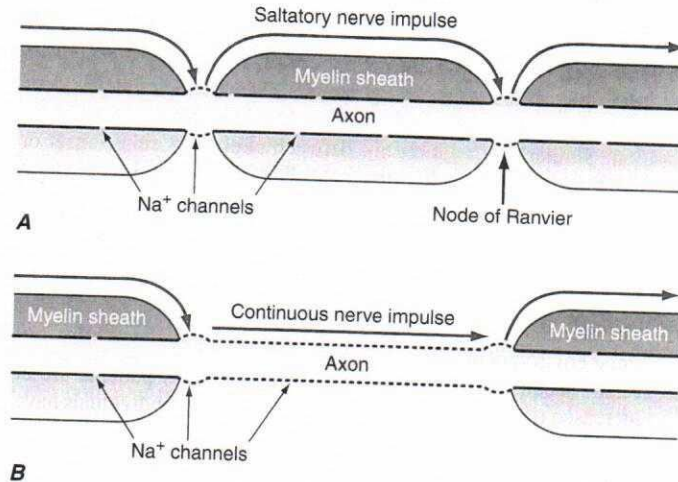
FIGURE 359-1 Nerve conduction in myelinated and demyelinated axons. *A.* Saltatory nerve conduction in myelinated axons occurs with the nerve impulse jumping from one node of Ranvier to the next. Sodium channels are concentrated at the nodes where axonal depolarization occurs. *B.* Following demyelination, the sodium channels are redistributed along the axon, thereby supporting continuous propogation of the nerve action potential in this region.

vary from hour to hour or in association with fever or exercise. Conduction slowing occurs when the demyelinated segments support only (slow) continuous nerve impulse propagation.

Epidemiology MS is approximately twice as common in women as in men. The age of onset is typically between 20 and 40 years (slightly later in men than in women). Rarely, it can begin as early as 2 years of age or as late as the eighth decade.

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 (2 per 100,000), in other parts of Asia, in equatorial Africa, and in the Middle East. In general, prevalence increases with increasing distance from the equator, although certain exceptions are notable. Thus, the incidence of MS in the Eskimo population of Alaska is rare compared to the incidence in Caucasians living at similar latitudes. Similarly, native South Africans have a markedly lower prevalence compared to South Africans of European descent who live in the same geographic area. However, distinctive migration patterns of certain populations may artifactually suggest a relationship between MS and climate. Thus, when Scandanavians migrated to the United States or when the Scots migrated to New Zealand, they tended to migrate preferentially to places (e.g., the northern United States or southern New Zealand) with similar climates to their native lands. Such considerations point to potential genetic mechanisms (see below) rather than to an influence of temperate climate per se.

CHANGES IN INCIDENCE/PREVALENCE Studies from the United States, Europe, Australia, and the Middle East suggest that the prevalence of MS may be increasing, although improved methods of diagnosis may account for the apparent change. Other reports suggest that individuals who move from an area of high prevalence to one of low prevalence (or vice versa) before the age of 15 years adopt the risk of MS in their

new environment, whereas if they move after this age, they retain the risk of their native land. The reliability of these observations is uncertain, although, if correct, they would suggest an environmental factor in the pathogenesis of MS.

REPORTED CLUSTERS   Clusters of MS cases are occasionally reported. Often these apparent epidemics cannot be distinguished easily from chance occurrences, although some reports (e.g., the clustering of MS cases in the Faeroe Islands after British occupation during World War II) are more convincing than others. Such clustering, however, seems to be rare.

The Relationship of MS to Trauma and Stress   The existing evidence does not support any association of trauma with either MS onset or exacerbation. Similarly, a relationship between stress and either onset or exacerbation of MS has not been established, although this area is not easily studied because of difficulties in quantifying stress.

GENETIC CONSIDERATIONS   A genetic susceptibility to MS exists, as evidenced by the following observations:

1. The prevalence of MS differs among ethnic groups residing in the same environment.
2. First-, second-, and third-degree relatives of MS patients are at increased risk for the disease. Siblings of affected individuals have a lifetime risk of 2 to 5%, whereas the risk to parents or children of affected individuals is somewhat lower.
3. Twin studies demonstrate concordance rates of 25 to 30% in monozygotic twins compared to only 2 to 5% in dizygotic twins (similar to the risk in nontwin siblings).

