458 Multiple Sclerosis and Other Demyelinating Diseases

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Demyelinating disorders are immune-mediated conditions characterized by preferential 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, the most common disease in this category, is second only to trauma as a cause of neurologic disability beginning in early to middle adulthood.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disease of the CNS characterized by chronic inflammation, demyelination, gliosis (scarring), and neuronal loss; the course can be relapsing-remitting or progressive. Lesions of MS typically develop at different times and in different CNS locations (i.e., MS is said to be disseminated in time and space). Approximately 350,000 individuals in the United States and 2.5 million individuals worldwide are affected. The clinical course can be extremely variable, ranging from a benign condition to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments.

PATHOGENESIS

Pathology New MS lesions begin with perivenular cuffing by inflammatory mononuclear cells, predominantly T cells and macrophages, which also infiltrate the surrounding white matter. At sites of inflammation, the blood-brain barrier (BBB) is disrupted, but unlike vasculitis, the vessel wall is preserved. Involvement of the humoral immune system is also evident; small numbers of B lymphocytes also infiltrate the nervous system, myelin-specific autoantibodies are present on degenerating myelin sheaths, and complement is activated. Demyelination is the hallmark of the pathology, and evidence of myelin degeneration is found at the earliest time points of tissue injury. A remarkable feature of MS plaques is that oligodendrocyte precursor cells survive—and in many lesions are present in even greater numbers than in normal tissue—but these cells fail to differentiate into mature myelin-producing cells. In some lesions, surviving oligodendrocytes or those that differentiate from precursor cells partially remyelinate the surviving naked axons, producing so-called *shadow plaques*. As lesions evolve, there is prominent astrocytic proliferation (gliosis). Over time, ectopic lymphocyte follicle-like structures, consisting of aggregates of T and B cells resembling secondary lymphoid tissue, appear in the meninges and especially overlying deep cortical sulci and also in perivascular spaces. Although relative sparing of axons is typical of MS, partial or total axonal destruction can also occur, especially within highly inflammatory lesions. Thus MS is not solely a disease of myelin, and neuronal pathology is increasingly recognized as a major contributor to irreversible neurologic disability. Inflammation, demyelination, and plaque formation are also present in the cerebral cortex, and significant axon loss indicating death of neurons is widespread, especially in advanced cases (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. 458-1). 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. 458-1). This redistribution ultimately allows continuous propagation of nerve action potentials through the demyelinated segment. Conduction block may be incomplete, affecting high- but not low-frequency volleys of impulses. Variable conduction block can occur with raised body temperature or metabolic alterations and may explain clinical fluctuations that vary from hour to hour or appear with fever or exercise. Conduction slowing occurs when the demyelinated segments of the axonal membrane are reorganized to support continuous (slow) nerve impulse propagation.

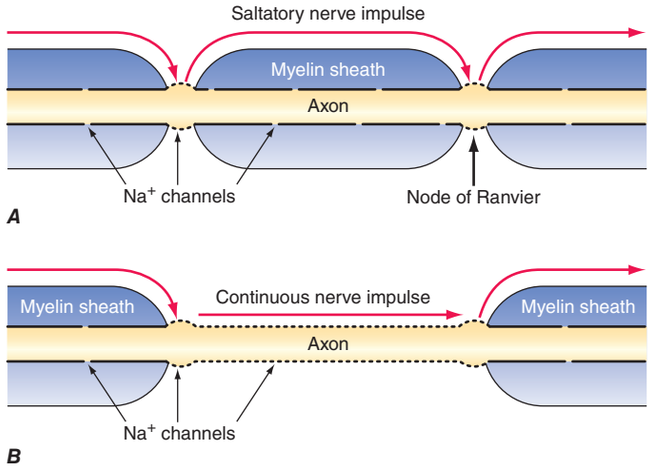


FIGURE 458-1 Nerve conduction in myelinated and demyelinated axons. ***A.*** Saltatory nerve conduction in myelinated axons occurs with the nerve impulse jumping from one node of Ranvier to the next. Sodium channels (shown as breaks in the solid black line) are concentrated at the nodes where axonal 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.

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 a small percentage of cases begin before the age of 10 years.

Geographical gradients have been repeatedly observed in MS, with the highest known prevalence for MS (250 per 100,000) in the Orkney Islands, located north of Scotland. In other temperate zone areas (e.g., northern North America, northern Europe, southern Australia, and southern New Zealand), the prevalence of MS is 0.1–0.2%. By contrast, in the tropics (e.g., Asia, equatorial Africa, and the Middle East), the prevalence is often 10- to 20-fold less.

The prevalence of MS has increased steadily (and dramatically) in several regions around the world over the past half-century, presumably reflecting the impact of some environmental shift. Moreover, the fact that this increase has occurred primarily (or exclusively) in women indicates that women are more responsive to this environmental change.

Well-established risk factors for MS include vitamin D deficiency, exposure to Epstein-Barr virus (EBV) after early childhood, and cigarette smoking.

Vitamin D deficiency is associated with an increase in MS risk, and data suggest that ongoing deficiency may also increase disease activity after MS begins. Immunoregulatory effects of vitamin D could explain these apparent relationships. Exposure of the skin to ultraviolet-B (UVB) radiation from the sun is essential for the biosynthesis of vitamin D, and this endogenous production is the most important source of vitamin D in most individuals; a diet rich in fatty fish represents another source of vitamin D. At high latitudes, the amount of UVB radiation reaching the earth's surface is often insufficient, particularly during winter months, and consequently, low serum levels of vitamin D are common in temperate zones. The common practice to avoid direct

sun exposure and the widespread use of sun block, which (at sun protection factor [SPF] 15) blocks 94% of the incoming UVB radiation, would be expected to exacerbate any population-wide vitamin D deficiency.

Evidence of a remote EBV infection playing some role in MS is supported by numerous epidemiologic and laboratory studies. A higher risk of infectious mononucleosis (associated with relatively late EBV infection) and higher antibody titers to latency-associated EBV nuclear antigen have been repeatedly associated with MS risk, although a causal role for EBV has not been established.

A history of cigarette smoking has also been associated with MS risk. Interestingly, in an animal model of MS, the lung was identified as a critical site for activation of pathogenic T lymphocytes responsible for autoimmune demyelination.

Recent data in MS models have also shown that high levels of dietary sodium activate pathogenic autoreactive T lymphocytes, suggesting that consumption of a high-salt diet, now widespread in the Western world, might be part of the explanation for the observed increase in the prevalence of MS in recent years.

GENETIC CONSIDERATIONS

Whites 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 458-1).

Susceptibility to MS is polygenic, with each gene contributing a relatively small amount to the overall risk. The strongest susceptibility signal in genome-wide studies maps to the HLA-DRB1 gene in the class II region of the major histocompatibility complex (MHC), and this association accounts for approximately 10% of the disease risk. This HLA association, which was first described several decades ago, suggests that MS, at its core, is an antigen-specific autoimmune disease. Whole-genome association studies have now identified approximately 110 other MS susceptibility variants, each of which individually has only a modest effect on MS risk. Most of these MS-associated genes have known roles in the adaptive immune system, for example the genes for the interleukin (IL) 7 receptor (CD127), IL-2 receptor (CD25), and T cell costimulatory molecule LFA-3 (CD58); some variants also influence susceptibility to other autoimmune diseases in addition to MS. The variants identified so far all lack specificity and sensitivity for MS; thus, at present, they are not useful for diagnosis or to predict the future course of the disease.

IMMUNOLOGY A proinflammatory autoimmune response directed against a component of CNS myelin, and perhaps other neural elements as well, remains the cornerstone of current concepts of MS pathogenesis.

AUTOREACTIVE T LYMPHOCYTES Myelin basic protein (MBP), an intracellular protein involved in myelin compaction, is an important T cell antigen in experimental allergic encephalomyelitis (EAE), a laboratory model, and 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, *DRB1*15:01* 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. Two different populations of proinflammatory T cells are likely to mediate autoimmunity in MS. T-helper type 1 (T_H1) cells producing interferon γ (IFN-γ) are one key effector population, and more recently, a role for highly proinflammatory T_H17 T cells has been established. T_H17 cells are induced by transforming growth factor β (TGF-β) and IL-6 and are amplified by IL-21 and IL-23. T_H17 cells, and levels of their corresponding cytokine IL-17, are increased in MS lesions and also in the circulation of people with active MS. High circulating levels of IL-17 may also be a marker of a more severe course of MS. T_H1 cytokines, including IL-2, tumor necrosis factor (TNF)-α, and IFN-γ, also play key roles in activating and maintaining autoimmune responses, and TNF-α and IFN-γ may directly injure oligodendrocytes or the myelin membrane.

TABLE 458-1 RISK OF DEVELOPING MULTIPLE SCLEROSIS (MS)

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

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. Clonally restricted populations of activated, antigen-experienced, memory B cells and plasma cells are present in MS lesions, in lymphoid follicle-like structures in the meninges overlying the cerebral cortex, and in the CSF. Similar or identical clonal populations are found in each compartment, indicating that a highly focused B cell response is occurring locally within the CNS in MS. Myelin-specific autoantibodies, some directed against an extracellular myelin protein, myelin oligodendrocyte glycoprotein (MOG), have been detected bound to vesiculated myelin debris in MS plaques. In the CSF, elevated levels of locally synthesized immunoglobulins and oligoclonal antibodies, derived from clonally restricted CNS B cells and plasma cells, are also characteristic of MS. The pattern of oligoclonal banding is unique to each individual, and attempts to identify the targets of these antibodies have been largely unsuccessful.

TRIGGERS Serial magnetic resonance imaging (MRI) studies in early relapsing-remitting MS reveal that bursts of focal inflammatory disease activity occur far more frequently than would have been predicted by the frequency of relapses. Thus, early in MS, most disease activity is clinically silent. Although the triggers causing these bursts are unknown, molecular mimicry between environmental agents, presumably pathogens, and myelin antigens activating pathogenic T cells may be responsible (Chap. 377e).

Neurodegeneration Axonal damage occurs in every newly formed MS lesion, and cumulative axonal loss is considered to be one important cause of irreversible neurologic disability in MS. As many as 70% of axons are lost from the lateral corticospinal (e.g., motor) tracts in patients with advanced paraparesis from MS, and longitudinal MRI studies suggest there is progressive axonal loss over time within established, inactive lesions. Demyelination can result in reduced trophic support for axons, redistribution of ion channels, and destabilization of action potential membrane potentials. Axons can adapt initially to these injuries, but over time, distal and retrograde degeneration often occurs. Therefore, promoting remyelination remains an important therapeutic goal.

In progressive MS, a key unresolved question is whether the primary neurodegenerative process occurs primarily in the cerebral cortex, the white matter, or in some combination of the two sites. As noted above, meningeal infiltrates of B and T cells are particularly prominent in progressive MS cases, and these "lymphoid follicles" are associated with underlying microglial activation, gray matter plaques, and loss of cortical neurons. White matter lesions may also contribute to late progressive MS; inactive plaques are often noninflammatory at the center, but at the edges, microglia and macrophages and evidence of ongoing axonal injury can be found. This suggests that a simmering, and possibly concentrically expanding, axonopathy may be present, even in the most chronic cases. In addition, a diffuse low-grade inflammation across large areas of white matter may be present, associated with reduced myelin staining and axonal injury ("dirty white matter"). Another characteristic of progressive MS is that inflammation is often present without a concomitant disruption of the BBB; possibly, this feature might explain the failure of immunotherapies not capable of crossing the BBB to benefit patients with progressive MS.

Evidence supports a role of one, or more likely several, of the following mechanisms in progressive MS. Axonal and neuronal death may result from glutamate-mediated excitotoxicity, oxidative injury, iron accumulation, and/or mitochondrial failure either occurring as a consequence of free-radical damage or due to accumulation of deletions in mitochondrial DNA.

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, approximately 0.1% of individuals who were asymptomatic during life will be found, unexpectedly, to have pathologic evidence of MS. Similarly, in the modern era, 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 458-2)**. Examination often reveals evidence of neurologic dysfunction, often in asymptomatic locations. For example, a patient may present with symptoms in one leg but signs in both.

Weakness of the limbs may manifest as loss of strength, speed, or dexterity, as fatigue, or as a disturbance of gait. Exercise-induced weakness is a characteristic symptom of MS. The weakness is of the upper motor neuron type **(Chap. 30)** and is usually accompanied by other pyramidal signs such as spasticity, hyperreflexia, and Babinski signs. Occasionally a tendon reflex may be lost (simulating a lower motor neuron lesion) if an MS lesion disrupts the afferent reflex fibers in the spinal cord **(see Fig. 30-2)**.

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

Optic neuritis (ON) presents as diminished visual acuity, dimness, or decreased color perception (desaturation) in the central field of vision. These symptoms can be mild or may progress to severe visual loss. Rarely, there is complete loss of light perception. Visual symptoms are generally monocular but may be bilateral. Periorbital pain (aggravated by eye movement) often precedes or accompanies the visual loss. An afferent pupillary defect **(Chap. 39)** 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 uncommon and should raise the possibility of alternative diagnoses such as sarcoid or lymphoma.

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

Diplopia may 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 **(Chaps. 41e and 42)**.

TABLE 458-2 INITIAL SYMPTOMS OF MS

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

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

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

Depression, experienced by approximately half of patients, can be reactive, endogenous, or part of the illness itself and can contribute to fatigue.

Fatigue **(Chap. 29)** is experienced by 90% of patients; this symptom is the most common reason for work-related disability in MS. Fatigue can be exacerbated by elevated temperatures, depression, expending exceptional effort to accomplish basic activities of daily living, or sleep disturbances (e.g., from frequent nocturnal awakenings to urinate).

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. 455)**. 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. 28)**. *Hearing loss* **(Chap. 43)** 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 shock–like sensation (typically induced by flexion or other movements of the neck) that radiates down

the back into the legs. Rarely, it radiates into the arms. It is generally self-limited but may persist for years. Lhermitte's symptom can also occur with other disorders of the cervical spinal cord (e.g., cervical spondylosis).

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. 455) can occur when the demyelinating lesion involves the root entry (or exit) zone of the fifth, seventh, and ninth cranial nerve, respectively. Trigeminal neuralgia (tic douloureux) is a very brief lancinating facial pain often triggered by an afferent input from the face or teeth. Most cases of trigeminal neuralgia are not MS related; however, atypical features such as onset before age 50 years, bilateral symptoms, objective sensory loss, or nonparoxysmal pain should raise the possibility that MS could be responsible.

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

DISEASE COURSE

Four clinical types of MS exist (Fig. 458-2):

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). With initial attacks, there is often substantial or complete recovery over the ensuing weeks to months, but as attacks continue over time recovery may be less evident (Fig. 458-2*A*). Between attacks, patients are neurologically stable.
2. *Secondary progressive MS* (SPMS) always begins as RRMS (Fig. 458-2*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% 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. 458-2*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). Despite these differences, PPMS appears to represent the same underlying illness as RRMS.
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. 458-2*D*).