The inheritance of MS cannot be explained by a simple genetic model. Susceptibility is probably polygenic, with each gene contributing a relatively small amount to the overall risk. It is also likely that genetic heterogeneity (different susceptibilities among individuals) also exists. The major histocompatibility complex (MHC) on chromosome 6p21 (encoding proteins involved in presenting peptide antigens to T cells) is the most important MS susceptibility region identified to date. MS susceptibility is associated with the class II region of the MHC, specifically with the DR2 (DRB1*1501) allele and its corresponding haplotype. Other genetic regions implicated in MS susceptibility are located on chromosomal regions 19q35 and 17q13.

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 are often found in the blood or cerebrospinal fluid (CSF) of MS patients and, occasionally also, in MS lesions. Moreover, DR2 may influence the autoimmune response because it binds with high affinity to a fragment of MBP (spanning amino acids 89 to 96), stimulating T cell responses to this self-protein.

AUTOANTIBODIES   Autoantibodies, directed against myelin antigens such as myelin oligodendrocyte glycoprotein (MOG), probably act in concert with a pathogenic T cell response to cause the demyelinating lesions in many patients. Recent evidence suggests that the presence of anti MOG antibodies in the serum of patients with a clinically isolated syndrome (CIS) is highly predictive of the development of MS in the future. Also, evidence of an abnormal humoral immune response is present in the CSF of MS patients. Membrane attack complexes (from complement-mediated antibody damage) can be detected in CSF, and elevated CSF immunoglobulin (synthesized locally) is characteristic of MS. Oligoclonal antibody (derived from expansion of a selected group of plasma cells) is present in most cases. Oligoclonal immunoglobulin is also detected in other chronic inflammatory conditions,

including infections, and thus is not specific to MS. The pattern of banding is unique to each individual, and attempts to identify the targets of these antibodies have been unsuccessful.

CYTOKINES (Chap. 295)   The proinflammatory T_H1 cytokines such as interleukin (IL) 2, tumor necrosis factor (TNF) α, and interferon (IFN) γ are thought to be central to MS pathogenesis and some (e.g., TNF α and IFN-γ) may directly injure oligodendrocytes or the myelin membranes. Nevertheless, the notion of an isolated T_H1 imbalance causing MS is probably simplistic. The presence of autoantibodies in MS suggests that regulatory T_H2 cytokines (including IL-4, -5, and -10) may also play a pathogenic role. Moreover, T_H1-based therapies have often proved to be unhelpful or, in the case of certain TNF-α inhibitors, harmful to patients.

TRIGGERS   Magnetic resonance imaging (MRI) has demonstrated bursts of disease activity 7 to 10 times more frequently than is clinically apparent. This finding indicates that there is a large reservoir of subclinical disease activity in MS, especially during the early stages of the disease. 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. 299)

Microbiology   As noted above, epidemiologic evidence supports the role of an environmental exposure in MS. 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. The best studied experimental model of virus-induced demyelinating disease is infection with Theiler virus, a murine coronavirus similar to measles, which produces a chronic oligodendrocyte infection with multifocal perivascular lymphocytic infiltration and demyelination, closely resembling lesions of MS.

High antibody titers against many viruses have been reported in serum and CSF of MS patients, including measles, herpes simplex, varicella, rubella, Epstein-Barr, and influenza C and some parainfluenza strains. Numerous viruses and bacteria (or their genomic sequences) have been recovered from MS tissues and fluids. Most recently human herpes virus type 6 (HHV-6) and *Chlamydia pneumoniae* have been implicated, although a causal role for any infectious agent in MS remains unproven.

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 other cases an MRI scan obtained for an unrelated reason may show evidence of asymptomatic MS. Symptoms of MS are extremely varied and depend upon the location of lesions within the CNS (Table 359-1). Examination generally reveals evidence of neurologic dysfunction, often in asymptomatic locations. For example, a patient may present with symptoms in one leg and signs in both.

TABLE 359-1   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.

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. 20) and is frequently 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. 21) 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. It is often accompanied by painful spasms and can interfere with a patient's ability to ambulate or work or with self-care. Occasionally, spasticity may provide nonvolitional support for the body weight during ambulation. In these cases, treatment of spasticity may actually do more harm than good.

Optic neuritis (ON) generally 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 occur bilaterally. Periorbital pain (aggravated by eye movement) often precedes or accompanies the visual loss. An afferent pupillary defect (Chap. 25) may be found. 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. →*ON is discussed in detail in Chap. 25.*

Visual blurring in MS may result from ON or diplopia. Visual blurring that resolves when either eye is covered is due to 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. 25). 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) suggests 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. 21). Ataxia may also involve the head and trunk or the voice, producing a characteristic cerebellar dysarthria (scanning speech). The true extent of cerebellar involvement may be difficult to determine in an individual patient, because motor and sensory deficits can affect coordination and weakness may interfere with coordination testing.

Bladder and bowel dysfunction arise from different causes and frequently different types of dysfunction coexist. 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). Stoppage of the urinary stream is accomplished with a coordinated sphincter contraction and detrusor relaxation. Bladder-stretch (during filling) activates this reflex, which is inhibited by supraspinal (voluntary) input. Symptoms of bladder dysfunction are present in >90% of MS patients and, in a third, dysfunction results in weekly or more frequent episodes of incontinence.

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, thereby producing hesitancy. It can also lead to urinary retention, large postvoid residual volumes, 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 also occurs but is rare.

Depression, experienced by 50 to 60% 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 and is moderate or severe in half. Symptoms include generalized motor weakness, limited ability to concentrate, extreme lassitude, loss of energy, decreased endurance, and an overwhelming sense of exhaustion that requires the patient to rest or fall asleep. Fatigue (either alone or with other symptoms) 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). MS-related fatigue may be maximum during mid-afternoon or continuous throughout the day, and it is often difficult to treat.

Sexual dysfunction is common in MS. Men report impotence, less desire, impaired genital sensation, impaired ejaculation, and inability to achieve/maintain an erection. Women report genital numbness, diminished orgasmic response, decreased libido, unpleasant sensations during intercourse, and diminished vaginal lubrication. Adductor spasticity (in women) can also interfere with intercourse, and urinary incontinence (in either men or women) can be problematic.

Facial weakness due to a lesion in the intraparenchymal pathway of the seventh cranial nerve may resemble idiopathic Bell's palsy. However, unlike Bell's palsy, facial weakness in MS is generally not associated with ipsilateral loss of taste sensation or retroauricular pain (Chap. 355).

Vertigo may appear suddenly and resemble acute labyrinthitis. A brainstem rather than end-organ origin is suggested by the presence of coexisting trigeminal or facial nerve involvement; vertical nystagmus; or nystagmus that has no latency to onset, no direction reversal, and doesn't fatigue (Chap. 20). 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, transient unilateral visual blurring or loss may occur during a hot shower or with physical exercise (*Uhthoff's symptom*). It is common for MS symptoms to worsen transiently, sometimes dramatically, during febrile illnesses (see pseudoexacerbation, below). Such heat-related symptoms probably result from transient conduction block (see above).

Lhermitte's symptom is the electric shock–like sensation (evoked by neck flexion or other movement) 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 spine (e.g., cervical spondylosis).

Paroxysmal symptoms are distinguished by their brief duration (30 s to 2 min), high frequency (5 to 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 include Lhermitte's symptom; tonic con-

tractions of a limb, face, or trunk (tonic seizures); paroxysmal dysarthria/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 ephaptically to adjacent white matter tracts.

Trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia can occur when the demyelinating lesion involves the root entry (or exit) zone of the fifth, seventh, and ninth cranial nerve, respectively. *Trigeminal neuralgia* (tic douloureux) is a very brief lancinating facial pain often triggered by an afferent input from the face or teeth. Most cases of trigeminal neuralgia are not MS-related. However, the occurrence of atypical features (Chap. 355) such as the onset before age 50 years, bilateral symptoms, objective sensory loss, or nonparoxysmal pain should raise concerns that a symptomatic cause such as MS is 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. 359-2):

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). Often, but not invariably, there is complete recovery over the ensuing weeks to months (Fig. 359-2A). 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. 359-2B). At some point, however, the RRMS 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. Approximately 50% of patients with RRMS will have developed SPMS after 15 years, and longer follow-up points indicate that the great majority of RRMS ultimately evolves into SPMS. Thus, 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. 359-2C). Compared to RRMS, the
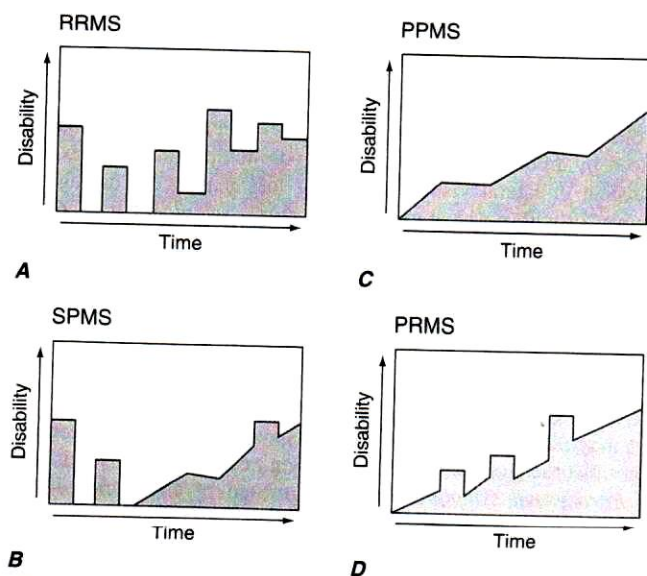
sex distribution is more even, the disease begins later in life (mean age, ~40 years), and disability develops faster. Whether PPMS is an unusual phenotype of the same underlying illness as RRMS or whether these are distinct illnesses is unknown.