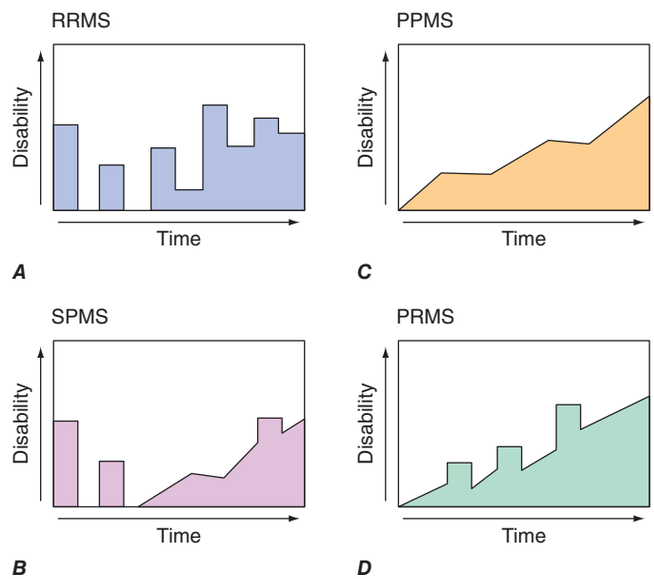


FIGURE 458-2 Clinical course of multiple sclerosis (MS). ***A.*** Relapsing/remitting MS (RRMS). ***B.*** Secondary progressive MS (SPMS). ***C.*** Primary progressive MS (PPMS). ***D.*** Progressive/relapsing MS (PRMS).

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 458-3). Symptoms must last for >24 h and occur as distinct episodes that are separated by a month or more. In patients who have only one of the two required signs on neurologic examination, the second may be documented by abnormal tests such as MRI or evoked potentials (EPs). Similarly, in the most recent diagnostic scheme, the second clinical event (in time) may be supported solely by MRI findings, consisting of either the development of new focal white matter lesions on MRI or the simultaneous presence of both an enhancing lesion and a nonenhancing lesion in an asymptomatic location. In patients whose course is progressive from onset for ≥6 months without superimposed relapses, documentation of intrathecal IgG synthesis may be used to support a diagnosis of PPMS.

DIAGNOSTIC TESTS

Magnetic Resonance Imaging MRI has revolutionized the diagnosis and management of MS (Fig. 458-3); characteristic abnormalities are found in >95% of patients, although more than 90% of the lesions visualized by MRI are asymptomatic. An increase in vascular permeability from a breakdown of the BBB is detected by leakage of intravenous gadolinium (Gd) into the parenchyma. Such leakage occurs early in the development of an MS lesion and serves as a useful marker of inflammation. Gd enhancement typically persists for 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. Current criteria for the use of MRI in the diagnosis of MS are shown in Table 458-3.

The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical 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 methods such as magnetization transfer ratio (MTR) imaging and proton magnetic resonance spectroscopic imaging (MRSI) may ultimately serve as surrogate markers of clinical disability. MRSI can quantitate molecules such as *N*-acetyl aspartate, which

TABLE 458-3 DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS (MS)

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
2 or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a further clinical attack implicating a different CNS site
1 attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space • ≥1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a second clinical attack implicating a different CNS site AND For dissemination in time • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack
Insidious neurologic progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) PLUS 2 out of the 3 following criteria Evidence for dissemination in space in the brain based on ≥1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions Evidence for dissemination in space in the spinal cord based on ≥2 T2+ lesions in the cord Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis.

Source: From CH Polman et al: Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the "McDonald Criteria." Ann Neurol 69:292, 2011.

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 458-3). Abnormalities on one or more EP modalities occur in 80–90% of MS patients. EP abnormalities are not specific to MS, although a marked delay in the latency of a specific EP component (as opposed to a reduced amplitude or distorted wave-shape) is suggestive of demyelination.

Cerebrospinal Fluid CSF abnormalities found in MS include a mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG. The total CSF protein is usually normal. 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 bands (OCBs) by agarose gel electrophoresis in the CSF also assesses intrathecal production of IgG. Two or more discrete OCBs, not present in a paired serum sample, are found in >75% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients, the number of bands may increase with time.

A mild CSF pleocytosis (>5 cells/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 >1 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 458-4), 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 (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. In the current era, the disorders most likely to be mistaken for MS are neuromyelitis optica (see below), sarcoid, vascular disorders (including antiphospholipid syndrome and vasculitis), and rarely CNS lymphoma. 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 clinically evident MS ultimately experience progressive neurologic disability. In older studies conducted mostly before disease-modifying therapies for MS were widely available, 15 years after onset, only 20% of patients had no functional limitation, and between one-third and one-half progressed to SPMS and required assistance with ambulation; furthermore, 25 years after onset, ~80% of MS patients reached this level of disability. The long-term prognosis for untreated MS appears to have improved in recent years, at least in part because of the development of therapies for the early relapsing form of the disease. Although the prognosis in an individual is

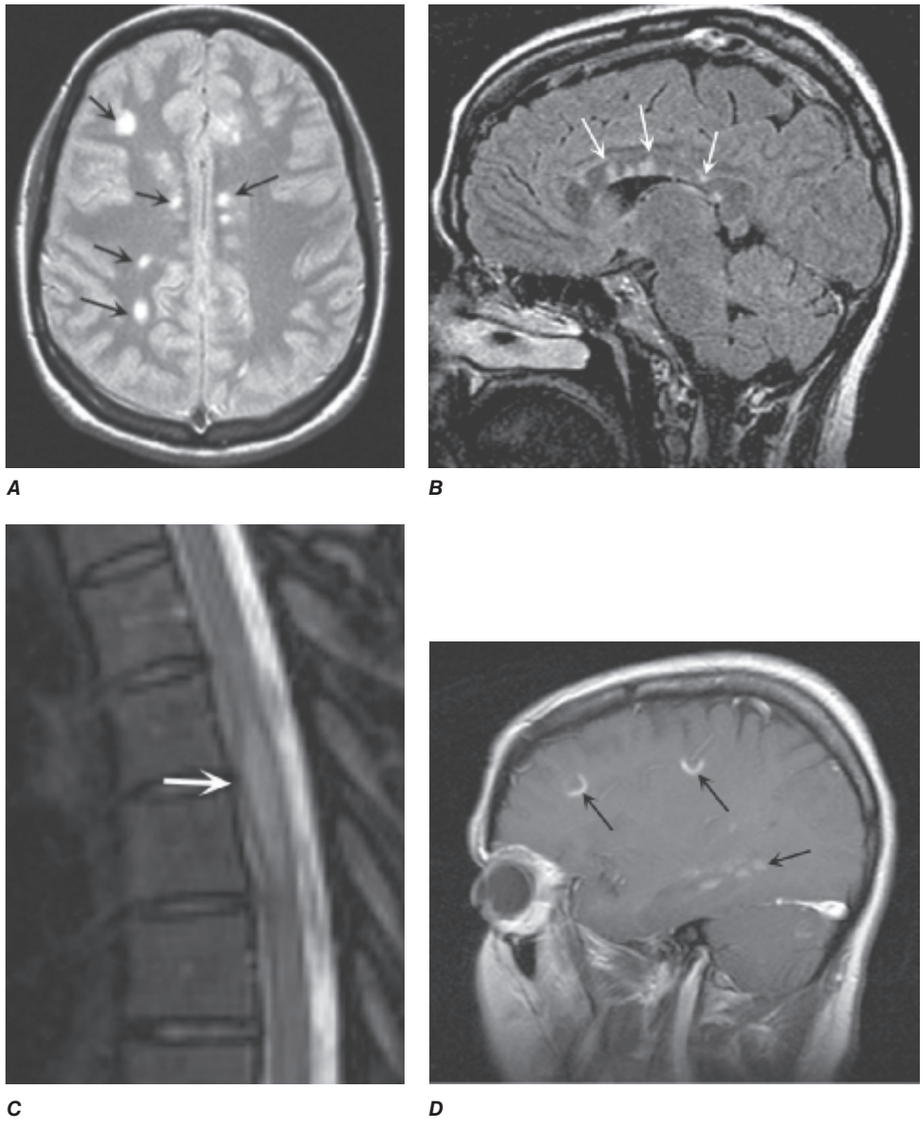


FIGURE 458-3 **Magnetic resonance imaging findings in multiple sclerosis (MS).** ***A.*** Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. ***B.*** Sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) image in which the high signal of cerebrospinal fluid (CSF) has been suppressed. CSF appears dark, whereas areas of brain edema or demyelination appear high in signal as shown here in the corpus callosum (*arrows*). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. ***C.*** Sagittal T2-weighted fast spin echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the midthoracic spinal cord. ***D.*** Sagittal T1-weighted image obtained after the intravenous administration of gadolinium DTPA reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (*arrows*).

difficult to establish, certain clinical features suggest a more favorable prognosis. These include ON or sensory symptoms at onset; fewer than two relapses in the first year of illness; and minimal impairment after 5 years. By contrast, patients with truncal ataxia, action tremor, pyramidal symptoms, or a progressive disease course are more likely to become disabled. Patients with a long-term favorable course are likely to have developed fewer MRI lesions during the early years of disease, and vice versa. 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 20 years is ~80%. Conversely, with a normal brain MRI, the likelihood of developing MS is <20%. Similarly, the presence of two or more Gd-enhancing lesions at baseline is highly predictive of future MS, as is the appearance of either new T2-weighted lesions or new Gd enhancement ≥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 can also result from suicide. Early disease-modifying therapy seems to reduce this excess mortality.