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. 359-2D). The early stages of RPMS are indistinguishable from those of PPMS (i.e., until the first clinical attack).

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 359-2). 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 certain abnormal paraclinical tests such as MRI or evoked potentials (EPs). In patients who experience gradual progression of disability for ≥6 months without superimposed relapses, documentation of intrathecal IgG and visual EP testing may be used to support the diagnosis.

DIAGNOSTIC TESTS ■ Magnetic Resonance Imaging

MRI has revolutionized the diagnosis and management of MS (Fig. 359-3); 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 up to 3 months, 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

FIGURE 359-2   Clinical course of multiple sclerosis (MS). *A.* Relapsing/remitting MS. *B.* Secondary progressive MS. *C.* Primary progressive MS. *D.* Progressive/relapsing MS.

TABLE 359-2   *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.

ventricular surface, corresponding to the pathologic pattern of perivenous demyelination (Dawson's fingers). Lesions are multifocal within the brain, brainstem, and spinal cord. Lesions in the anterior corpus callosum are helpful diagnostically because this site is usually spared in cerebrovascular disease. Different criteria for the use of MRI in the diagnosis of MS have been proposed (Table 359-2).

The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical disability. Approximately one-third of T2-weighted lesions appear as hypointense lesions (black holes) on T1-weighted imaging. Black holes may be a better marker of irreversible demyelination and axonal loss than T2 hyperintensities, although even this measure depends upon the timing of the image acquisition (e.g., most acute Gd-enhancing T2 lesions are T1 dark).

Newer MRI measures such as brain atrophy, 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 (NAA), 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 359-2). Abnormalities on one or more EP modalities occur in 80 to 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) 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. A more complicated formula, the IgG synthesis rate, makes certain assumptions but uses the same 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
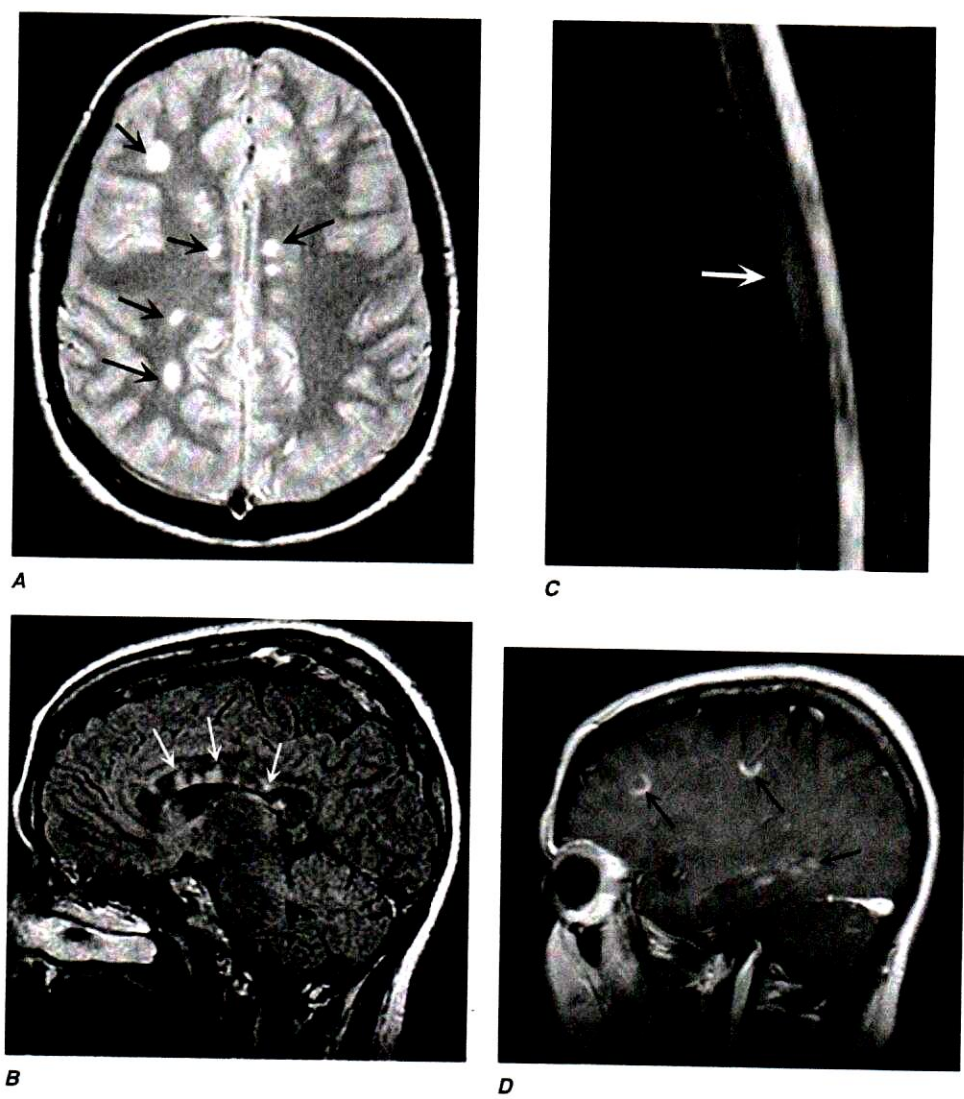
FIGURE 359-3   MRI findings in MS. *A.* Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. *B.* Sagittal T2-weighted FLAIR (fluid attenuated inversion recovery) image in which the high signal of CSF has been suppressed. 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*).