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

TABLE 458-4 DISORDERS THAT CAN MIMIC MULTIPLE SCLEROSIS (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-1/2 infection)
Vascular malformations (especially spinal dural AV fistulas)
Vasculitis (primary CNS or other)
Vitamin B_{12} deficiency

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

generally discontinued during pregnancy, although the actual risk from the interferons and glatiramer acetate (see below) appears to be low.

TREATMENT MULTIPLE SCLEROSIS

Therapy for MS can be divided into several categories: (1) treatment of acute attacks, (2) treatment with disease-modifying agents that reduce the biologic activity of MS, and (3) symptomatic therapy. Treatments that promote remyelination or neural repair do not currently exist, but several promising approaches are being actively investigated.

The Expanded Disability Status Score (EDSS) is a widely used measure of neurologic impairment in MS **(Table 458-5)**. 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. When the clinical change is thought to reflect a pseudoexacerbation, glucocorticoid treatment is inappropriate. Glucocorticoids are used to manage either first attacks or acute exacerbations. They provide short-term clinical benefit by reducing the severity and shortening the duration of attacks. Whether treatment provides any long-term benefit on the course of the illness is less clear. Therefore, mild attacks are often not treated. Physical and occupational therapy can help with mobility and manual dexterity.

Glucocorticoid treatment is usually administered as intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks. Orally administered methylprednisolone or dexamethasone (in equivalent dosages) can be substituted for the intravenous portion of the therapy, although gastrointestinal complications are more common by this route. Outpatient treatment is almost always possible.

Side effects of short-term glucocorticoid therapy include fluid retention, potassium loss, weight gain, gastric disturbances, acne, and emotional lability. Concurrent use of a low-salt, potassium-rich diet and avoidance of potassium-wasting diuretics are advisable. Lithium carbonate (300 mg orally bid) may help 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). Proton pump inhibitors such as pantoprazole (40 mg orally bid) may reduce the likelihood of gastritis, especially when large doses are administered orally. Plasma exchange (five to seven exchanges: 40–60 mL/kg per exchange, every other day for 14 days) may benefit patients with fulminant attacks of demyelination that are unresponsive to glucocorticoids. However, the cost is high, and conclusive evidence of efficacy is lacking.

DISEASE-MODIFYING THERAPIES FOR RELAPSING FORMS OF MS (RRMS, SPMS WITH EXACERBATIONS)

Ten such agents are approved by the U.S. Food and Drug Administration (FDA): (1) IFN-β-1a (Avonex), (2) IFN-β-1a (Rebif), (3) IFN-β-1b (Betaseron or Extavia), (4) glatiramer acetate (Copaxone), (5) natalizumab (Tysabri), (6) fingolimod (Gilenya), (7) dimethyl fumarate (Tecfidera), (8) teriflunomide (Aubagio), (9) mitoxantrone (Novantrone), and (10) alemtuzumab (Lemtrada). Several other promising agents are in varying stages of product development. Each of these treatments can also be used in SPMS patients who continue to experience attacks, both because SPMS can be difficult to distinguish from RRMS and because the available clinical trials, although not definitive, suggest that such patients may sometimes derive therapeutic benefit. Thus, in several phase 3 clinical trials, recipients of each of these agents experienced fewer clinical exacerbations and fewer new MRI lesions compared to placebo recipients **(Table 458-6)**. Because of its potential toxicity as an immunosuppressant, mitoxantrone is generally reserved for patients with progressive disability who have failed other treatments. When considering the data in Table 458-6, however, it is important to note that the relative efficacy of the different agents cannot be determined by cross-trial comparisons. Relative efficacy can only be assessed from nonbiased head-to-head clinical trials.

Interferon-β IFN-β is a class I interferon originally identified by its antiviral properties. Efficacy in MS probably results from immunomodulatory properties including (1) downregulating expression of MHC molecules on antigen-presenting cells, (2) reducing proinflammatory and increasing regulatory cytokine levels, (3) inhibiting T cell proliferation, and (4) limiting the trafficking of inflammatory cells in the CNS. IFN-β reduces the attack rate and 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. Head-to-head trials suggest that dosing IFN-β more frequently and at higher doses has better efficacy but is also more likely to induce neutralizing antibodies (see below). IFN-β-1a (Avonex), 30 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 or Extavia), 250 μg, is administered by subcutaneous injection every other 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. 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 due to IFN-β therapy usually subside over time.

TABLE 458-5 SCORING SYSTEMS FOR MULTIPLE SCLEROSIS (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) although 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: Adapted from JF Kurtzke: Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 33:1444, 1983.

Approximately 2–10% of IFN-β-1a (Avonex) recipients, 15–25% of IFN-β-1a (Rebif) recipients, and 30–40% of IFN-β-1b (Betaseron/Extavia) recipients develop neutralizing antibodies to IFN-β, which may disappear over time. Two very large randomized trials (one with >2000 patients) provide unequivocal evidence that neutralizing antibodies reduce efficacy as determined by several MRI outcomes. Paradoxically, however, these same trials, despite abundant statistical power, failed to demonstrate any concomitant impact on the clinical outcomes of disability and relapse rate. The reason for this clinical-radiologic dissociation is unresolved. 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.

Glatiramer Acetate 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

TABLE 458-6 TWO-YEAR OUTCOMES FOR FDA-APPROVED THERAPIES FOR MULTIPLE SCLEROSIS[a]

	Clinical Outcomes[b]		MRI Outcomes[c]	
Dose, Route, and Schedule	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]
FGM, 0.5 mg PO qd	−55%[e]	−34%[f]	−74%[e]	−23%[e]
DMF, 240 mg PO bid	−52%[e]	−40%[f]	−71%[e]	NR
TF, 14 mg PO qd	−31%[e]	−26%[g]	−70%[e]	−20%[g]

[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 magnetic resonance imaging (MRI) disease burden, which was calculated as the difference in the median percent change between the treated and placebo groups. [b]Severity = 1 point Expanded Disability Status Score progression, sustained for 3 months (in the IFN-β-1a 30 μg qw trial, this change was sustained for 6 months; in the IFN-β-1b trial, this was over 3 years). [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 T2-weighted MRI. [e]$p = .001$. [f]$p = .01$. [g]$p = .05$.

Abbreviations: DMF, dimethyl fumarate; FDA, U.S. Food and Drug Administration; FGM, fingolimod; GA, glatiramer acetate; IFN-β, interferon β; IM, intramuscular; IV, intravenous; MTX, mitoxantrone; NR, not reported; NS, not significant; NTZ, natalizumab; PO, oral; q3mo, once every 3 months; qd, daily; qmo, once per month; qod, every other day; qw, once per week; qyr, once per year; SC, subcutaneous; TF, teriflunomide; tiw, three times per week.

the balance between proinflammatory and regulatory cytokines. Glatiramer acetate reduces the attack rate (whether measured clinically or by MRI) in RRMS. Glatiramer acetate also benefits disease severity measures, although, for clinical disability, this is less well established than for IFN-β. Nevertheless, two very large head-to-head trials demonstrated that the impact of glatiramer acetate on clinical relapse rates and disability was comparable to high-dose, high-frequency IFN-β. Therefore, glatiramer acetate should be considered as an equally effective alternative to IFN-β in RRMS patients. Its usefulness in progressive disease is unknown. Glatiramer acetate is administered by subcutaneous injection of either 20 mg every day or 40 mg thrice weekly. Injection-site reactions also occur with glatiramer acetate. Initially, these were thought to be less severe than with IFN-β, although two recent head-to-head comparisons of high-dose, high-frequency IFN-β to daily glatiramer acetate did not bear out this impression. In addition, 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. Finally, some patients experience lipoatrophy, which, on occasion, can be disfiguring and require cessation of treatment.

Natalizumab 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. Natalizumab is highly effective in reducing the attack rate and significantly improves all measures of disease severity in MS (both clinical and MRI). Moreover, it is well-tolerated, and the dosing schedule of monthly intravenous infusions makes it very convenient for patients. However, progressive multifocal leukoencephalopathy (PML), a life-threatening condition resulting from infection by the John Cunningham (JC) virus, has occurred in approximately 0.3% of patients treated with natalizumab. The incidence of PML is very low in the first year of treatment but then rises by the second year to reach a level of about 2 cases per 1000 patients per year. Nevertheless, the measurement of antibodies against the JC virus in the serum can be used to stratify this risk. Thus, in patients who do not have these antibodies, the risk of PML is either minimal or nonexistent (as long as they remain JC antibody free). Conversely, in patients who have these antibodies (especially those who have them in high titer), the risk may be as high as 0.6% or greater. The risk is also high in patients who have previously received immunosuppressive therapy. Natalizumab is currently recommended only for JC antibody–negative patients, unless they have failed alternative therapies or if they have a particularly aggressive disease course. Head-to-head data show that natalizumab is superior to low-dose (weekly) IFN-β-1a in RRMS. However, its relative efficacy compared to other agents has not been established conclusively.

Natalizumab, 300 mg, is administered by IV infusion each month. 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 (only half of which persist).

The major concern with long-term treatment is the risk of PML. Approximately half of the adult population is JC antibody positive, indicating that they experienced an asymptomatic infection with the JC virus at some time in the past. Nevertheless, because the risk is extremely low during the first year of treatment with natalizumab (regardless of antibody status), natalizumab can still be used safely in JC antibody–positive patients for a period of 12 months. After this time, in antibody-positive patients, a change to another disease-modifying therapy should be strongly considered. By contrast, persistently antibody-negative patients can be continued on treatment indefinitely. Up to 2% of seronegative MS patients undergoing treatment with natalizumab seroconvert annually; thus it is recommended that JC antibody status be assessed at 6-month intervals in all patients receiving treatment with this agent.

Fingolimod Fingolimod is a sphingosine-1-phosphate (S1P) inhibitor that prevents the egress of lymphocytes from the secondary lymphoid organs such as the lymph nodes and spleen. Its mechanism of action is probably due, in part, to the trapping of lymphocytes in the periphery and inhibiting their trafficking to the CNS. Fingolimod reduces the attack rate and significantly improves all measures of disease severity in MS. It is well tolerated, and the daily oral dosing schedule makes it very convenient for patients. A large head-to-head phase 3 randomized study demonstrated the superiority of fingolimod over low-dose (weekly) IFN-β-1a. However, its relative efficacy compared to other agents has not been established conclusively.

Fingolimod, 0.5 mg, is administered orally each day. Treatment with fingolimod is also, in general, well tolerated. Mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia) are more common than in controls, sometimes requiring discontinuation of the medication. First- and second-degree heart block and bradycardia can also occur when fingolimod therapy is initiated. A 6-h period of observation (including electrocardiogram monitoring) is recommended for all patients receiving their first dose, and individuals with preexisting cardiac disease should probably not be treated with this agent. Other side effects

include macular edema and, rarely, disseminated varicella-zoster virus (VZV) infection; prior to initiating therapy with fingolimod, an ophthalmic exam and VZV vaccination for seronegative individuals are indicated.

Dimethyl Fumarate (DMF) Although the precise mechanisms of action of DMF are not fully understood, it seems to have anti-inflammatory effects through its modulation of the expression of proinflammatory and anti-inflammatory cytokines. Also, DMF inhibits the ubiquitylation and degradation of nuclear factor E2-related factor 2 (Nrf2)—a transcription factor that binds to the antioxidant response elements (AREs) located on the DNA and thereby induces the transcription of several antioxidant proteins. DMF reduces the attack rate and significantly improves all measures of disease severity in MS patients. However, its twice-daily oral dosing schedule makes it somewhat less convenient for patients than daily oral therapies. In addition, compliance is likely to be less with a twice-daily dosing regimen—a factor that could be of concern given the observation (in a small clinical trial) that once-daily DMF lacks efficacy. A head-to-head trial provided evidence that DMF was superior to glatiramer acetate on some outcome measures.

DMF, 240 mg, is administered orally twice each day. Gastrointestinal side effects (abdominal discomfort, nausea, vomiting, flushing, and diarrhea) are common at the start of therapy but generally subside with continued administration. Other adverse events included mild decreases in neutrophil and lymphocyte counts and mild elevations in liver enzymes. Nevertheless, in general, treatment with DMF is well tolerated after an initial period of adjustment. Following the release of DMF, four cases of PML were reported in patients receiving other products (not Tecfidera) that contained DMF. Each of these patients was lymphocytopenic, and most had received previous immunosuppressant therapy so that the relationship of DMF to the PML (if any) in these cases is uncertain. Nevertheless, these reports underscore the fact, stated previously, that long-term safety can never be guaranteed by the results of short-term trials. In the case of DMF for MS, only time and experience will tell us whether or not there is any cause for concern.

Teriflunomide Teriflunomide inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase, which is a key part of the pathway for de novo pyrimidine biosynthesis from carbamoyl phosphate and aspartate. It is the active metabolite of the drug leflunomide (FDA-approved for rheumatoid arthritis), and it exerts its anti-inflammatory effects by limiting the proliferation of rapidly dividing T and B cells. This enzyme is not involved in the so-called "salvage pathway," by which existing pyrimidine pools are recycled for DNA and RNA synthesis in resting and homeostatically proliferating cells. Consequently, teriflunomide is considered to be cytostatic rather than cytotoxic. Teriflunomide reduces the attack rate and significantly improves all measures of disease severity in MS patients. It is well tolerated, and its daily oral dosing schedule makes it very convenient for patients. A head-to-head trial suggested the equivalence, but not superiority, of teriflunomide and high-dose (thrice-weekly) IFN-β-1a. Teriflunomide, either 7 or 14 mg, is administered orally each day. In the pivotal clinical trials, mild hair thinning and gastrointestinal symptoms (nausea and diarrhea) were more common than in controls, but in general, treatment with teriflunomide was well tolerated. As with any new agent, the long-term safety is not guaranteed by the results of short-term trials. A major limitation, especially in women of childbearing age, is its possible teratogenicity (pregnancy category X); teriflunomide can remain in the bloodstream for 2 years, and it is recommended that exposed men and women who wish to conceive receive cholestyramine or activated charcoal to eliminate residual drug.

Mitoxantrone Hydrochloride Mitoxantrone, an anthracenedione, exerts its antineoplastic action by (1) intercalating into DNA and producing both strand breaks and interstrand cross-links, (2) interfering with RNA synthesis, and (3) inhibiting topoisomerase II (involved in DNA repair). The FDA approved mitoxantrone on the basis of a single (relatively small) phase 3 clinical trial in Europe, in addition to an even smaller phase 2 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 from mitoxantrone, estimated as at least a 1% lifetime risk, and this complication has been reported in several mitoxantrone-treated MS patients.