found in 75 to 90% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients the number of bands present 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 359-3), 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

TABLE 359-3 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 immunodifficiency 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 leukemia/lymphoma virus; AV, arteriovenous; CNS, central nervous system.

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 (stroke-like) onset or with mild symptoms and a normal neurologic examination. Rarely, intense inflammation and swelling may produce a mass lesion that mimics a primary or metastatic tumor. 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 VDRL should probably be obtained in all patients with suspected MS.

PROGNOSIS Most patients with MS experience progressive neurologic disability. Fifteen years after onset, only 20% of patients have no functional limitation; 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. Patients with ON or sensory symptoms at onset, patients who recover completely from early attacks, patients <40 years at onset (but not beginning in childhood), women, patients with RRMS, patients with fewer than two relapses in the first year of illness, and patients with minimal impairment after 5 years do better than patients without these clinical features. By contrast, patients with truncal ataxia, action tremor, pyramidal symptoms, or a progressive disease course are more likely to become disabled. A purely progressive disease course carries a graver outlook at all disease stages than does a disease course accompanied by occasional relapses.

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%, although it may be underestimated by existing natural history studies. One recent study of patients with benign MS 15 years after onset reported that, although most patients had developed disability by 25 years, those patients with entirely normal neurologic examinations maintained 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 to 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 episode. Typical abnormalities on EP testing and CSF examination provide similar prognostic information, although these relationships are not as well characterized.

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 post-partum. When considering the pregnancy year as a whole (i.e., 9 months pregnancy plus 3 months post-partum), the overall disease course is unaffected. Decisions about childbearing should thus be made based upon (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 quite low.

Rx **TREATMENT**

Current 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 measure of neurologic impairment in MS (Table 359-4). The EDSS provides a useful snapshot of the disease status of a patient at a given time and a composite picture of the disease course over time. Most patients with EDSS scores <3.5 have RRMS, walk normally, and are not disabled; by contrast, patients with EDSS scores >5.5 have progressive MS (SPMS or PPMS) and are gait-impaired and occupationally disabled.

Acute Attacks or Initial Demyelinating Episodes When patients experience an 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. As a result, mild attacks are often not treated. Physical and occupational therapy can help with mobility and manual dexterity.

Glucocorticoid treatment is administered as intravenous methylprednisolone, 500 to 1000 mg/d for 3 to 5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60 to 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 (7 exchanges: 54 mL/kg or 1.1 plasma volumes 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, because the cost is high, and the evidence of efficacy is preliminary, plasma exchange should be considered only in selected cases.

TABLE 359-4 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, Neurology 33:1444, 1983.

Disease-Modifying Therapies for Relapsing Forms of MS (RRMS SPMS with Exacerbations) Four such agents are approved in the United States: (1) IFN-β1a (Avonex), (2) IFN-β1a (Rebif); (3) IFN-β1b (Betaseron); and (4) glatiramer acetate (Copaxone). Each of these treatments is also used in SPMS patients who still experience attacks, because SPMS can be difficult to distinguish from RRMS and the clinical trials suggest that such patients also derive therapeutic benefit. In Phase III clinical trials, recipients of IFNβ1b, IFNβ1a, and glatiramer acetate experienced ~30% fewer clinical exacerbations and fewer new MRI lesions compared to placebo recipients. Mitoxantrone (Novantrone), an immune suppressant, has also been approved in the United States, although, because of its potential toxicity, it is generally reserved for patients with progressive disability who have failed other treatments.