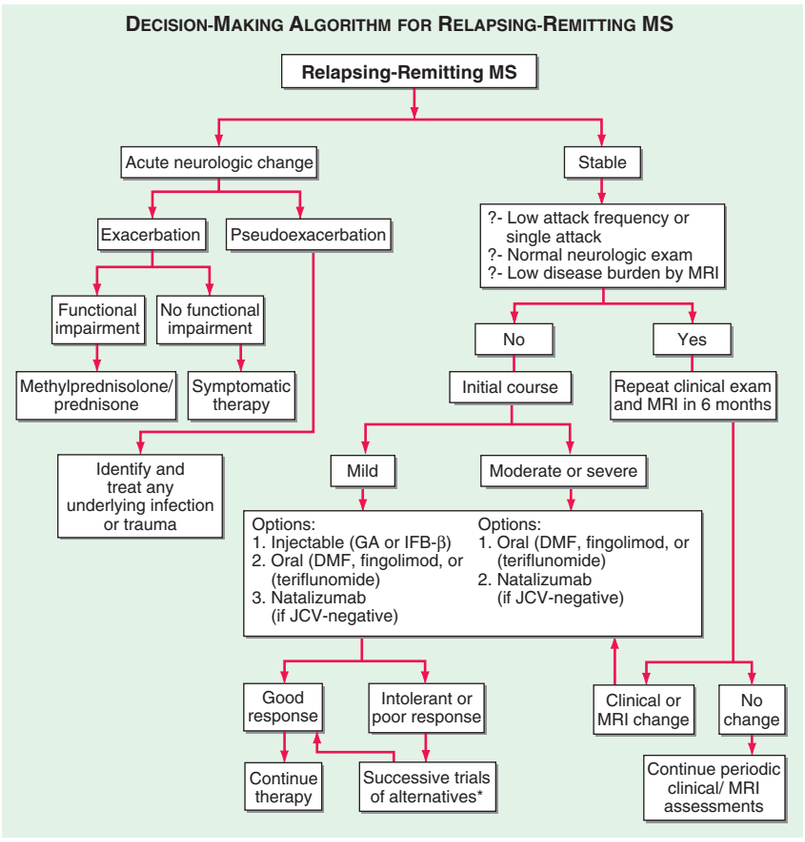
Because of these risks, and a growing list of alternative therapies, mitoxantrone is now only rarely used for MS. It should not be used as a first-line agent in either RRMS or relapsing SPMS, but might be considered in selected patients with a progressive course who have failed other therapies.

Alemtuzumab Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen, which is expressed on both monocytes and lymphocytes. It causes lymphocyte depletion (of both B and T cells) and a change in the composition of lymphocyte subsets. Both of these changes, particularly the impact on lymphocyte subsets, are long lasting. In preliminary trials, alemtuzumab markedly reduced the attack rate and significantly improved all measures of disease severity in MS patients. In two phase 3 trials, however, its impact on clinical disability was less convincing. Notably, both trials used the active comparator of thrice-weekly, high-dose IFN-β-1a. The European and Canadian drug agencies were the first to approve this agent for use in RRMS; the FDA has also approved alemtuzumab, but only after an appeal following initial disapproval. The reasons for the initial disapproval were based on a perceived lack of a convincing disability effect and concerns over potential toxicity. The toxicities of concern were the occurrence (during the trial or thereafter) of (1) autoimmune diseases including thyroiditis, Graves' disease, thrombocytopenia, hemolytic anemia, pancytopenia, antiglomerular basement membrane disease, and membranous glomerulonephritis; (2) malignancies including thyroid cancer, melanoma, breast cancer, and human papillomavirus (HPV)–related cancers; (3) serious infections; and (4) infusion reactions.

Initiating and Changing Treatment Previously, most patients with relapsing forms of MS received injectable agents (IFN-β or glatiramer acetate) as first-line therapy. However, with the introduction of effective and probably safe oral agents, including DMF, fingolimod, and teriflunomide, this has begun to change. In addition, the monthly infusion therapy natalizumab, which is highly effective, well tolerated, and apparently safe in JC antibody–negative patients, provides an attractive option in many cases. As noted above, with the exception of the first-generation injectable agents, long-term safety data are not available, and for the most part, comparative data are lacking. The value of combination therapy is also largely unknown, although a recent clinical trial demonstrated no added benefit to the combination of glatiramer acetate with low-dose, once-weekly IFN-β-1a.

Despite these unknowns, clinicians need to make decisions based on the best available evidence, coupled with practical considerations. One reasonable approach stratifies initial decision-making based on two levels of disease aggressiveness **(Fig. 458-4)**.

MILD INITIAL COURSE In the case of recent onset, normal exam or minimal impairment (EDSS ≤2.5 or less), or low disease activity, either an injectable (IFN-β or glatiramer acetate) or an oral (DMF,



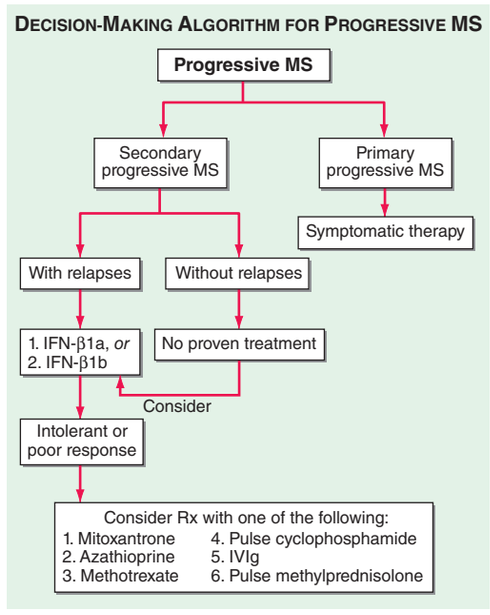


FIGURE 458-4 **Therapeutic decision-making for multiple sclerosis (MS).** *Can include trials of different preparations of interferon β (IFN-β, particularly advancing from once-weekly (Avonex) to a more frequent (e.g., Rebif, Betaseron/Extavia) dosing regimen. Options also include use of natalizumab in JC virus–positive patients. MRI, magnetic resonance imaging.

fingolimod, or teriflunomide) agent is reasonable. Although head-to-head comparisons are not available, natalizumab is thought to be more effective than these other agents, and therefore, this therapy can be considered even in minimally affected, JCV antibody–seronegative patients. The injectable agents (IFN-β and glatiramer acetate) have a superb track record for safety but have a high nuisance factor due to the need for frequent injections, as well as bothersome side effects that contribute to noncompliance. Some of the oral agents (DMF and fingolimod) are probably more effective than the injectables, but long-term risks are mostly unknown; DMF produces bothersome gastrointestinal symptoms in many patients at least initially (can be mitigated by beginning at one-quarter strength and gradually advancing to full dose), and fingolimod can lead to bradycardia and other cardiac disturbances of unclear clinical significance. Teriflunomide may be less effective than the other oral agents, and there are concerns about its possible long-lasting pregnancy risks. Nevertheless, its long-term safety has likely been established because of its extensive human exposure as the active metabolite of leflunomide—a drug long approved by the FDA.

MODERATE OR SEVERE INITIAL COURSE In highly active disease or moderate impairment (EDSS >2.5), either a highly effective oral agent (DMF or fingolimod) or, if the patient is JC virus antibody seronegative, infusion therapy with natalizumab is recommended.

Regardless of which agent is chosen first, treatment should probably be changed in patients who continue to have relapses, progressive neurologic impairment or, arguably, ongoing evidence of subclinical MRI activity (Fig. 458-4).

The long-term impact of these treatments on the disease course remains controversial, although several recent studies have shown that these agents improve the long-term outcome of MS including a prolongation of the time to reach certain disability outcomes (e.g., SPMS and requiring assistance to ambulate) and reduction in MS-related mortality. These benefits seem most conspicuous when treatment begins early in the RRMS stage of the illness. Unfortunately, however, already established progressive symptoms do not respond well to treatment with these disease-modifying therapies. Because progressive symptoms are likely to result from accumulated axonal and neuronal loss, many experts now believe that very early treatment with a disease-modifying drug is appropriate for most MS patients. It may also be 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, however, should be followed closely with periodic brain MRI scans; the need for therapy is reassessed if scans reveal evidence of ongoing, subclinical disease. Finally, vitamin D deficiency should be corrected in all patients with MS, and generally this requires oral supplementation with vitamin D_3, 4000 to 5000 IU daily.