INTERFERON β AND GLATIRAMER ACETATE IFN-β is a class I interferon originally identified by its antiviral properties. Efficacy in MS, however, 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.

IFN-β reduces the attack rate (whether measured clinically or by MRI) in MS patients. It also improves disease severity measures such as EDSS progression and MRI-documented disease burden. The efficacy of IFN-β in SPMS patients is less convincing than the efficacy

in RRMS patients. 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. However, its usefulness in progressive disease is entirely unknown.

The long-term efficacy of these treatments remains largely unknown. For the interferons, clear-cut beneficial effects in reducing the relapse rate and, more substantially, in reducing CNS inflammation inferred by MRI has not been matched by similar success in treating patients with progressive symptoms (see below). This discordance has led to a reconsideration of the MS disease process as having two separate phases: inflammatory and neurodegenerative. In this model, the former leads to attacks and the latter to progression. It is likely that a gradual loss of axons underlies progressive MS symptoms, and this process could hypothetically result from loss of trophic influences provided by intact myelin. If true, then an MS attack early in the course might lead to a progressive symptom many years later. Because of this possibility, many experts currently 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 need to be followed closely with periodic brain MRI scans; the need for therapy is reassessed if the scans reveal evidence of ongoing, subclinical disease.

Most treated patients with relapsing forms of MS receive IFN-β as first-line therapy. Regardless of which agent is chosen first, treatment should probably be altered in patents who continue to have frequent attacks or progressive disability (Fig. 359-4). The value of combination therapy is unknown.

IFN-β1a (Avonex), 30 μg, is administered by intramuscular injection once every week. IFN-β1a (Rebif), 44 μg, is administered by subcutaneous injection three times per week. IFN-β1b (Betaseron), 250 μg, is administered by subcutaneous injection every other day. Glatiramer acetate, 20 mg, is administered by subcutaneous injection every day. 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 auto-injector. 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 to 10% of IFN-β1a (Avonex) recipients, 15 to 25% of IFN-β1a (Rebif) recipients, and 30 to 40% of IFN-β1b (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. 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 matter. Conversely, for a patient doing poorly on therapy, alternative

A

Relapsing-Remitting MS

- Acute neurologic change
  - Exacerbation
    - Functional impairment → Methylprednisolone/ prednisone
    - No functional impairment → Symptomatic therapy
  - Pseudoexacerbation → Identify and treat any underlying infection or trauma
- Stable
  - ?- Low attack frequency or single attack
  - ?- Normal neurologic exam
  - ?- Low disease burden by MRI
    - No → Prophylaxis 1. IFN-β1a, or 2. IFN-β1b, or 3. Glatiramer acetate
      - Good response → Continue therapy
      - Intolerant or poor response → Successive trials of alternatives → Intolerant or poor response → Consider Rx with one of the following: 1. Mitoxantrone 4. Pulse cyclophosphamide / 2. Azathioprine 5. IVIg / 3. Methotrexate 6. Pulse methylprednisolone
    - Yes → Repeat clinical exam and MRI in 6 months
      - Clinical or MRI change
      - No change → Continue periodic clinical/ MRI assessments

B

Progressive MS

- Secondary progressive MS
  - With relapses → 1. IFN-β1a, or 2. IFN-β1b
  - Without relapses → No proven treatment
  - Consider → Intolerant or poor response → Consider Rx with one of the following: 1. Mitoxantrone 4. Pulse cyclophosphamide / 2. Azathioprine 5. IVIg / 3. Methotrexate 6. Pulse methylprednisolone
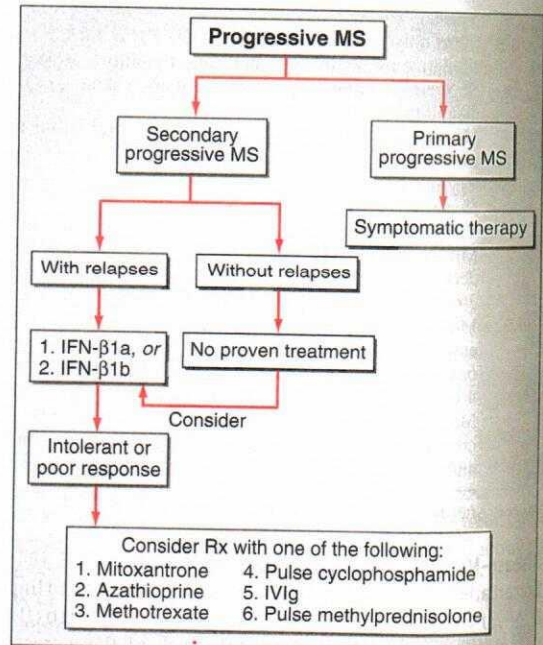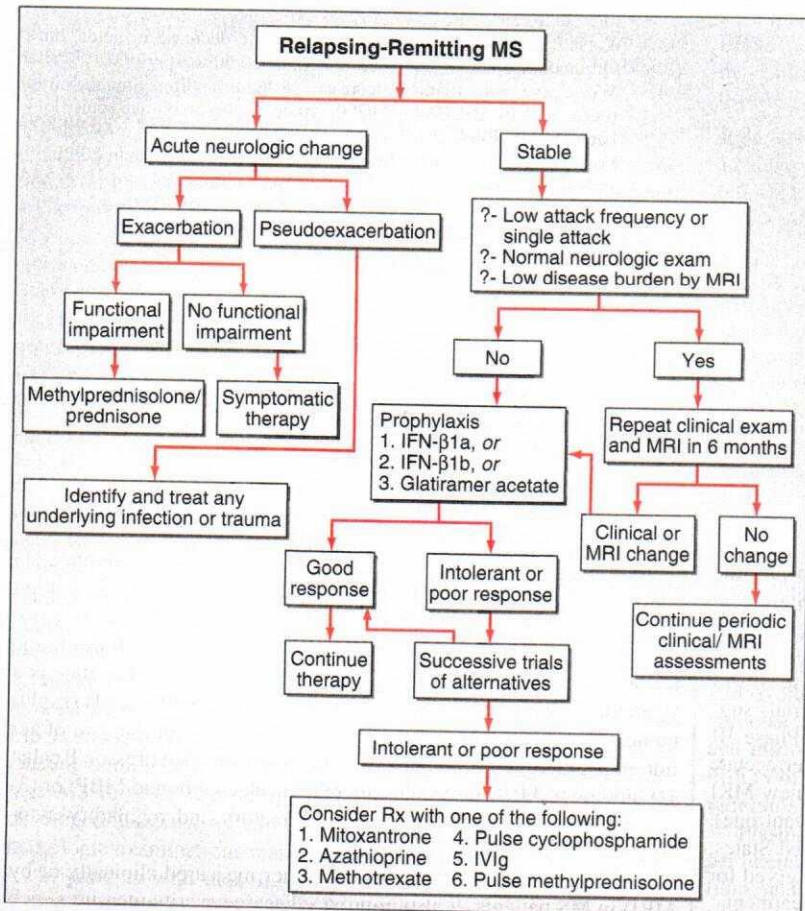- Primary progressive MS → Symptomatic therapy

FIGURE 359-4 Therapeutic decision making for MS.

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-β1b. 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.

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 produce cardiac problems (e.g., cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure). As a result, a cumulative dose >140 mg/m² is not recommended. At currently approved doses (12 mg/m² every 3 months), the maximum duration of therapy can be only 2 to 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 without Relapses 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.

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 an apparent lack of efficacy. A trial of mitoxantrone in PPMS is in progress.

Off-Label Treatment Options for RRMS and SPMS *Azathioprine* (2 to 3 mg/kg body weight) 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 to 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/m², every other month) may be helpful for treatment-refractory patients who are (1) otherwise in good health, (2) ambulatory, and (3) <40 years of age. Because cyclophosphamide can be used for periods in excess of 3 years, it may be preferable to mitoxantrone in these circumstances.

Intravenous immunoglobulin (IVIg), administered in monthly pulses (up to 1 g/kg) for up to 2 years, appears to reduce annual exacerbation rates. However, its use is limited because of its high cost, questions about optimal dose, and uncertainty about its 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, calcium orotate, bee stings, cow colostrum, hyperbaric oxygen, procarin (a combination of histamine and caffeine), chelation, acupuncture, acupressure, various Chinese herbal remedies, and removal of mercury amalgam tooth fillings, among many others. Patients should avoid costly or potentially hazardous unproven treatments. Many such treatments lack biologic plausibility. For example, no reliable case of mercury poisoning resembling typical MS has ever been described.