DISEASE-MODIFYING THERAPIES FOR PROGRESSIVE MS

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. All of the other agents have not yet 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 therapies have been convincingly shown to modify the course of PPMS. A phase 3 clinical trial of glatiramer acetate in PPMS was stopped because of lack of efficacy. A phase 2/3 trial of the monoclonal antibody rituximab (anti-CD20) in PPMS was

also negative, but in a preplanned secondary analysis, treatment appeared to modestly slow disability progression in patients with Gd-enhancing lesions at entry; the results of a follow-up trial with a fully humanized monoclonal anti-CD20 therapy (ocrelizumab) will soon be available.

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/week) was shown in one study to slow the progression of upper extremity dysfunction in SPMS. Because of the possibility of developing irreversible liver damage, some experts recommend a blind liver biopsy after 2 years of therapy.

Cyclophosphamide (700 mg/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 having any impact on long-term disability.

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 EBV, human herpesvirus (HHV) 6, or chlamydia have been suggested for MS, these reports are unconfirmed, and treatment with antiviral agents or antibiotics is not recommended.

Most recently, chronic cerebrospinal insufficiency (CCSVI) has been proposed as a cause of MS, and vascular-surgical intervention is recommended. However, the failure of independent investigators to even approximate the initial claims of 100% sensitivity and 100% specificity for the diagnostic procedure have raised considerable doubt that CCSVI is a real entity. Certainly, any potentially dangerous surgery should be avoided until more rigorous science is available.

SYMPTOMATIC THERAPY

For all patients, it is useful to encourage attention to a healthy lifestyle, including maintaining an optimistic outlook, a healthy diet, and regular exercise as tolerated (swimming is often well-tolerated because of the cooling effect of cold water). It is reasonable also to correct vitamin D deficiency with oral vitamin D and to recommend dietary supplementation with long-chain (omega-3) unsaturated fatty acids (present in oily fish such as salmon), because of their biologic plausibility for MS pathogenesis, safety, and general health benefits.

Ataxia/tremor is often intractable. Clonazepam, 1.5–20 mg/d; primidone, 50–250 mg/d; propranolol, 40–200 mg/d; or ondansetron, 8–16 mg/d, may help. Wrist weights occasionally reduce tremor in the arm or hand. Thalamotomy 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 baclofen (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydrochloride (10–60 mg/d). For severe spasticity, a baclofen pump (delivering medication directly into the CSF) can provide substantial relief.

Weakness can sometimes be improved with the use of potassium channel blockers such as 4-aminopyridine (10–40 mg/d) and 3,4-diaminopyridine (40–80 mg/d), particularly in the setting where lower extremity weakness interferes with the patient's ability to ambulate. The FDA has approved 4-aminopyridine (at 20 mg/d), and this can be obtained either as dalfampridine (Ampyra) or, more cheaply, through a compounding pharmacy. The principle concern with the use of these agents is the possibility of inducing seizures at high doses.

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

Bladder dysfunction management is best guided by urodynamic testing. Evening fluid restriction or frequent voluntary voiding may help *detrusor hyperreflexia*. If these methods fail, propantheline bromide (10–15 mg/d), oxybutynin (5–15 mg/d), hyoscyamine sulfate (0.5–0.75 mg/d), tolterodine tartrate (2–4 mg/d), or 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 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 (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), tadalafil (5–20 mg), or vardenafil (5–20 mg), taken 1–2 h before sex, is now the standard treatment for maintaining erections.

PROMISING EXPERIMENTAL THERAPIES

Numerous clinical trials are currently under way. These include studies on (1) monoclonal antibodies against CD20 to deplete B cells and against the IL-2 receptor; (2) selective oral

sphingosine-1-phosphate receptor antagonists to sequester lymphocytes in secondary lymphoid organs; (3) estriol to induce a pregnancy-like state; (4) molecules to promote remyelination; and (4) bone marrow transplantation.

CLINICAL VARIANTS OF MS

Acute MS (*Marburg's variant*) is a fulminant demyelinating process that in some cases progresses inexorably to death within 1–2 years. Typically, there are no remissions. 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.

NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO; Devic's disease) is an aggressive inflammatory disorder characterized by recurrent attacks of ON and myelitis (Table 458-7). NMO is more frequent in women than men (>3:1), typically begins in childhood or early adulthood but can arise at any age, and is uncommon in whites compared with individuals of Asian and African ancestry. Attacks of ON can be bilateral (rare in MS) or unilateral; myelitis can be severe and transverse (rare in MS) and is typically longitudinally extensive, involving three or more contiguous vertebral segments. Also in contrast to MS, progressive symptoms do not occur in NMO. The brain MRI was earlier thought to be normal in NMO, but it is now recognized that in approximately half of cases, there are lesions involving the hypothalamus causing an endocrinopathy; the lower brainstem presenting as intractable hiccoughs or vomiting from involvement of the area postrema in the lower medulla; or the cerebral hemispheres producing focal symptoms, encephalopathy, or seizures. Large MRI lesions in the cerebral hemispheres can be asymptomatic, sometimes have a "cloud-like" appearance and, unlike MS lesions, are often not destructive, and can resolve completely. Spinal cord MRI lesions typically consist of focal enhancing areas of swelling and tissue destruction, extending over three or more spinal cord segments, and on axial sequences, these are centered on the gray matter of the cord. CSF findings include pleocytosis greater than that observed in MS, with neutrophils and eosinophils present in some cases; OCBs are uncommon, occurring in fewer than 30% of NMO patients. The pathology of NMO is a distinctive astrocytopathy with inflammation, a loss of astrocytes, and an absence of staining of the water channel protein aquaporin-4 by immunohistochemistry, plus thickened blood vessel walls, demyelination, and deposition of antibody and complement.

NMO is best understood as a syndrome with diverse causes. Up to 40% of patients have a systemic autoimmune disorder, often systemic lupus erythematosus, Sjögren's syndrome, perinuclear antineutrophil cytoplasmic antibody (p-ANCA)–associated vasculitis, myasthenia gravis, Hashimoto's thyroiditis, or mixed connective tissue disease. In others, onset may be associated with acute infection with VZV, EBV, HIV, or tuberculosis. Rare cases appear to be paraneoplastic and associated with breast, lung, or other cancers. NMO is often idiopathic, however. NMO is usually disabling over time; in one series, respiratory failure from cervical myelitis was present in one-third of patients, and 8 years after onset, 60% of patients were blind and more than half had permanent paralysis of one or more limbs.

A highly specific autoantibody directed against aquaporin-4 is present in the sera of approximately two-thirds of patients with a clinical diagnosis of NMO. Seropositive patients have a very high risk for future relapses; more than half will relapse within 1 year if untreated. Aquaporin-4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces, as well as at paranodal regions near nodes of Ranvier. It is likely that aquaporin-4 antibodies are pathogenic, as passive transfer of antibodies from NMO patients into laboratory animals reproduce histologic features of the disease.

When MS affects individuals of African or Asian ancestry, there is a propensity for demyelinating lesions to involve predominantly the optic nerve and spinal cord, an MS subtype termed *opticospinal MS*. Interestingly, some individuals with opticospinal MS are seropositive for aquaporin-4 antibodies, suggesting that such cases represent an NMO spectrum disorder.

TABLE 458-7 DIAGNOSTIC CRITERIA FOR NEUROMYELITIS OPTICA

Required:

1. Optic neuritis
2. Acute transverse myelitis

Supportive (2 of 3 criteria required):

1. Longitudinally extensive cord lesion extending over 3 or more vertebral segments
2. Brain magnetic resonance imaging normal or not meeting criteria for multiple sclerosis
3. Aquaporin-4 seropositivity

Source: Adapted from DM Wingerchuk et al: Neurology 66:1485, 2006.