Although potential roles for human herpes virus 6 and/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 to 40 mg/d; and 3,4-di-aminopyridine, 40 to 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 to 20 mg/d; mysoline, 50 to 250 mg/d; propranolol, 40 to 200 mg/d; or ondansetron, 8 to 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 to 120 mg/d), diazepam (2 to 40 mg/d), tizanidine (8 to 32 mg/d), dantroline (25 to 400 mg/d), and cyclobenzaprine hydrochloride (10 to 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 to 1000 mg/d; phenytoin, 300 to 600 mg/d; or gabapentin, 300 to 3600 mg/d), antidepressants (amitriptyline, 25 to 150 mg/d; nortryptiline, 25 to 150 mg/d; desipramine, 100 to 300 mg/d; or venlafaxine, 75 to 225 mg/d), or antiarrhythmics (mexiletine, 300 to 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 to 15 mg/d), oxybutinin (5 to 15 mg/d), hycosamine sulfate (0.5 to 0.75 mg/d), or tolteridine tartrate (2 to 4 mg/d) may help. Coadministration of pseudoephedrine (30 to 60 mg) is sometimes beneficial.

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

Urinary tract infections should be treated promptly. Patients with large postvoid 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 (fluoxitine, 20 to 80 mg/d, or sertraline, 50 to 200 mg/d); the tricyclic antidepressants, (amitriptyline, 25 to 150 mg/d, nortryptiline, 25 to 150 mg/d, or desipramine, 100 to 300 mg/d); and the non-tricyclic antidepressants (venlafaxine, 75 to 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), pemoline (37.5 to 75 mg/d), methylphenidate (5 to 25 mg/d), or modafinil (100 to 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 to 600 mg/d; carbamazepine, 50 to 400 mg/d; phenytoin, 50 to 300 mg/d; or gabapentin, 600 to 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 to 100 mg) taken 1 to 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 α_4-integrin to prevent adhesion of lymphocytes to endothelial surfaces, against CD52 to induce global lymphocyte depletion, or against CD20 to deplete B cells selectively; (4) use of statins as immunomodulators; (5) estriol to induce a pregnancy-like state; (6) bone marrow transplants; and (7) schwann cell transplants.

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 areas of necrosis and thickening of blood vessel walls. 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 or HIV. More frequently, however, NMO is idiopathic and probably represents an MS variant.

Occasional patients present with apparent NMO but have periventricular MRI changes indicating typical MS. Furthermore, in the MS disease model EAE, immunization with peptides of MOG can produce an NMO-like disorder. 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 or interferons are sometimes used in the hope that further relapses will be prevented.

Acute MS (Marburg's variant) is a fulminant demyelinating process that progresses to death within 1 to 2 years. Typically, there are no remissions. Diagnosis is established by biopsy or at autopsy, revealing widespread demyelination, axonal loss, edema, and macro-phage infiltration. Discrete plaques may also be seen. Recent evidence strongly supports an antibody-mediated process in the demyelinating lesions. 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 of Weston Hurst, 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 to 2 in 10^6 immunizations). ADEM is now most frequently associated with varicella (chickenpox) infections (1 in 4000 to 10,000 cases). It may also follow infection with rubella, mumps, influenza, parainfluenza, and infectious mononucleosis viruses and with *Mycoplasma*. Some patients may have a nonspecific upper respiratory infection or no known antecedent illness.

An autoimmune response to MBP can be detected in the CSF from many patients with ADEM. This response has been most clearly established after rabies vaccination and infection with measles virus. With measles infection, the induction of immune responses to a variety of CNS antigens may occur, but only the response to MBP correlates with the development of ADEM. Many cases of postvaccinal encephalomyelitis may result from sensitization with brain material that contaminates the viral vaccines. 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 to 1.5 g/L (50 to 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 or 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.

℞ TREATMENT

Initial treatment is with high-dose glucocorticoids as for exacerbations of MS (see above). Patients who fail to respond may benefit from a course of plasma exchange or intravenous immunoglobulin. The prognosis reflects the severity of the underlying acute illness. Measles encephalomyelitis is associated with a mortality rate of 5 to 20%, and most survivors have permanent neurologic sequelae. Children who recover may have persistent seizures and behavioral and learning disorders.

FURTHER READING

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360 MENINGITIS, ENCEPHALITIS, BRAIN ABSCESS, AND EMPYEMA
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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. 360-1)   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 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 including papilledema or a depressed level of consciousness should undergo computed tomography (CT) or magnetic resonance imaging (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 mental status (e.g., somnolence, coma), seizures, or focal neurologic deficits only rarely 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. 121) 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. 127) 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 colo-