TREATMENT NEUROMYELITIS OPTICA

Disease-modifying therapies have not been rigorously studied in NMO. Acute attacks of NMO are usually treated with high-dose glucocorticoids (solumedrol 1–2 g/d for 5–10 days followed by a prednisone taper). Plasma exchange (typically 7 qod exchanges of 1.5 plasma volumes) has also been used empirically for acute episodes that fail to respond to glucocorticoids. Given the unfavorable natural history of untreated NMO, prophylaxis against relapses is recommended for most patients using one of the following regimens: mycophenylate mofetil (250 mg bid gradually increasing to 1000 mg bid); B cell depletion with anti-CD20 monoclonal antibody (rituximab); or a combination of glucocorticoids (500 mg IV methylprednisolone daily for 5 days; then oral prednisone 1 mg/kg per day for 2 months, followed by slow taper) plus azathioprine (2 mg/kg per day started on week 3). Available evidence suggests that use of IFN-β is ineffective and paradoxically may increase the risk of NMO relapses.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) has a monophasic course and is most frequently associated with an antecedent infection (postinfectious encephalomyelitis); approximately 5% of ADEM cases follow immunization (postvaccinal encephalomyelitis). ADEM is far more common in children than adults, and many adult cases initially thought to represent ADEM subsequently experience late relapses qualifying as either MS or another chronic inflammatory disorder such as vasculitis, sarcoid, or lymphoma. The hallmark of ADEM is the presence of widely scattered small foci of perivenular inflammation and demyelination, in contrast to larger confluent demyelinating lesions typical of MS. In the most explosive form of ADEM, acute hemorrhagic leukoencephalitis, the lesions are vasculitic and hemorrhagic, and the clinical course is devastating.

Postinfectious encephalomyelitis is most frequently associated with the viral exanthems of childhood. Infection with measles virus is the most common antecedent (1 in 1000 cases). Worldwide, measles encephalomyelitis is still common, although use of the live measles vaccine has dramatically reduced its incidence in developed countries. An ADEM-like illness rarely follows vaccination with live measles vaccine (1–2 in 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, EBV, HHV-6, HIV, other viruses, and *Mycoplasma pneumoniae*. Some patients may have a nonspecific upper respiratory infection or no known antecedent illness. In addition to measles, postvaccinal encephalomyelitis may also follow the administration

of vaccines for smallpox (5 cases per million), the Semple rabies, and Japanese encephalitis. Modern vaccines that do not require viral culture in CNS tissue have reduced the ADEM risk.

All forms of ADEM presumably result from a cross-reactive immune response to the infectious agent or vaccine that then triggers an inflammatory demyelinating response. Autoantibodies to MBP and to other myelin antigens have been detected in the CSF from some patients with ADEM. 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 or greater, occurs in 80% of patients. Occasional patients have higher counts or a mixed polymorphonuclear-lymphocytic pattern during the initial days of the illness. Transient CSF oligoclonal banding has been reported. MRI usually reveals extensive changes in the brain and spinal cord, consisting of white matter hyperintensities on T2 and fluid-attenuated inversion recovery sequences with Gd enhancement on T1-weighted sequences.

DIAGNOSIS

The diagnosis is most reliably established when there is a history of recent vaccination or viral exanthematous illness. In severe cases with predominantly cerebral involvement, acute encephalitis due to infection with herpes simplex or other viruses including HIV may be difficult to exclude (Chap. 164); other considerations include hypercoagulable states including the antiphospholipid antibody syndrome, vasculitis, neurosarcoid, primary CNS lymphoma, or metastatic cancer. An explosive presentation of MS can mimic ADEM, and especially in adults, it may not be possible to distinguish these conditions at onset. The simultaneous onset of disseminated symptoms and signs is common in ADEM and rare in MS. Similarly, meningismus, drowsiness, coma, and seizures suggest ADEM rather than MS. Unlike MS, in ADEM, optic nerve involvement is generally bilateral and transverse myelopathy complete. MRI findings that favor ADEM include extensive and relatively symmetric white matter abnormalities, basal ganglia or cortical gray matter lesions, and Gd enhancement of all abnormal areas. By contrast, OCBs in the CSF are more common in MS. In one study of adult patients initially thought to have ADEM, 30% experienced additional relapses over a follow-up period of 3 years, and they were reclassified as having MS. Occasional patients with "recurrent ADEM" have also been reported, especially children; however, it is not possible to distinguish this entity from atypical MS.

TREATMENT ACUTE DISSEMINATED ENCEPHALOMYELITIS

Initial treatment is with high-dose glucocorticoids as for exacerbations of NMO (see above); depending on the response, treatment may need to be continued for 8 weeks. Patients who fail to respond within a few days may benefit from a course of plasma exchange or intravenous immunoglobulin. The prognosis reflects the severity of the underlying acute illness. In recent case series of presumptive ADEM in adults, mortality rates of 5–20% are reported, and many survivors have permanent neurologic sequelae.

SECTION 3 NERVE AND MUSCLE DISORDERS

459 Peripheral Neuropathy

Anthony A. Amato, Richard J. Barohn

Peripheral nerves are composed of sensory, motor, and autonomic elements. Diseases can affect the cell body of a neuron or its peripheral processes, namely the axons or the encasing myelin sheaths. Most peripheral nerves are mixed and contain sensory and motor as well as autonomic fibers. Nerves can be subdivided into three major classes: large myelinated, small myelinated, and small unmyelinated. Motor axons are usually large myelinated fibers that conduct rapidly (approximately 50 m/s). Sensory fibers may be any of the three types. Large-diameter sensory fibers conduct proprioception and vibratory sensation to the brain, while the smaller-diameter myelinated and unmyelinated fibers transmit pain and temperature sensation. Autonomic nerves are also small in diameter. Thus, peripheral neuropathies can impair sensory, motor, or autonomic function, either singly or in combination. Peripheral neuropathies are further classified into those that primarily affect the cell body (e.g., neuronopathy or ganglionopathy), myelin (myelinopathy), and the axon (axonopathy). These different classes of peripheral neuropathies have distinct clinical and electrophysiologic features. This chapter discusses the clinical approach to a patient suspected of having a peripheral neuropathy, as well as specific neuropathies, including hereditary and acquired neuropathies. **The inflammatory neuropathies are discussed in Chap. 460.**

GENERAL APPROACH

In approaching a patient with a neuropathy, the clinician has three main goals: (1) identify where the lesion is, (2) identify the cause, and (3) determine the proper treatment. The first goal is accomplished by obtaining a thorough history, neurologic examination, and electrodiagnostic and other laboratory studies (Fig. 459-1). While gathering this information, seven key questions are asked (Table 459-1), the answers to which can usually identify the category of pathology that is present (Table 459-2). Despite an extensive evaluation, in approximately half of patients, no etiology is ever found; these patients typically have a predominately sensory polyneuropathy and have been labeled as having idiopathic or cryptogenic sensory polyneuropathy (CSPN).

INFORMATION FROM THE HISTORY AND PHYSICAL EXAMINATION: SEVEN KEY QUESTIONS (TABLE 459-1)

1. What Systems are Involved? It is important to determine if the patient's symptoms and signs are motor, sensory, autonomic, or a combination of these. If the patient has only weakness without any evidence of sensory or autonomic dysfunction, a motor neuropathy, neuromuscular junction abnormality, or myopathy should be considered. Some peripheral neuropathies are associated with significant autonomic nervous system dysfunction. Symptoms of autonomic involvement include fainting spells or orthostatic lightheadedness; heat intolerance; or any bowel, bladder, or sexual dysfunction (Chap. 454). There will typically be an orthostatic fall in blood pressure without an appropriate increase in heart rate. Autonomic dysfunction in the absence of diabetes should